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THE DOMESTIC AND INTERNATIONAL IMPACTS OF THE 2009-H1N1 INFLUENZA A PANDEMIC

Global Challenges, Global Solutions

Workshop Summary

David A. Relman, Eileen R. Choffnes, and Alison Mack, *Rapporteurs*

Forum on Microbial Threats

Board on Global Health

INSTITUTE OF MEDICINE
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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Cover image: A stained glass window 21″ × 56″ depicting the natural history of influenza viruses and zoonotic exchange in the emergence of new strains is shown in reduced size. Based on the work done at St. Jude Children's Research Hospital supported by American Lebanese Syrian Associated Charities and the National Institute of Allergy and Infectious Diseases. Artist: Jenny Hammond, Highgreenleycleugh, Northumberland, England. Commissioned by Rob and Marjorie Webster.

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Willing is not enough; we must do."
—Goethe

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Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

Roger Breeze, Centaur Science Group
John Pottage, Infectious Disease Medicine Development Center, GlaxoSmithKline
P. Frederick Sparling, School of Medicine, University of North Carolina
Mary Wilson, Department of Population and International Health, Harvard University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was overseen by **Dr. Melvin Worth**. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Acknowledgments

The Forum on Emerging Infections was created by the Institute of Medicine (IOM) in 1996 in response to a request from the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). The purpose of the Forum is to provide structured opportunities for leaders from government, academia, and industry to meet and examine issues of shared concern regarding research, prevention, detection, and management of emerging or reemerging infectious diseases. In pursuing this task, the Forum provides a venue to foster the exchange of information and ideas, identify areas in need of greater attention, clarify policy issues by enhancing knowledge and identifying points of agreement, and inform decision makers about science and policy issues. The Forum seeks to illuminate issues rather than resolve them; for this reason, it does not provide advice or recommendations on any specific policy initiative pending before any agency or organization. Its value derives instead from the diversity of its membership and from the contributions that individual members make throughout the activities of the Forum. In September 2003, the Forum changed its name to the Forum on Microbial Threats.

The Forum on Microbial Threats, and the IOM, wish to express their warmest appreciation to the individuals and organizations who gave their valuable time to provide information and advice to the Forum through their participation in this workshop. A full list of presenters may be found in Appendix A.

The Forum is indebted to the IOM staff who contributed during the course of the workshop and the production of this workshop summary. On behalf of the Forum, we gratefully acknowledge the efforts led by Dr. Eileen Choffnes, director of the Forum; Kate Skoczdopole, senior program associate; K. C. Ostapkovich, research associate; Kenisha Peters, senior program assistant; and Robert Gasior,

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[1]Dr. Kawaoka was a speaker at the workshop.
[2]Dr. Lipsitch was a speaker at the workshop.

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[3]Dr. Worobey was a speaker at the workshop.

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

BOXES

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Workshop Overview[1]

THE DOMESTIC AND INTERNATIONAL IMPACTS OF THE 2009-H1N1 INFLUENZA A PANDEMIC: GLOBAL CHALLENGES, GLOBAL SOLUTIONS

In March and early April 2009, a new, swine-origin 2009-H1N1 influenza A virus (S-OIV)[2] emerged in Mexico and the United States. During the first few weeks of surveillance, the virus spread by human-to-human transmission worldwide to over 30 countries, causing the World Heath Organization (WHO) to raise its pandemic alert level to Phase 5 of 6. On June 11, 2009, the WHO raised the worldwide pandemic alert level to Phase 6 in response to the sustained global spread of the 2009-H1N1 influenza A virus. President Obama, on October 24, 2009, signed an official proclamation declaring the 2009-H1N1 influenza A swine flu outbreak a national emergency in the United States (The White House, 2009). This declaration does "hereby find and proclaim that, given that the rapid increase in illness across the Nation may overburden health care resources and that the temporary waiver of certain standard Federal requirements may be warranted in order to enable U.S. health care facilities to implement emergency operations plans, the 2009 H1N1 influenza pandemic in the United States constitutes a national emergency."

[1]The Forum's role was limited to planning the workshop, and this workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop.

[2]While this pandemic H1N1 strain of influenza A virus has gone by many, many names—including "swine flu"—since it was first recognized and characterized in April 2009, for the purposes of *this* document we refer to it using the nomenclature found in the *Report to the President on the U.S. Preparations for 2009-H1N1 Influenza* (PCAST, 2009).

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This novel, swine-origin, influenza A virus has now become the first pandemic of the twenty-first century. The international scientific, public health, security, and policy communities quickly mobilized to characterize the novel virus (hereinafter 2009-H1N1 influenza A) and address its potential effects. Within six months of the discovery of the 2009-H1N1 influenza A virus, researchers had gained considerable knowledge about the latest pandemic influenza virus and produced a vaccine against it, but many scientific and policy questions raised by the 2009-H1N1 influenza A virus remained to be answered.

The arrival of an influenza pandemic in 2009 was both anticipated and unexpected. That a novel, readily transmissible, influenza virus would spread widely and rapidly along with its globe-trotting hosts seemed inevitable; that this pandemic strain emerged in the Americas, rather than Asia, surprised many infectious disease experts. "We have all been preparing for a pandemic," veteran flu researcher Robert Webster of St. Jude Children's Research Hospital remarked recently (Webster, 2009). "H5N1 [Avian influenza] has been at the top of our list and surprise, surprise, 2009-H1N1 influenza A came out of left field."

In the months since the initial identification of the 2009-H1N1 influenza A virus, the disease has now spread to over 213 countries and territories while scientists, healthcare providers, policy makers, the media, and the general public attempted to anticipate, and mitigate, the myriad potential consequences of the evolving pandemic. Studies of the evolution of influenza viruses attest to their essential unpredictability, but knowledge gathered during the recent influenza season in the Southern Hemisphere can inform strategies to address the expected resurgence of 2009-H1N1 influenza A with winter's return to the Northern Hemisphere. This effort will also be advanced by the ongoing evaluations of public health capacities to address current and future challenges presented by this pandemic, its economic repercussions, and its sociopolitical effects.

In the recent past, the Institute of Medicine's (IOM's) Forum on Microbial Threats has convened several workshops focused on pandemic disease emergence, spread, and response. The first followed the emergence of severe acute respiratory syndrome (SARS) in 2003 (IOM, 2004); others considered the potential global threat posed by H5N1 influenza virus (IOM, 2004, 2005, 2007a,b) and the dynamics of infectious disease transmission in a highly interconnected world (IOM, 2010). Within months of its declaration as the first pandemic of the twenty-first century, the Forum convened a 2-day public workshop, on September 15th and 16th, 2009, to discuss the domestic and international impacts of, and responses to, the 2009-H1N1 influenza A pandemic. Through invited presentations and discussions, participants explored the origins, evolution, and epidemiology of the 2009-H1N1 influenza A virus; potential lessons learned from 2009-H1N1 influenza A infection patterns in the Southern Hemisphere; the role of disease detection, surveillance, and reporting in mapping and anticipating disease spread and evaluating the effects of mitigation measures; progress toward and prospects for vaccine and drug development and availability; considerations

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for the use of nonpharmaceutical interventions to reduce 2009-H1N1 influenza A transmission; and the global public health responses to the pandemic as it continues to unfold.

Organization of the Workshop Summary

This workshop summary was prepared by the rapporteurs for the Forum's members and includes a collection of individually authored papers and commentary. Sections of the workshop summary not specifically attributed to an individual reflect the views of the rapporteurs and not those of the Forum on Microbial Threats, its sponsors, or the IOM. The contents of the unattributed sections are based on the presentations and discussions at the workshop.

The workshop summary is organized into sections as a topic-by-topic description of the presentations and discussions that took place at the workshop. Its purpose is to present lessons from relevant experience, to delineate a range of pivotal issues and their respective problems, and to offer potential responses as discussed and described by the workshop participants. Manuscripts and reprinted articles, submitted by some but not all of the workshop's participants, may be found in Appendixes A1 through A14.

Although this workshop summary provides an account of the individual presentations, it also reflects an important aspect of the Forum's philosophy. The workshop functions as a dialogue among representatives from different sectors of the infectious disease communities and allows them to present their beliefs about which areas may merit further attention. These proceedings summarize only the statements of participants in the workshop and are not intended to be an exhaustive exploration of the subject matter or represent the findings, conclusions, or recommendations of a consensus committee process.

2009-H1N1 Influenza A in Context

This workshop took place amid broad-based, global efforts to characterize the 2009-H1N1 influenza A virus, determine its evolutionary origins, and evaluate its potential public health and socioeconomic consequences, while monitoring and mitigating the impact of a fast-moving pandemic. The presentations summarized in this report, and the original contributions by the speakers collected in Appendix A, offer a snapshot of these activities taken in the late summer of 2009, as the Northern Hemisphere's flu season approached and as the United States prepared to undertake a campaign of mass immunization against 2009-H1N1 influenza A.

What Is Influenza?

The influenza viruses are members of the family *Orthomyxoviridae* and include influenza virus types A, B, and C (see Box WO-1). Influenza is typically

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transmitted from infected mammals through the air by coughs or sneezes, creating aerosols containing the virus, and from infected birds through their droppings. Influenza can also be transmitted by saliva, nasal secretions, and feces. Infections occur through contact with these bodily fluids or with contaminated surfaces. Influenza viruses can remain infectious for about one week at human body temperature, for more than 30 days at 0°C (32°F), and indefinitely at very low temperatures (such as lakes in northeast Siberia). They can be inactivated easily by disinfectants and detergents.

Box WO-1 provides a general overview of influenza virus classification, structure, and life cycle. For a complete overview on this topic and an extensive reference list please see Treanor (2010).

The scientific and public health response to the 2009-H1N1 influenza A pandemic was both informed and influenced by observations of past pandemics and seasonal influenza epidemics, by the response to an abortive pandemic threat from H1N1 swine influenza in 1976, and from ongoing efforts to address the pandemic threat posed by the highly pathogenic H5N1 avian influenza, following its emergence in humans in 1997. In this section, we review these events in order to establish the 2009-H1N1 influenza A pandemic within a historic and scientific context.

Ten apparent influenza pandemics, five of which occurred during the nineteenth century, have been recorded over the past 300 years. The three twentieth-century pandemics—presented in Table WO-1—which began in 1918, 1957, and 1968, respectively, are known to have been caused by three different antigenic subtypes[3] of the influenza A virus, denoted H1N1, H2N2, and H3N2 in order of their emergence (Morens et al., 2009). While these pandemics varied widely in terms of their geographic origins and epidemiological characteristics, all gave warnings of their arrival, featured significant increases in mortality among younger age groups (a phenomenon known as "pandemic age shift"), and continued to cause morbidity and mortality months to years beyond their peaks (Simonsen et al., 2005) as will be discussed in greater detail, below.

1918–1919: "Mother of All Pandemics"

Beginning in the spring of 1918, the H1N1 influenza virus that infected approximately one-third of the world's population was exceptionally virulent (IOM, 2005; Taubenberger and Morens, 2006). It caused an estimated 50–100 million deaths, with a case-fatality rate of greater than 2.5 percent (compared with less

[3]Every influenza A virus has a gene coding for 1 of 16 possible hemagglutinin (HA) surface proteins and another gene coding for 1 of 9 possible neuraminidase (NA) surface proteins. HA facilitates viral attachment to host tissues; NA is involved in the release of viral progeny from the host. Of the 144 possible combinations of H and N genes, only 3 (H1N1, H2N2, and H3N2) have ever been found in truly human-adapted viruses (Morens et al., 2009).

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than 0.1 percent for other pandemic strains). As Morens et al. (2009) point out, all influenza pandemics since that time, and indeed most cases of influenza A worldwide (other than human infections from avian viruses such as H5N1 and H7N7), have been caused by descendants of the 1918 virus, as illustrated in Figure WO-2. These include the H2N2 (1957) and H3N2 (1968) viruses, which possessed key genes from the 1918 virus along with additional avian influenza genes. Hence, the 1918 H1N1 virus is truly the "mother" of all influenza pandemics.

In the spring of 1918, a "herald wave" of relatively mild influenza cases occurred in New York City. That fall, a second wave of severe disease (and in many places, a subsequent wave in early 1919) produced significantly higher rates of mortality among people between the ages of 20 and 34, and particularly among pregnant women, than is typical of seasonal influenza epidemics (Simonsen et al., 2005). Two conditions tended to occur (both individually and in combination) in these fatal H1N1 cases: bronchopneumonia, likely caused by a secondary bacterial infection, and severe acute respiratory distress, often leading to cyanosis (CIDRAP, 2009).

Despite its depiction as the "Spanish flu,"[4] the geographic origin of the 1918 H1N1 strain of the influenza virus remains a mystery (CIDRAP, 2009). It is likely that the virus, which had previously infected birds, emerged as a human pathogen in the Midwestern United States and accompanied American troops to Europe during World War I. Some investigators believe that the avian virus jumped into swine at approximately the same time it began to infect humans (Morens et al., 2009; Zimmer and Burke, 2009). Others contend, based on viral phylogeny, that genetic components of the 1918 pandemic strain circulated among swine and humans as early as 1911, which in turn suggests that the pandemic virus was generated by reassortment over a period of years and not introduced directly from birds into humans (Smith et al., 2009). Swine are believed to act as a "mixing vessel" for the reassortment of avian and human viruses (Salomon and Webster, 2009). As noted earlier, such events in doubly infected pigs generated the 1957 and 1968 pandemic influenza strains.

1957: A Model for 2009?

Between 1957 and 1958, an estimated 25 percent of the U.S. population was infected with pandemic H2N2 influenza, resulting in nearly 70,000 fatalities out of an estimated 1 million deaths worldwide (CIDRAP, 2009; Henderson et

[4]"America in 1918 was a nation at war. Draft call-ups, bond drives, troop shipments were all in high gear when the flu epidemic appeared. American soldiers from Fort Riley carried the disease to the trenches of Europe, where it mutated into a killer virus. The disease would later be dubbed, inaccurately, Spanish influenza. Spain had suffered from a devastating outbreak of influenza in May and June of 1918. The country, being a non-combatant in the war, did not censor news of the epidemic that was cutting through its population and was therefore incorrectly identified as its place of origin" (PBS, 2009).

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BOX WO-1
The Influenza Life Cycle[a]

The ***Orthomyxoviridae*** are a family of single-stranded RNA viruses that includes five genera: Influenza virus A, Influenza virus B, Influenza virus C, Isavirus, and Thogotovirus. A sixth has recently been described (Presti et al., 2009). The first genus contains viruses that cause influenza in vertebrates, including birds, humans, and other mammals. Influenza B and C viruses circulate in humans. Isaviruses infect salmon; thogotoviruses infect both vertebrates and invertebrates such as ticks (Ely, 1999; Jones and Nuttall, 1989; Raynard et al., 2001).

Viral Replication

Viruses can only replicate in living cells. Influenza infection and replication is a multistep process: the virus must first bind to and enter the cell, then deliver its genome to a site where it can produce new copies of viral proteins and RNA, assemble these components into new viral particles, and finally exit the host cell.

Influenza viruses infect epithelial cells of the respiratory tract by attaching to sialic acid receptors. The virus particle contains a genome consisting of eight single stranded, negative sense RNA genes surrounded by viral proteins and a host-derived lipid membrane. The surface of the virus particle contains spikes of hemagglutinin (HA) that are responsible for attachment of virions to the cell surface. The HA binds to sialic acid receptors located at the tip of glycan chains conjugated to host cell membrane proteins and lipids (stage 1 in Figure WO-1)—typically in the nose, throat, and lungs of mammals and in the intestines of birds. Multivalent binding of the virus particle to the cell triggers uptake by endocytosis and subsequent fusion of the viral envelope to the endosome membrane, delivering the genome into the host cell cytoplasm.

Once inside the cell, the acidic conditions in the endosome cause two events to happen: first part of the HA protein fuses the viral envelope with the vacuole's membrane, then the M2 ion channel allows protons to move through the viral envelope and acidify the core of the virus, which causes the core to disassemble and release the viral RNA and core proteins. The viral RNA (vRNA) molecules, accessory proteins, and RNA-dependent RNA polymerase are then released into the cytoplasm (stage 2). The M2 ion channel is blocked by amantadine drugs, preventing infection.

These core proteins and vRNA form a complex that is transported into the cell nucleus, where the RNA-dependent RNA polymerase begins transcribing complementary positive-sense vRNA (stages 3a and 3b). The vRNA is either exported into the cytoplasm and translated (stage 4) or remains in the nucleus. Newly synthesised viral proteins are either secreted through the Golgi apparatus onto the cell surface (in the case of neuraminidase and hemagglutinin, stage 5b) or transported back into the nucleus to bind vRNA and form new viral genome particles (stage 5a). Other viral proteins have multiple actions in the host cell,

[a]For a complete overview on this topic and an extensive reference list please see Treanor (2010) and Wikipedia (2009).

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including degrading cellular mRNA and using the released nucleotides for vRNA synthesis and also inhibiting translation of host cell mRNAs.

Negative-sense vRNAs that form the genomes of future viruses, RNA-dependent RNA polymerase, and other viral proteins are assembled into a virion. HA and neuraminidase molecules cluster into a bulge in the cell membrane. The vRNA and viral core proteins leave the nucleus and enter this membrane protrusion (stage 6). The mature virus buds off from the cell in a sphere of host phospholipid membrane, acquiring HA and neuraminidase with this membrane coat (stage 7). As before, the viruses adhere to the cell through hemagglutinin; the mature viruses detach once their neuraminidase has cleaved sialic acid residues from the host cell. Drugs that inhibit neuraminidase, such as oseltamivir, therefore prevent the release of new infectious viruses and halt viral replication. After the release of new influenza viruses, the host cell dies (Figure WO-1).

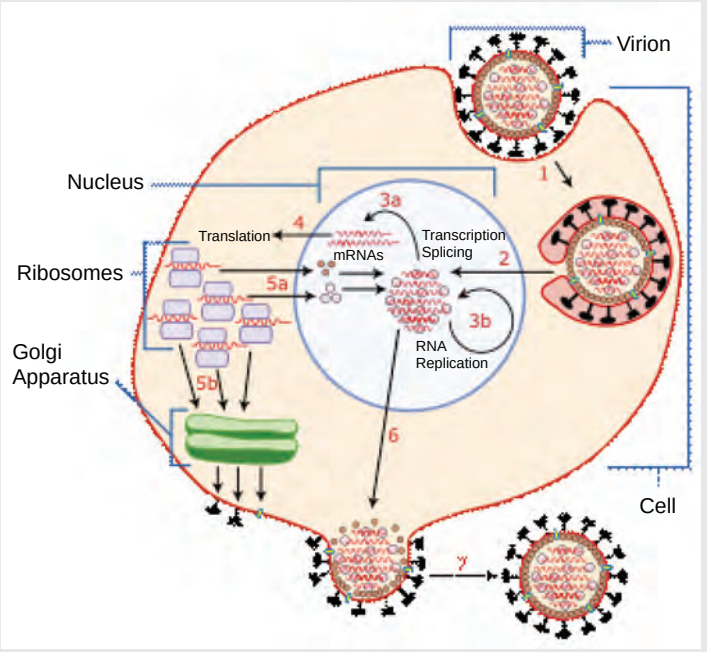

FIGURE WO-1 Host cell invasion and replication by the influenza virus. The steps in this process are discussed in the text.
SOURCE: Wikipedia (2007 [figure], 2009 [text]).

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TABLE WO-1 Mortality Associated with Influenza Pandemics and Selected Seasonal Epidemic Events, 1918-2009[a]

Years	Circulating Virus (genetic mechanism)	Excess Deaths from Any Cause (no. per 100,000 persons/yr)
1918-1919	**H1N1 (viral introduction), pandemic**	**598.0**
1928-1929	H1N1 (drift)	96.7
1934-1936	H1N1 (drift)	52.0
1947-1948	H1N1 A (intrasubtypic reassortment)	8.9
1951-1953	H1N1 (intrasubtypic reassortment)	34.1
1957-1958	**H2N2 (antigenic shift), pandemic**	**40.6**
1968-1969	**H3N2 (antigenic shift), pandemic**	**16.9**
1972-1973	H3N2 A Port Chalmers (drift)	11.8
1975-1976	H3N2 (drift) and H1N1 ("swine flu" outbreak)	12.4
1977-1978	H3N2 (drift) and H1N1 (viral return)	21.0
1997-1999	H3N2 A Sydney (intrasubtypic reassortment) and H1N1 (drift)	49.5
2003-2004	H3N2 A Fujian (intrasubtypic reassortment) and H1N1 (drift)	17.1
2009	H3N2 and H1N1 (drift) and swine-origin H1N1 (viral introduction), pandemic	?

[a]Mortality data include deaths associated with all influenza A and B viruses combined. Many of these data have been calculated with the use of differing methods and may not be strictly comparable (Noble, 1982; Thompson et al., 2003). The 1934, 1951, and 1997 data span 2 years.
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al., 2009). Once again, influenza morbidity and mortality were skewed toward younger people (ages 5 to 35) compared with nonpandemic years. The first U.S. cases of what became known as the "Asian flu," reported in June 1957, followed outbreaks on military bases in Korea and Japan in April and May of that year (Henderson et al., 2009). Throughout the summer of 1957, outbreaks of mild illness occurred throughout the United States in conference centers, summer camps, migrant workers' barracks, and other such institutional settings. Although these local outbreaks were characterized by attack rates that in some cases exceeded 50 percent, little community-wide transmission appeared until schools reopened in the Fall.

Beginning in mid-September, an epidemic wave of influenza swept U.S. communities (Henderson et al., 2009). Vaccine (which was no more than 60 percent effective against the virus) became available in limited supply in October, but

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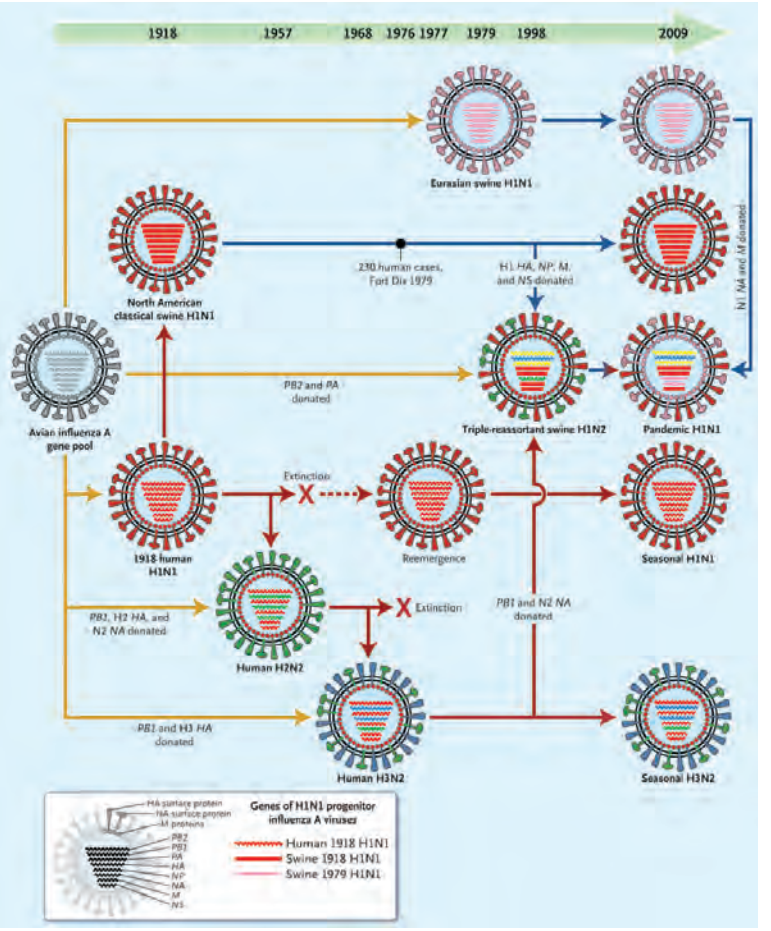

FIGURE WO-2 Genetic relationships among human and relevant swine influenza viruses, 1918–2009. Yellow arrows reflect exportation of one or more genes from the avian influenza A virus gene pool. The dashed red arrow indicates a period without circulation. Solid red arrows indicate the evolutionary paths of human influenza virus lineages; solid blue arrows, of swine influenza virus lineages; and the blue-to-red arrow, of a swine-origin human influenza virus. All influenza A viruses contain eight genes that encode the following proteins (shown from top to bottom within each virus): polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin (HA), nuclear protein (NP), neuraminidase (NA), matrix proteins (M), and nonstructural proteins (NS). The genes of the 1918 human and swine H1N1 and the 1979 H1N1 influenza A viruses were all recently descended from avian influenza A genes, and some have been "donated" to the pandemic human H1N1 strain.

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it was too little, too late to slow the progression of the epidemic across the United States. By mid-November, numbers of new cases and deaths from influenza and pneumonia had leveled off and begun to decline. Following a return to normal levels in December, a second wave of excess mortality due to respiratory illness began in January 1958 and peaked the following month.

Henderson et al. (2009) note several similarities in epidemiologic behavior between the 1957 H2N2 pandemic and the 2009 H1N1 pandemic: both arose early in the year and spread widely during the spring, both abated over the early summer months in the Northern Hemisphere while major epidemics developed in the Southern Hemisphere (as is also typical of seasonal influenza), and both (to date) were marked by relatively mild illness with low case-fatality rates.

1968 (United States) and 1969 (Europe)

Pandemic H3N2 emerged in Hong Kong in 1968 and spread rapidly across the globe. During the winter of 1968-1969, the virus caused an estimated 40,000 deaths in the United States, but in Europe, it inexplicably smoldered until the following winter before causing significant morbidity and mortality (Simonsen et al., 2005). That this pandemic was the least deadly of the three twentieth-century pandemics may be due to the fact that only the H antigen in H3N2 had "shifted" with respect to the previous pandemic H2N2 strain. In people born before 1891, the presence of H3 antibodies may have also afforded this otherwise vulnerable population some degree of protective immunity against the H3N2 influenza A virus. In the United States, people between the ages of 45 to 64 were shown to have a threefold higher risk of death from pandemic H3N2 than from epidemic influenza during the years prior to and following the pandemic (Simonsen et al., 2005).

1976 Swine Flu: The Pandemic that Wasn't

Early in 1976, an outbreak of swine-origin influenza among military personnel at Fort Dix, New Jersey, resulted in 13 confirmed cases, including one death (CIDRAP, 2009). Serologic studies suggested that more than 200 soldiers had been infected with an H1N1 virus and that person-to-person transmission had occurred (Sencer and Millar, 2006). The outbreak, however, never spread beyond Fort Dix. Its origin remains unknown (CIDRAP, 2009). The major events in the swine flu vaccination campaign, adapted from Neustadt and Feinberg (1978), are presented in Box WO-2.

Similarities between the 1976 H1N1 virus and the 1918 H1N1 pandemic strain prompted concern that a similarly devastating pandemic was imminent, recalled keynote speaker David Sencer, who in 1976 was the director of the Centers for Disease Control (CDC). He reviewed the process by which the decision was made to start a mass vaccination program to protect the American public from

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BOX WO-2
The 1976 Swine Flu Campaign: Chronology of Major Events

1976

- Mid-January: Large number of cases of respiratory disease are reported among Army recruits at Fort Dix, New Jersey; Walter Reed Army Laboratory identifies adenovirus as cause of earlier outbreak of respiratory disease at Fort Meade, Maryland.
- February 13: Scientists at CDC confirm that the isolates are indeed swine-type influenza A viruses; at Sencer's request, Dr. Walter Dowdle, head of CDC's labs, notifies scientists and health officials across the country of the A swine discovery, and invites them to a meeting at CDC the next day.
- March 24: President goes before television cameras to announce that he is recommending a mass vaccination program for all Americans and urges that Congress immediately pass a special $135 million appropriation.
- October 1: First swine flu shots given.
- November 12: Case of Guillain-Barré Syndrome in Minnesota vaccinee.
- December 16: Sencer conducts morning conference call, his third in four days, with 20 experts from NIAID, BoB [Bureau of Biologics] and the states, conferees agree on recommendation of a one month suspension to allow for investigation of link; Sencer calls Cooper with the recommendation; Cooper confers with Mathews and Cavanaugh; telephones Salk; President okays suspension.

1977

- January 14: ACIP meets in Atlanta and concludes that the moratorium on all influenza vaccine ought to be lifted; observes that flu shots do appear to entail some slight additional risk of contracting Guillain-Barré (estimated at one case for every 100,000 to 200,000 vaccinations); recommends that main focus of resumed program should be on high risk group.

SOURCE: Adapted with permission from Neustadt and Fineberg (1978).

this apparent threat, and then—amid political wrangling and media scrutiny—to suspend that program less than three months later in order to investigate a possible serious side-effect of the vaccine (see Sencer and Millar in Appendix A11). Sencer said that the intention of his remarks was to highlight "what went right" in this series of events that is often referred to as a "fiasco" or "debacle" (Neustadt and Fineberg, 1978).

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Within days of the identification of the 1918-like H1N1 virus from Fort Dix, representatives from the military, the National Institutes of Health, the Food and Drug Administration (FDA), and the New Jersey Department of Health met to determine a plan of action, which included heightened disease surveillance in and around Fort Dix, determining whether infected individuals had prior contact with pigs (which turned out to be negative), and serologic testing of recruits to determine viral spread at Fort Dix (Sencer and Millar, 2006). While the virus had spread from person to person among more than 200 military recruits on the base, no additional cases of swine flu were ever detected in the community surrounding Fort Dix. These findings were reviewed by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Public Health Service, which concluded that the new virus had pandemic potential and that an immunization program should be launched in order to reduce the morbidity and mortality associated with a possible influenza pandemic.

After considering several alternative responses to these recommendations, Sencer, in his capacity as director of the CDC, proposed that private pharmaceutical companies under contract to the federal government should produce enough vaccine to immunize the entire U.S. population against H1N1, and that immunization should proceed as quickly as possible through federally funded programs organized and conducted by state health departments (Sencer and Millar, 2006). Federal legislation[5] to this effect was quickly passed and vaccine production and testing began. Progress toward mass immunization was temporarily stalled when the vaccine manufacturers demanded indemnification against claims of any adverse reactions associated with the vaccines. After the federal government acceded to this demand, more than sufficient vaccine was produced to immunize more than 40 million people within 10 weeks, beginning on October 1, 1976.

After cases of Guillain-Barré Syndrome (GBS)—an extremely rare disorder in which the body's immune system attacks part of the peripheral nervous system—were diagnosed in some recipients shortly after vaccination with the swine flu vaccine, anxiety arose about whether the vaccine was causally associated with this rare disorder. On December 16, federal officials suspended all immunizations in order to investigate this possibility. This action essentially ended the swine flu immunization program. According to Sencer, despite the controversy it engendered, this program achieved success in several areas, most notably surveillance for disease transmission and adverse events associated with the vaccine, as well as the rapid and effective implementation of mass immunization on an unprecedented scale.

[5]National Influenza Program (P.L. 94-380): An act to amend the Public Health Service Act to authorize the establishment and implementation of an emergency national swine flu immunization program and to provide an exclusive remedy for personal injury or death arising out of the manufacture, distribution, or administration of the swine flu vaccine under such program. For more information, see http://thomas.loc.gov/cgi-bin/bdquery/z?d094:SN03735:@@@L&summ2=m& (accessed November 5, 2009).

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Events surrounding the 1976 outbreak offer lessons to policy makers as they address the current "swine flu" pandemic, Sencer observed. First and foremost, he advised, one must "expect the unexpected" (the failure of a pandemic to arise despite transmission of a virus with pandemic potential, or the appearance of "excess" cases of a rare disorder associated with immunization, for example) and prepare in advance to cope with surprises. Second, he noted that effective communication of health policies by medical experts prevents the appearance that these policies are driven by politics rather than science. Finally, he said, "when lives are at stake, it is better to err on the side of overreaction than underreaction. Because of the unpredictability of influenza, responsible public health leaders must be willing to take risks on behalf of the public. This requires personal courage and a reasonable amount of understanding by the politicians to whom these public health leaders are accountable."

All policy decisions entail risks and benefits to decision makers, as well as to those directly affected by the decision, Sencer added. "In 1976, the federal government wisely opted to put protection of the public first," he concluded, "just as the current [a]dministration is doing and doing exceedingly well."[6]

H5N1: A Persistent Pandemic Threat

Sometime prior to 1997, the H5N1 strain of avian influenza (bird flu) virus began circulating in poultry in parts of Asia (Pandemic Plan, 2005). In the first documented instance of human infection, the virus caused 18 cases and 6 deaths in Hong Kong in 1997. The outbreak in humans coincided with outbreaks of highly pathogenic H5N1 in poultry on farms and in live markets (Pandemic Plan, 2005). Because of the potential for further poultry-to-human spread of H5N1 viruses in the poultry markets, the Hong Kong government enlisted government employees from several agencies to assist in the Hong Kong-wide slaughter of chickens and other fowl. This 4-day effort, beginning on December 29, resulted in the slaughter of 1.5 million chickens and several hundred thousand other domestic fowl (Bridges et al., 2002). Many experts believe that the destruction of the Hong Kong Special Administrative Region's entire poultry population of 1.5 million birds averted a pandemic by immediately removing opportunities for further human exposure (WHO, 2005b). Following the poultry eradication campaign in Hong Kong, the H5N1 influenza virus did not reappear until the end of 2003 (WHO, 2005b).

In early 2004, millions of birds died as the highly pathogenic H5N1 avian influenza (HPAI) spread rapidly across Asia (Pandemic Plan, 2005; WHO, 2005b). Massive culling of birds occurred in Thailand and Vietnam following the deaths of 23 of 34 patients, respectively, with confirmed H5N1 infections (Pandemic Plan, 2005; WHO, 2005b).

[6]For a more in-depth, dispassionate, analysis of the U.S. government's response to the 1976 swine flu "epidemic" see Neustadt and Feinberg's (1978) *The Swine Flu Affair*.

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> Near the end of January, the situation in poultry exploded. Outbreaks in the Republic of Korea, Vietnam, Japan, and Thailand were followed by reports in Cambodia, Lao People's Democratic Republic, Indonesia, and China.
>
> The H5N1 outbreaks in poultry were historically unprecedented. Previously, Highly Pathogenic Avian Influenza (HPAI) was considered a rare disease. Never before had HPAI spread so widely and rapidly to cause outbreaks in so many countries at once. Within three months, more than 120 million birds died or were destroyed. (Pandemic Plan, 2005)

Responding to the threat presented by this newly emerged and highly pathogenic virus, public health agencies at all levels began preparations for a pandemic that has yet to materialize (IOM, 2005, 2007a,b). Although human-to-human transmission of H5N1 has apparently occurred in a few cases, the vast majority of human infections have come from contact with infected poultry.[7]

The current H5N1 virus tends to bind deep inside mammalian lung tissues, as compared with seasonal influenza viruses, which attach to nasal and pharyngeal tissues, and from which they are more easily spread by coughs and sneezes (Shinya et al., 2006; van Riel et al., 2006). However, with time—particularly given the establishment of the virus in Asia—H5N1 may evolve more efficient transmission among humans and other mammalian hosts, or it may reassort with highly transmissible influenza A viruses, such as the current H1N1 pandemic strain.

2009-H1N1 Influenza A: A Predictable Surprise

Preparations for the emergence of a human pandemic strain of H5N1 influenza led to the detection of the first U.S. cases of 2009-H1N1 influenza A, according to Nancy Cox of the CDC. One of two initial U.S. cases of 2009-H1N1 influenza A, which occurred in children in southern California, was discovered in a trial of an investigational diagnostic tool that had been developed to detect the H5N1 influenza A virus; the other human case was identified from a sample collected as part of an influenza surveillance project (CDC, 2009e). "We were really focusing on the emergence of H5N1," Cox explained, "so the device was calibrated to detect influenza A-positive samples and to determine if they were H3, H1, or H5. This particular sample from the first case was negative for H3, H1, and H5 but positive for influenza A, so the San Diego public health officials were notified," she explained.

The first specimen was sent to a reference laboratory in the state health department of Wisconsin, where researchers were unable to determine the viral subtype using the latest polymerase chain reaction (PCR)-based influenza assay

[7] A wide range of domestic and wild avian species can be infected with influenza viruses, and wild and domestic animals mix, in some settings. Migratory avian species can also be infected.

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developed by the CDC. Based on preliminary genetic characterization, CDC scientists identified the strain as a novel H1N1 swine triple-reassortant virus (CDC, 2009e). However, Cox continued, the PCR results and the lack of apparent contact between the patient and pigs led the CDC investigators to suspect that this virus was "something different," so they quickly sequenced the complete viral genome and reported their findings to the WHO. Soon thereafter, the CDC learned of the second patient and confirmed the involvement of the novel H1N1 virus strain in this case as well.

At the same time—mid-April 2009—a similar series of events, as described by speaker Guillermo Ruiz-Palacios of the National Institute of Medical Sciences and Nutrition in Mexico City, occurred in Mexico (see also CDC, 2009f). The first two cases of 2009-H1N1 influenza A to be discovered in Mexico were, at first, thought to be SARS, he said. When investigators in Mexico City failed to identify the SARS coronavirus or any other pathogen capable of inducing severe respiratory distress, samples were sent simultaneously to the CDC in Atlanta and to Health Canada in Winnipeg for further testing. The Canadian laboratory received and tested the samples first, and determined that a swine influenza virus was the cause of illness in the Mexican index cases. On April 23, the Mexican, Canadian, and American investigators all realized that they were characterizing the same H1N1 influenza A virus. The number of 2009-H1N1 influenza A cases mounted in Mexico and the United States as the virus quickly spread globally. On June 11, 2009, the WHO raised the worldwide pandemic alert level to Phase 6 in response to the sustained global proliferation of the novel influenza A (H1N1) virus.

In a world poised to prevent a devastating H5N1 avian influenza pandemic originating out of Asia, the appearance of an influenza pandemic in the form of a relatively mild (to date) swine-origin virus originating (apparently) in the Americas was a surprise. The rapid spread of the 2009-H1N1 influenza A virus has only underscored the reality that international travel and commerce has provided an efficient link to the rest of the world for the spread of emerging infectious diseases—a reality confirmed in a recently published communication in the *New England Journal of Medicine* (Khan et al., 2009). Today, international travel and commerce (most notably the explosive growth of commercial air transportation over the past 50 years) drives the rapid, global distribution of microbial pathogens and the organisms that harbor them (Gubler, 1998; IOM, 2003). International air-traffic patterns,[8] as illustrated in Figure WO-3, provided a sensitive predictor of H1N1 importation and yet another example of the ability of contemporary travelers to move between most places in the world in less time than the incubation period for many infectious diseases (Wilson, 2003).

The 2009-H1N1 influenza A pandemic also underscores the role of the animal–human interface as a factor in infectious disease emergence, spread, and

[8]The "patterns" of international air traffic include travel and trade routes as well as the volume of travel and travelers between nodes in the air traffic system.

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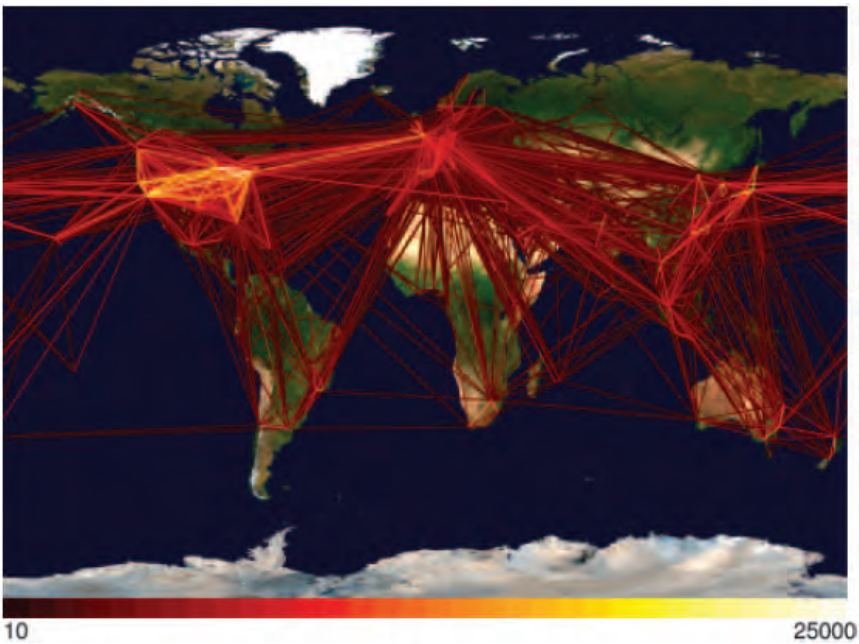

FIGURE WO-3 The rate of globalization has accelerated to the point where we are connected as never before via globalized travel and trade networks.
SOURCE: Reprinted with permission from Hufnagel et al. (2004).

establishment (IOM, 2003, 2010). This too was anticipated. Having documented a rapid increase in the phylogenetic and antigenic diversity of circulating swine influenza strains in the United States, Webby and coauthors (2004) presciently warned that "the growing complexity of influenza at this animal–human interface and the presence of viruses with a seemingly high affinity for reassortment makes the United States swine population an increasingly important reservoir of viruses with human pandemic potential" (Webby et al., 2004).

Their concern was shared by the CDC, according to Cox, who noted that participants in a CDC-sponsored meeting of the Council of State and Territorial Epidemiologists on influenza at the animal–human interface held in early April 2009—before all but a very few epidemiologists were aware of 2009-H1N1 influenza A—had identified a series of goals to address what was to them a theoretical risk. These goals included:

- the speedier identification of novel influenza A virus (IAV) infections in humans;
- assessment of risk for the potential for human-to-human transmission of novel IAVs;

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- identifying risk groups for severe disease;
- the development and global distribution of diagnostic reagents capable of identifying novel IAV infections; and
- the development of vaccine strain candidates of novel IAVs with pandemic potential.

"Little did we know that later on in that very month we would be exercising all of these goals very actively," Cox recalled.

As Cox and several other participants in the September workshop observed, had the global public and animal health communities recognized the diversity of influenza viruses present in the world's swine populations as a zoonotic threat worthy of surveillance, the emergence of 2009-H1N1 influenza A may have been anticipated and recognized at an even earlier stage of the disease's emergence out of Mexico (see also discussion in a subsequent section, "The Scientific Response"). However, as speaker Kennedy Shortridge of the University of Hong Kong observed, the global response to the new virus has been swift. "It's something that wouldn't have been possible 15 years ago," he added, "so we've come a long way."

Many speakers and discussants also noted that this relatively mild pandemic, identified prior to its global spread by researchers poised to respond to the potential threat from the highly pathogenic H5N1 avian influenza virus, presents significant opportunities to improve influenza surveillance and monitoring, refine epidemiologic models, and enhance pandemic preparations in anticipation of the next "killer flu."

Situation Assessment and Future Challenges

In late June 2009, President Obama requested that his Council of Advisors on Science and Technology (PCAST) undertake an evaluation of the 2009-H1N1 influenza A pandemic and the nation's response to a probable recurrence in the fall of 2009. Their report, issued in early August, examines and critiques the emerging federal response to a second wave and suggests additional opportunities for mitigation (PCAST, 2009). A similar process occurred at this workshop, as participants assessed the 2009-H1N1 influenza A pandemic to date and anticipated an H1N1 influenza A resurgence in the Northern Hemisphere during the Fall influenza season.

In his keynote address to the workshop, Keiji Fukuda of the World Health Organization (WHO) noted several successes of the global response to the 2009-H1N1 influenza A pandemic, including:

- early detection and reporting of the novel virus;
- early and ongoing scientific investigations;
- functional global communications among countries and organizations;

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- wide sharing of viruses, genetic sequences, and related information;
- provision of assistance and guidance;
- on-time development and production of a pandemic vaccine;
- increased access to antiviral drugs; and
- modest enactment of trade and travel restrictions.

According to Fukuda, however, the 2009-H1N1 influenza A pandemic also highlighted and underscored the "tremendous disparities worldwide in terms of understanding, capacities, resources, and socioeconomic impact."

Among the many ongoing challenges associated with 2009-H1N1 influenza A, Fukuda identified two as particularly daunting: the need for clear messages in an increasingly complex and fast-changing communications environment, and the need to provide equitable access to resources to address this and other emerging pandemics. Nevertheless, it appears that the world has been spared for the moment from the "worst-case scenario" in as much as the morbidity and mortality associated with infection by the 2009-H1N1 influenza A virus to date has been mild to moderate for most people, and the pandemic arose in a highly developed region of the world where sophisticated systems were already in place and viruses, information, and assistance were freely shared. "We [were] extremely lucky in a number of respects," he concluded. "I don't think this is the kind of situation that we can count on in the future." Moreover, he went on to say that counting on such aspects of the current scenario as the basis for future planning would be a strategic mistake.

Characterizing the Virus

Cox reported that the CDC quickly generated an unprecedented amount of gene sequence data for the 2009-H1N1 influenza A virus—over 1,700 genes from more than 430 virus isolates obtained from 360 cases—in addition to multiple isolates from some cases of special interest. At the time of the workshop 70 entire viral genomes had been sequenced, she said, and many more gene sequences and total viral genomes have been contributed by laboratories globally. "I think we can really thank all of the public health labs and all of the hospitals and all of those who worked together so seamlessly to put this information into the public domain," she said.

These sequences, and subsequent initial experiments toward vaccine development, revealed a number of key characteristics of the 2009-H1N1 influenza A virus, summarized by Cox below:

- Its combination of gene segments had not been reported previously.
- It is a product of reassortment between European swine and North American swine lineage triple reassortant influenza A viruses, which likely occurred through a process of two or more steps.
- No genetic markers for severe disease were detected.

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- The collection of viral sequences was genetically and antigenically homogeneous, suggesting a single source introduction in humans; this simplified selection of a representative vaccine virus.
- Passage in eggs at limit dilution[9] and growth in tissue culture can select for viruses with altered antigenic properties.
- Unlike seasonal H1N1 viruses, 2009-H1N1 influenza A viruses grow to high titer without adaptation in the lungs of mice, ferrets, and macaques.
- It retains alpha-2,3 receptor binding properties that may allow it to replicate better in the human upper respiratory tract.
- It is resistant to amantadine and rimantadine; sporadic cases of resistance to oseltamivir have also been detected globally, mostly in association with pre-exposure prophylaxis.

Origins of the 2009-H1N1 Influenza A Genome

Viral isolates from index cases of 2009-H1N1 influenza A were characterized as "swine-origin" influenza on the basis of genomic analysis, which revealed their similarity to previously characterized swine influenza viruses (CDC, 2009e). In his workshop presentation speaker Michael Worobey of the University of Arizona described the further use of genomics to trace the evolution of the 2009-H1N1 influenza A virus and estimate the time of its emergence in humans (Smith et al., 2009). Taking advantage of steady rates of molecular evolution—that is, mutation rates revealed by sequence comparisons—typical of viruses in general and influenza viruses in particular, Worobey and coworkers compared the sequences of multiple 2009-H1N1 influenza A viral isolates, obtained between March and May 2009, with each other and with those of swine influenza viruses, using a technique called Bayesian molecular clock analysis. This enabled them to reconstruct the series of reassortment events that produced 2009-H1N1 influenza A, as illustrated in Figure WO-4.

When applied separately to each of the eight genes[10] that comprise the influenza A virus genome, this analysis revealed a combination of segments derived from two swine influenza lineages: the classical "triple-reassortant" H1N1 virus that has long circulated in Eurasia and North America, and a more recent "avian-like" Eurasian version of H1N1 virus that jumped from birds to pigs prior to 1979. Additional "molecular clock" calculations suggest that the progenitor of the 2009-H1N1 influenza A virus has been circulating in pigs for a decade or so and that the virus began to infect humans near the end of 2008, Worobey stated. Another speaker, Eddie Holmes of Pennsylvania State University, estimated that

[9]A method of obtaining a pure culture of bacteria or viruses by subculturing from the highest dilution in which the organism is demonstrably present (http://medical-dictionary.thefreedictionary.com/limit+dilution, accessed November 5, 2009).

[10]All influenza A viruses contain eight genes that encode for the following proteins: polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin (HA), nuclear protein (NP), neuraminidase (NA), matrix proteins (M), and nonstructural proteins (NS) (Morens et al., 2009).

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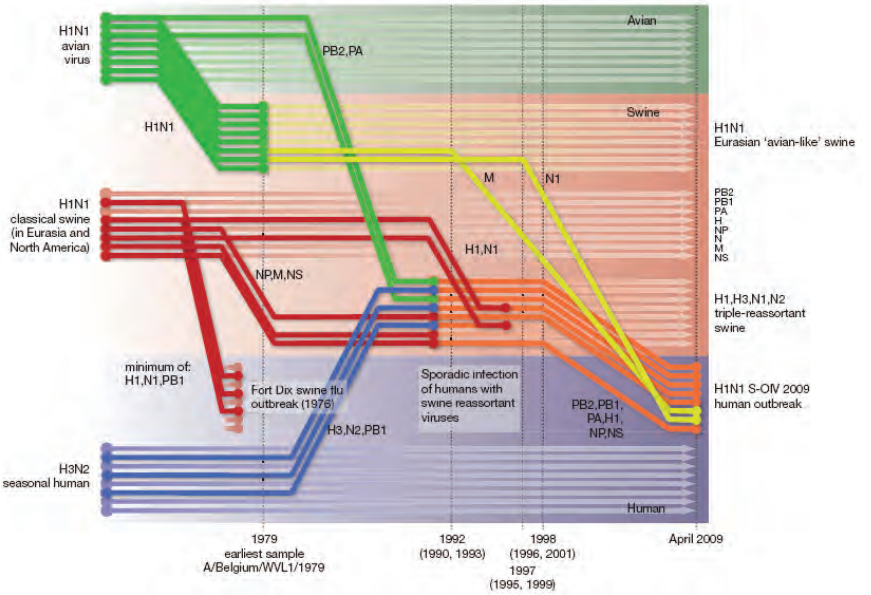

FIGURE WO-4 Reconstruction of the sequence of reassortment events leading up to the emergence of S-OIV. Shaded boxes represent host species; avian (green), swine (red), and human (grey). Colored lines represent interspecies-transmission pathways of influenza genes. The eight genomic segments are represented as parallel lines in descending order of size. Dates marked with dashed vertical lines on "elbows" indicate the mean time of divergence of the S-OIV genes from corresponding virus lineages. Reassortment events not involved with the emergence of human disease are omitted. Fort Dix refers to the last major outbreak of S-OIV in humans. The first triple-reassortant swine viruses were detected in 1998, but to improve clarity the origin of this lineage is placed earlier.
SOURCE: Reprinted from Smith et al. (2009) with permission from Nature Publishing Group.

2009-H1N1 influenza A emerged between late December 2008 and February 2009 based on genetic diversity in viral isolates collected worldwide between April and June 2009. Worobey noted that, upon making the transition to infecting humans, the viral "molecular clock" appeared to run significantly faster—though consistently so—than it had done in swine. This apparent acceleration in evolution rate in the new host could be driven by adaptation or permitted by relaxed selection for amino acid changes, Worobey said, adding that it might also be a transient condition or an artifact of the short period over which they had sampled for 2009-H1N1 influenza A viral evolution.

Worobey characterized the decade-long gap between the emergence of the precursor of the 2009-H1N1 influenza A virus in pigs and its subsequent jump

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to humans as a period of "unsampled diversity" in swine influenza viruses. Cox agreed and added that "the precise nature of the evolution and origin of the 2009 H1N1 viruses are unlikely to be well defined due to lack of influenza surveillance in swine and other susceptible mammalian hosts."

Ongoing Evolution of 2009-H1N1 Influenza A

Having considered the evolutionary origins of the 2009-H1N1 influenza A virus, discussion turned to this virus's evolutionary present and future. Presenter Eddie Holmes of Pennsylvania State University established a context for this topic by describing current knowledge on the evolution of seasonal influenza A viruses. Although most such research has focused on changes in the hemagglutinin (HA) protein, crucial both for its function and as the main component in seasonal influenza vaccine (Smith et al., 2004), attention has more recently turned to mutations occurring throughout the viral genome. Holmes and coworkers investigated the diversity of influenza A viral lineages within a restricted sampling area—New York State—between 1997 and 2005 (Nelson et al., 2007, 2008). There they found evidence that multiple flu strains were being introduced into the region each season, imported from a distant "mixing pot" of influenza viral strains. Research by others suggests that this global influenza reservoir is located in East and Southeast Asia (Russell et al., 2008).

As a result of this dynamic, each person carries millions of variant influenza viruses, and many are infected with completely different viral strains and even different influenza types (A and B), Holmes continued. Viral reassortments occur easily under these conditions. "Many people have discussed reassortment in terms of the various pandemic strains [and how they cross] species boundaries," he said. "We saw that reassortment happens frequently within a particular subtype . . . there's been lots of reassortment in the history of seasonal H1N1 viruses."

Regarding the short evolutionary history of the 2009-H1N1 influenza A virus, which he and coworkers have gleaned from their analysis of 409 complete genome sequences from human isolates obtained worldwide between April and July 2009, Holmes made three general observations about the global pool of 2009-H1N1 influenza A viruses:

- they currently have limited sequence diversity;
- their populations consist of multiple lineages; and
- local epidemics are characterized by founder effects.[11]

[11]Changes in gene frequencies that usually accompany starting a new population from a small number of individuals. The newly founded population is likely to have quite different gene frequencies than the source population because of sampling error (i.e., genetic drift). The newly founded population is also likely to have a less genetic variation than the source population (University of California Museum of Paleontology, 2009).

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Although these investigators did not find evidence of reassortment events involving the 2009-H1N1 influenza A virus, Holmes speculated that they were likely to have occurred, but could not be detected, due to the large degree of sequence similarity among these isolates. Few of the mutational changes that have occurred to date within the 2009-H1N1 influenza A viral genome are likely to affect viral function. Rather, he said, they were probably finding transient deleterious mutations, "most of which will be defective and won't get anywhere." Holmes observed that "it's very early days in this evolutionary process. We're five, six months into this epidemic. We can see some diversity. The real interesting evolutionary things will happen when [2009-H1N1 influenza A] starts to compete in the Northern and Southern hemispheres with the seasonal strains that co-circulate."

When asked how more representative collections of influenza strains might be obtained, Holmes recommended two complementary approaches. One is to choose a few locations and study them in detail, as he has done with the counties around New York City. The other is to obtain sequences from as many sites as possible, as has been attempted in comparisons of the HA antigens.

Pathology and Pathogenesis

While most human infections with 2009-H1N1 influenza A to date apparently have been mild, a significant number of cases have required hospitalization, and at least 16,713 deaths due to 2009-H1N1 influenza A had been reported to the WHO as of March 12, 2010 (WHO, 2010a). Investigations of fatal cases in the United States, described by speaker Sherif Zaki of the CDC, have provided valuable insights into the pathogenicity of 2009-H1N1 influenza A.

Of 137 fatal cases of suspected 2009-H1N1 influenza A occurring between April 29 and August 20, 2009, 77 were confirmed (about half by autopsy) by the CDC to have been caused by 2009-H1N1 influenza A, Zaki said. Other diagnoses in some of the suspect cases included leptospirosis, spotted-fever rickettsiosis, other bacterial infections, and sepsis. The median age of the 2009-H1N1 influenza A fatalities was 38 years (range 2 months to 84 years); the average duration of illness was 8 days (range 1 to 39 days). Underlying conditions—including extreme morbid obesity, hypertension, cardiovascular disease, pregnancy, and asthma—were associated with 90 percent of these patients.

Primary viral pneumonia is considered to be a major contributor—and in some cases the sole cause—of the many 2009-H1N1 influenza A deaths. However, Zaki noted, bacterial co-infections were present in about 30 percent of the fatal cases, most commonly involving *Streptococcus pneumonia*e which, he stressed, is in many cases a vaccine-preventable infection (Louie et al., 2009b). Pulmonary embolism was detected in about 15 percent of fatalities. While the significance of this finding is not clear, and may be related to acute respiratory distress syndrome (ARDS) or other co-morbid conditions, Zaki said he expects

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this percentage to rise now that pathologists are looking specifically for this condition in suspected 2009-H1N1 influenza A cases.

Zaki reported that histopathological studies of respiratory tissues from autopsied patients revealed several features not typically seen in fatal cases of seasonal influenza. Viral load, as visualized with antigen-based immunohistochemistry, was strikingly high in fatal cases of 2009-H1N1 influenza A compared with seasonal influenza. In addition, 2009-H1N1 influenza A viruses were present in peripheral lung tissues as seen in H5N1 avian influenza but not typically with seasonal influenza viruses, which target the upper respiratory tract. Lung tissues infected with 2009-H1N1 influenza A showed evidence of diffuse alveolar damage, the physical manifestation of ARDS (Figure WO-5)—an acute lung injury with a 40 percent case fatality rate. "This looks like avian flu on steroids," remarked Zaki, who added that recent studies suggest that 2009-H1N1 influenza A and H5N1 viruses bind to the same receptors in peripheral lung tissues (Childs et al., 2009; Soundararajan et al., 2009).

Similarly striking differences in pathogenesis between 2009-H1N1 influenza A and seasonal influenza have been observed in cellular and animal studies (Itoh

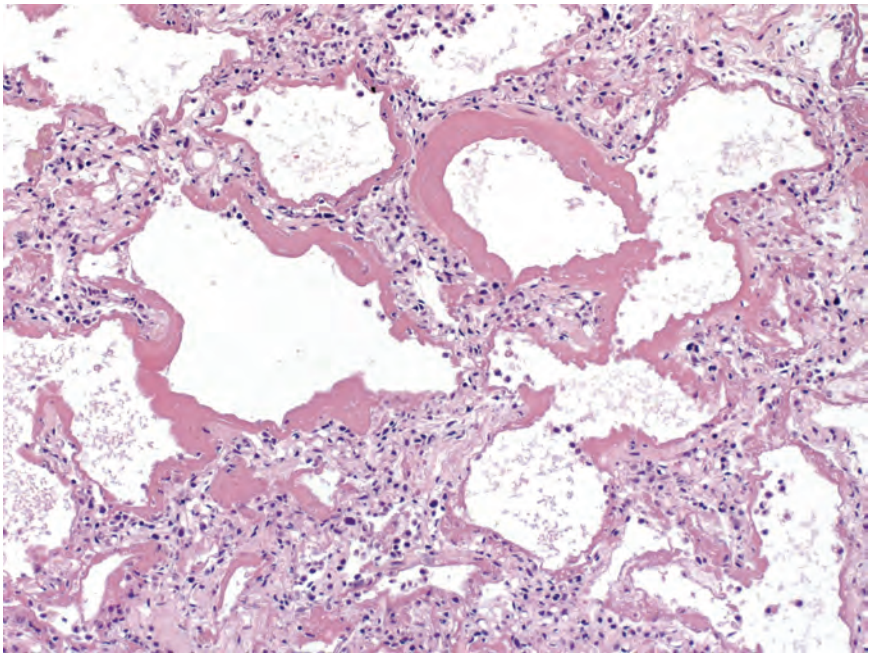

FIGURE WO-5 Lung tissues infected with 2009-H1N1 influenza A show evidence of diffuse alveolar damage, the physical manifestation of acute respiratory distress syndrome. SOURCE: Zaki (CDC).

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et al., 2009; Munster et al., 2009). To begin with, there is little physical resemblance between the spherical viral particles typical of seasonal H1N1 influenza and the filamentous 2009-H1N1 influenza A, as revealed by electronmicroscopy by speaker Yoshihiro Kawaoka, of the University of Wisconsin, and coworkers (Figure WO-6). The biological significance of these morphological differences is unknown (Itoh et al., 2009).

Kawaoka also described comparative studies of 2009-H1N1 influenza A and seasonal H1N1 infections in mice, ferrets, and macaques (nonhuman primates). All mice infected with 10^6 plaque-forming units (p.f.u.) of the index California isolate (CA04) of 2009-H1N1 influenza A died, while all those infected with the same concentration of 50 different variants of seasonal H1N1 viruses lost weight, but recovered. Only two of five 2009-H1N1 influenza A viral isolates (including CA04), however, were found to kill mice in this assay. All five 2009-H1N1 influenza A isolates were found to replicate well in both the trachea and the lung of the infected mice, while the seasonal H1N1 virus did not.

The researchers used a ferret model to compare 2009-H1N1 influenza A and seasonal H1N1 transmission. As illustrated in Figure WO-7, ferrets housed in separate cages, without direct or indirect contact, did not transmit the control virus, H5N1, but efficiently transmitted both seasonal H1N1 and 2009-H1N1 influenza A. Similar results were obtained by Munster et al. (2009) in a ferret pathogenesis model. These researchers also determined that while replication of seasonal H1N1 was confined to the nasal cavity of ferrets, 2009-H1N1 influenza

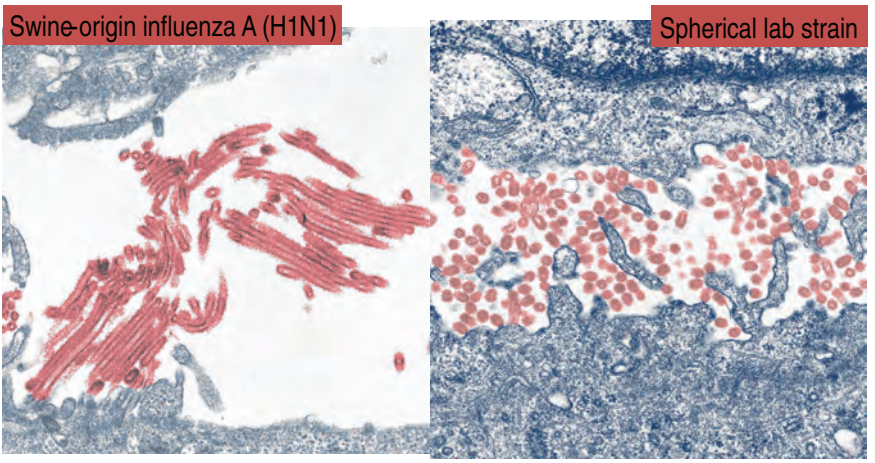

FIGURE WO-6 Spherical viral particles typical of seasonal H1N1 influenza, and the filamentous 2009-H1N1 influenza A.
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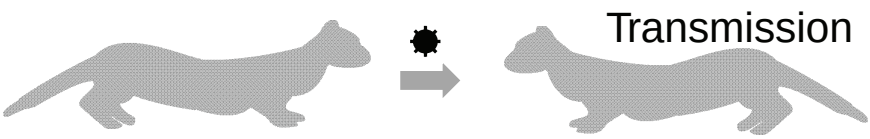

Virus transmission from infected animals to those in adjacent cages (no direct or indirect contact)

Swine-origin	Seasonal		Avian
A/Cal/04/09 (H1N1)	A/Kawasaki/ UTK-4/09 (H1N1)	A/Victoria/ 03/75 (H3N2)	A/duck/ Alberta/35/76 (H1N1)

FIGURE WO-7 Virus transmission from infected ferrets to those in adjacent cages. SOURCE: Kawaoka (2009).

A also replicated in the trachea, bronchi, and bronchioles. They also found that 2009-H1N1 influenza A was shed more profusely than was seasonal H1N1 from the ferret upper respiratory tract.

In cynomolgus macaques, Kawaoka and colleagues found that 2009-H1N1 influenza A replicated far more efficiently than did seasonal H1N1. As was also the case in mice and ferrets, the CA04 isolate of 2009-H1N1 influenza A appeared more damaging to lung tissue than the currently circulating seasonal H1N1 virus. While some macaques infected with seasonal H1N1 experienced mild lung lesions, the lungs of those infected with the 2009-H1N1 influenza A virus showed signs of severe disease, such as alveoli filled with fluid and inflammatory cells as illustrated in Figure WO-8.

"The ability of CA04 to replicate in the lungs of mice, ferrets and non-human primates, and to cause appreciable pathology in this organ, is reminiscent of infections with highly pathogenic H5N1 influenza viruses," Kawaoka and coworkers observed (Itoh et al., 2009). "We therefore speculate that the high replicative ability of [2009-H1N1 influenza A] might contribute to a viral pneumonia characterized by diffuse alveolar damage that contributes to hospitalizations and fatal cases where no other underlying health issues exist."

Potential Protections

CDC researchers measured the antibody response to the 2009-H1N1 influenza A resulting from previous influenza infection or vaccination in different age

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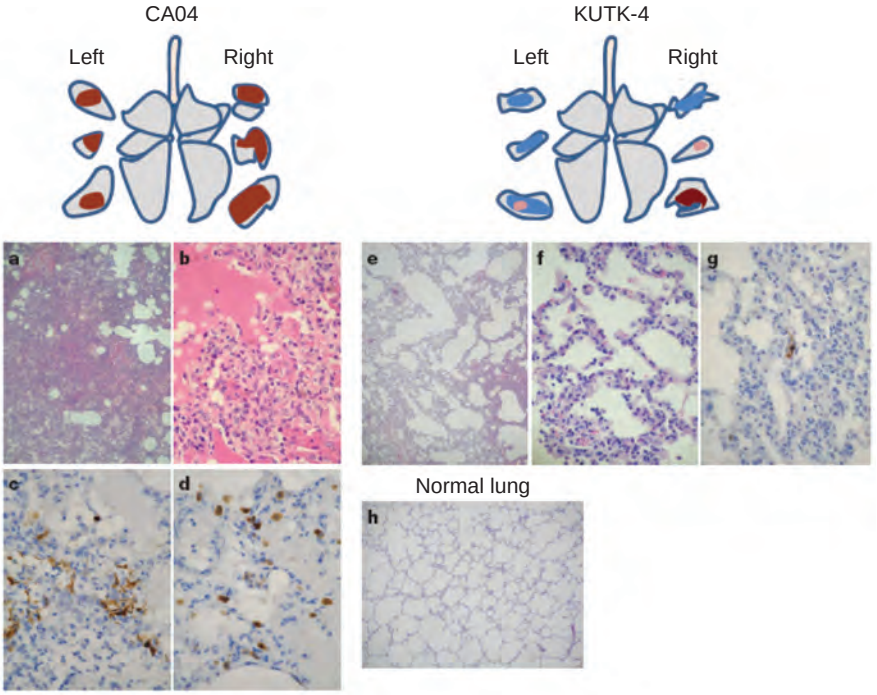

FIGURE WO-8 Pathological examination of the lungs of infected cynomolgus macaques. A-h, Representative of pathological images of CA04-infected (macaque no. 1, a-d), KUTK-4-infected (macaque no. 7, e-g) and mock-infected (h) lungs on day 3 after infection. One or two sections per lung lobe were examined. Representative findings are shown to depict the distribution of lesions in the sections (shown as cross-sections placed next to illustrations of each lung lobe), with or without viral antigen, as follows: brown, severe lung lesion containing moderate to many viral-antigen-positive cells; pink, mild lung lesions containing a few viral-antigen-positive cells; blue, lung lesions with alveolar wall thickening, with remaining air spaces unaffected. Original magnification: a, e, h, ×40; b-d, f, g, ×400.
SOURCE: Itoh et al. (2009).

groups in order to examine the possibility that humans might possess preexisting immunity to 2009-H1N1 influenza A and to evaluate the interaction of the virus with seasonal vaccine-induced antibodies (CDC, 2009d; Hancock et al., 2009). While only a very few people born after 1980 were found to have detectable cross-reactive antibodies against 2009-H1N1 influenza A, 34 percent of people born before 1950 had significant cross-reactive titers. Therefore, Cox said, "we postulate that the viruses that were circulating during the 1940s and early 1950s may have had cross-reactive epitopes on them," a hypothesis that the CDC is

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continuing to pursue. A workshop attendee, who had examined age-specific 2009-H1N1 influenza A fatality data from across the globe, found patterns to suggest that the residual immunity is to the pre-1957 strain of H1N1; he noted that a major antigenic shift occurred in the virus that year.

Kawaoka and coworkers also investigated cross-reactivity to 2009-H1N1 influenza A by examining two sets of sera, each representing a broad range of age groups: one collected before the emergence of 2009-H1N1 influenza A in 1999, and the other collected afterward, in April 2009 (Itoh et al., 2009). As illustrated in Figure WO-9, with few exceptions only individuals born before 1918 were shown to possess neutralizing antibodies against 2009-H1N1 influenza A. These investigators therefore concluded that only infection with the 1918 H1N1 virus—derivatives of which have been maintained in pigs in the years since the human

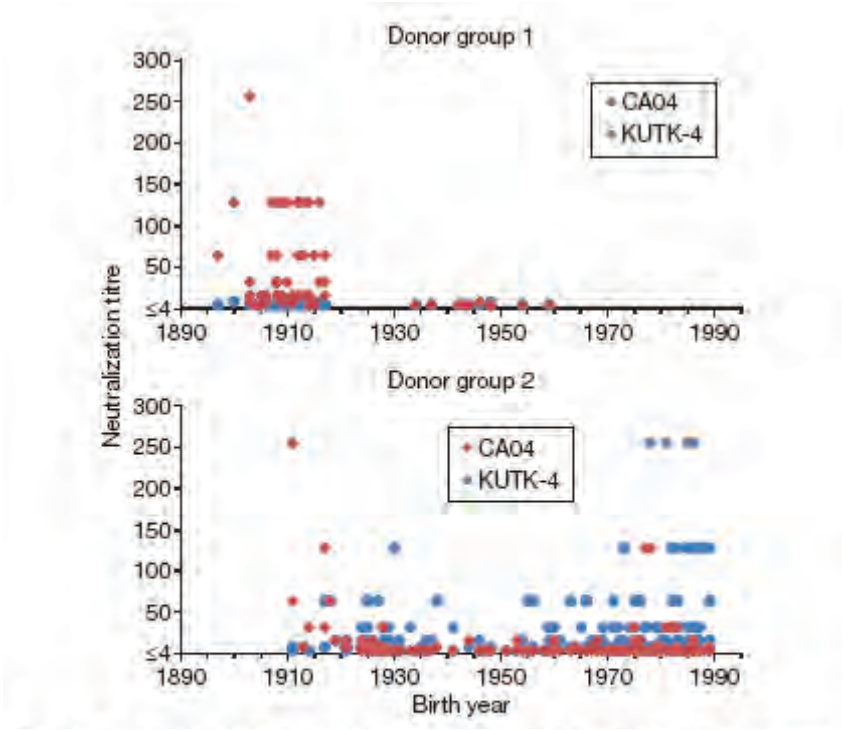

FIGURE WO-9 Neutralization activities in human sera against viruses. Human sera of donor groups 1 (collected in 1999) and 2 (collected in April and May of 2009) were subjected to neutralization assays with CA04 and KUTK-4. Because the sera of donor group 1 were collected in 1999, little neutralization activity was expected against KUTK-4, which was isolated in 2009.
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pandemic, and from which seasonal human H1N1 strains have diverged—could provide immunoprotection against 2009-H1N1 influenza A.

Both groups obtained similar data but interpreted them differently, Cox suggested. However, she added, the next step would be to examine these laboratory data in conjunction with epidemiological data, to determine whether the cross-reactive antibodies are actually protective. "What we've seen, not only for the Spring cases in the Northern Hemisphere, but also for the influenza seasons that occurred in the Southern Hemisphere, is that those over 60 are relatively spared from this disease." Outbreaks of 2009-H1N1 influenza A in nursing homes and long-term care facilities have yet to occur, she observed.

A recent study found that multiple major histocompatibility complex (MHC)–restricted epitopes[12] are conserved in the nucleoprotein,[13] matrix protein,[14] and hemagglutinin protein[15] of 2009-H1N1 influenza A (Xing and Cardona, 2009). The authors suggest that these epitopes may initiate the activation of infected macrophages[16] and antiviral cytokine[17] production, and help host defenses. They concluded that cross-reactive cell-mediated immunity[18] to pandemic (H1N1) 2009 virus through conserved MHC class I-restricted epitopes[19] may exist in persons previously immunized against, or exposed to, seasonal influenza.

Kawaoka also investigated the susceptibility of the 2009-H1N1 influenza A virus to a panel of antiviral drugs. As previously noted, there have been multiple sporadic isolations of oseltamivir-resistant 2009-H1N1 influenza A viruses. This is not surprising, he said, because about 18 percent of patients who

[12]The surface portion of an antigen capable of eliciting an immune response and of combining with the antibody produced to counter that response (http://medical-dictionary.thefreedictionary.com/epitopes, accessed November 5, 2009).

[13]Any of a group of substances found in the nuclei of all living cells and in viruses and composed of a protein and a nucleic acid (http://medical-dictionary.thefreedictionary.com/nucleoprotein, accessed November 5, 2009).

[14]Structural proteins linking the viral envelope with the virus core (http://encyclopedia.thefreedictionary.com/matrix+protein, accessed November 5, 2009).

[15]Hemagglutinin (HA) is a species-specific binding protein that allows for the virus to bind to the cell membrane of host respiratory cells and propagate through cellular processes (http://biology.kenyon.edu/BMB/Chime2/2005/Cerchiara-Holsberry/FRAMES/start.htm, accessed November 6, 2009).

[16]A type of white blood cell that ingests foreign material and is a key player in the immune response to foreign invaders such as infectious microorganisms (http://www.medterms.com/script/main/art.asp?articlekey=4238, accessed November 5, 2009).

[17]A human or animal factor that is induced by interferon in virus-infected cells and mediates interferon inhibition of virus replication (http://medical-dictionary.thefreedictionary.com/antiviral+protein, accessed November 6, 2009).

[18]An immune response that does not involve antibodies but rather involves the activation of macrophages, natural killer (NK) cells, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen (http://encyclopedia.thefreedictionary.com/cell-mediated+immunity, accessed November 5, 2009).

[19]MHC class I-restricted CD8+ T cells play a central role in protective immunity (http://tompoole.name/proxy.php?url=http://www.pnas.org/content/97/22/12210.full, accessed November 6, 2009).

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are infected with seasonal influenza and treated with oseltamivir harbor drug-resistant viruses. Using a mouse model, Kawaoka and coworkers tested licensed and experimental influenza drugs against 2009-H1N1 influenza A and found that the virus is sensitive to an experimental neuraminidase inhibitor and an experimental broad-spectrum viral RNA polymerase inhibitor, in addition to oseltamivir and zanimivir, as may be seen in Figure WO-10 (Itoh et al., 2009). For the time being, it seems, the antiviral "first line of defense" against 2009-H1N1 influenza A is holding (see the final section of this summary for further discussion of antiviral drugs for 2009-H1N1 influenza A).

The Pandemic's Progress

According to the WHO, as of April 4, 2010, 2009-H1N1 influenza A had spread to over 213 countries and had resulted in over 600,000 laboratory-confirmed cases and at least 17,700 deaths (WHO, 2010a,b). These numbers represent only the "tip of the iceberg" of morbidity and mortality associated with infection by the virus, as they reflect only those patients who have sought medical care and have undergone serologic, confirmatory, testing for the virus.

In mid-July, the WHO announced that "the increasing number of cases in many countries with sustained community transmission is making it extremely difficult, if not impossible, for countries to try and confirm them through laboratory testing" and that "the counting of individual cases is now no longer essential in such countries for monitoring either the level or nature of the risk posed by the pandemic virus or to guide implementation of the most appropriate response measures" (WHO, 2009b). Countries were urged to focus on diagnosing severe cases, and the WHO discontinued issuing country-specific counts of confirmed cases. The WHO began to provide a weekly "situation update" instead, gauging trends in four qualitative indicators: the global geographic spread of influenza, trends in acute respiratory diseases, the intensity of respiratory disease activity, and the impact of the pandemic on healthcare services (WHO, 2009d). Figure WO-11 depicts the global distribution and cumulative deaths due to 2009-H1N1 influenza A.

Because the 2009-H1N1 influenza A virus emerged just before the onset of the influenza season in the Southern Hemisphere, attention was focused on that region to see how the pandemic, and the virus itself, might evolve. Cox reported that, in general, the epidemiological characteristics of 2009-H1N1 influenza A noted in the initial disease wave in Central and North America—for example, attack rates, risk groups for infection, and disease severity—remained stable through the Southern Hemisphere's influenza season (see Box WO-3). In addition, the 2009-H1N1 influenza A virus itself also appeared unchanged: virus samples obtained from the Southern Hemisphere continued to match the vaccine seed isolate; the majority of Southern Hemisphere isolates were sensitive to neuraminidase inhibitors (unlike seasonal H1N1); and no genetic markers associated with severe influenza in other strains (e.g., the 1918 H1N1 pandemic virus

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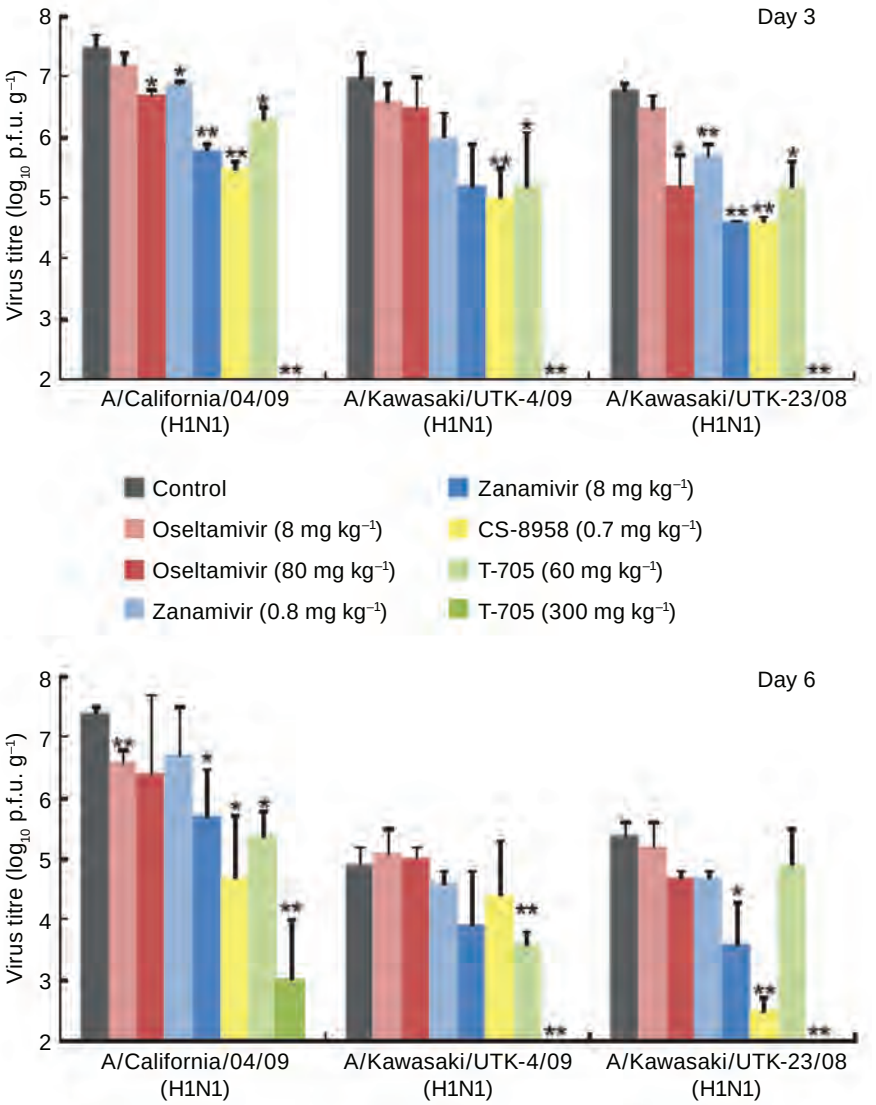

FIGURE WO-10 CA04 sensitivity to antiviral compounds in mice. Mice were intranasally inoculated with 10^4 p.f.u. (50 µl) of CA04, KUTK-4, or A/Kawasaki/UTK-23/08 (H1N1). At 1 h after infection, mice were administered oseltamivir phosphate, zanamivir, CS-8958, T-705, or distilled water and PBS (control). Three mice per group were killed on days 3 and 6 after infection and the virus titers in lungs were determined by plaque assays in MDCK cells; results are reported as means ± s.d. The statistical significance of differences in lung virus titers of control mice and those treated with antivirals were assessed by use of the Student's *t*-test (* $P < 0.05$; ** $P < 0.01$).
SOURCE: Itoh et al. (2009).

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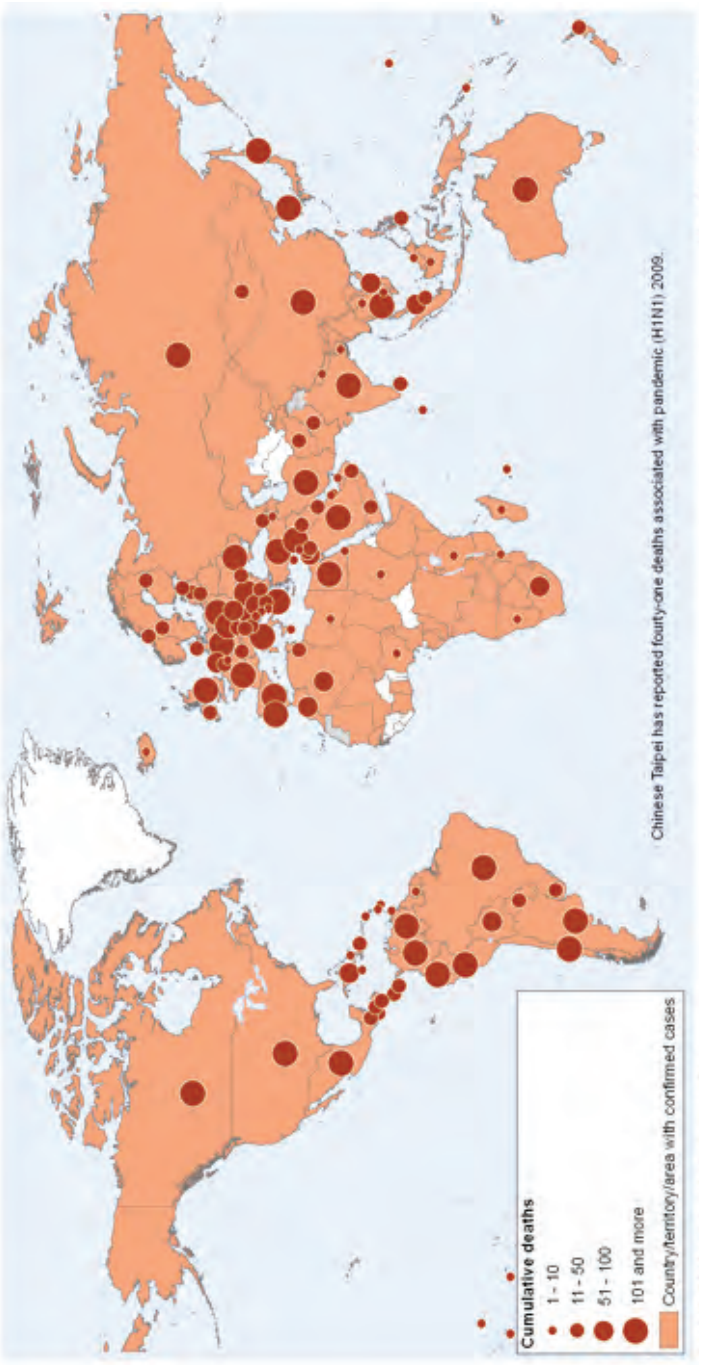

FIGURE WO-11 2009-H1N1 influenza A pandemic laboratory-confirmed cases and cumulative number of deaths as reported to WHO as of March 7, 2010.
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BOX WO-3
Clinical and Epidemiological Overview of 2009-H1N1 Influenza A

Transmission characteristics: In general, household secondary attack rates (a measure of the risk of someone being infected with a disease by an ill close contact) for 2009-H1N1 influenza A are slightly lower than attack rates for seasonal influenza. This suggests that pharmaceutical and nonpharmaceutical mitigation measures may appreciably limit the spread of 2009-H1N1 influenza A prior to the development of an effective vaccine. Indeed, the use of antiviral medications (which can reduce viral shedding) to treat cases or prevent influenza in household contacts may already have decreased secondary attack rates.

Age profile: Age-specific frequency of cases is highest among school-age children and young adults; the lowest frequency of cases occurs among the elderly.

Symptoms: Most people infected with 2009-H1N1 influenza A virus experience uncomplicated influenza-like illness, with full recovery within a week, even without medical treatment.

Severe cases: Small subsets of 2009-H1N1 influenza A patients rapidly develop very severe progressive pneumonia, which in turn is often associated with failure of other organs, or marked worsening of underlying asthma or chronic obstructive airway disease. Primary viral pneumonia is the most common finding in severe cases and a frequent cause of death. This is markedly different from severe cases of seasonal influenza, which tend to involve secondary bacterial infections.

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[a]The early treatment of bacterial infections may prevent severe complications and death. Antiviral treatment is recommended to treat infection and has also been used prophylactically in persons who have been exposed to H1N1 virus.

and H5N1 avian influenza virus) had been detected in any of the 2009-H1N1 influenza A virus isolates.

Several speakers described the recent Southern Hemisphere influenza season, during which the clinical and epidemiological characteristics of the morbidity and mortality associated with the 2009-H1N1 influenza A pandemic, as reflected in Box WO-3, remained essentially unchanged. Some Southern Hemisphere countries experienced simultaneous or serial epidemics of multiple viral diseases, as shown in Box WO-4. In many, but not all, cases the 2009-H1N1 influenza A virus eventually dominated other seasonal influenza strains. Much as Ruiz-Palacios found co-infections with multiple respiratory viruses (including parainfluenza 1, 2, and 3; respiratory syncytial virus [RSV]; and the coronavirus that causes bronchitis) in a majority of Mexican patients with severe disease, one might expect to find similar co-infections in other locations with multiple viral epidemics.

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Secondary bacterial infections have been found in approximately 30 percent of fatal cases of 2009-H1N1 influenza A. Bacteria frequently reported include *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-resistant strains in some cases. These infections can be prevented with antimicrobial (i.e., antibacterial, antiviral, antifungal agents) therapy during early treatment of 2009-H1N1 influenza A.[a]

Risk of severe or fatal illness is highest in three groups: pregnant women, especially during the third trimester of pregnancy; children younger than 2 years of age; and people with chronic lung disease, including asthma. However, significant numbers of severe cases occurred in previously healthy young people in the absence of any known predisposing risk factors. In addition, the overall fatality rate was highest in persons over 50 years of age (Louie et al., 2009a).

Comorbidities associated with severe 2009-H1N1 influenza A include cardiopulmonary diseases, diabetes, pregnancy, and morbid obesity.

Antiviral treatment and resistance: The 2009-H1N1 influenza A virus is sensitive to the neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®) and resistant to amantadine and rimantadine. There have, however, also been recent sporadic reports of oseltamivir resistance. Accumulating evidence suggests that prompt treatment of confirmed or suspected 2009-H1N1 influenza A with antiviral drugs reduces the severity of illness and improves the chances of survival.

SOURCES: CDC (2009b); Fukuda (2009); Munayco et al. (2009); Pourbohloul et al. (2009); WHO (2009f).

Workshop presentations offered epidemiological and clinical perspectives on the developing pandemic that ranged from the global to the local. The following discussion highlights information that contrasted with general trends as described in Box WO-3, or which provided novel clinical insights on the 2009-H1N1 influenza A virus.

The United States and Mexico

As is typical for the Northern Hemisphere, overall influenza activity declined over the summer in the United States. Localized outbreaks of 2009-H1N1 influenza A, some of them intense, however, continued to occur in different parts of the country (PCAST, 2009). More than 80 outbreaks occurred in summer camps in more than 40 states (Stein, 2009), and the southern United States, where many

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BOX WO-4
Influenza Trends, September 2009

Influenza viruses in circulation, 2009: Multiple viral subtypes (influenza A subtypes, pandemic H1N1, and influenza B) circulated throughout 2009 in both the Southern and Northern Hemispheres (Figures WO-12 and WO-13).

Southern Hemisphere influenza season: Several countries experienced multiple viral epidemics that included RSV, parainfluenza, and seasonal influenza (both H3N2 and H1N1); in some cases, 2009-H1N1 influenza A overpowered co-infecting viruses to become the predominant respiratory infection. The following figures, depicting annual influenza trends in Chile (Figure WO-14), Australia (Figure WO-15), Hong Kong (Figure WO-16), Cambodia (Figure WO-17), Kenya (Figure WO-18), South Africa (Figure WO-19), and New Zealand (Figure WO-20), illustrate the significance of 2009-H1N1 influenza A in the Southern Hemisphere 2009 influenza season.

As of September 11, 2009, as the Southern Hemisphere influenza season waned, the following trends in ILI were apparent:

- **Tropical regions:** A mixed picture, with some countries showing a decline in activity; others, sustained or increased activity.
- **Temperate regions, Southern Hemisphere:** Australia and temperate regions of South America had passed the peak of their winter influenza epidemic; some activity remained due to RSV.
- **Temperate regions, Northern Hemisphere:** In Japan, influenza activity exceeded the seasonal epidemic threshold, indicating an early beginning to the annual influenza season. Flu activity was also on the increase in Sweden and several regions of the Russian Federation, but most countries in Europe and Central and Western Asia reported declining activity.

SOURCES: Cox (2009); Fukuda (2009); Shortridge (2009).

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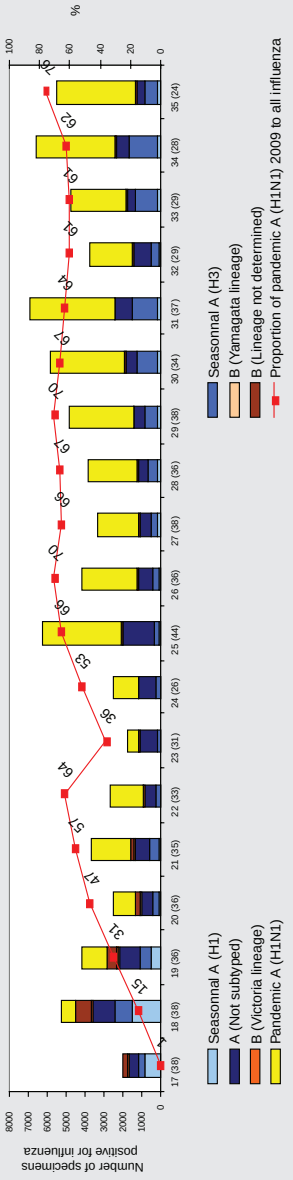

FIGURE WO-12 Number of specimens positive for influenza by subtype, Northern Hemisphere, April 19 to August 29, 2009 (weeks 17–35). Bars represent the number of specimens reported positive for influenza viruses during the reporting week represented in the x-axis. The x-axis also shows the number of countries that reported to FluNet during the respective week. Example: 17 (38) means that in week 17, 38 countries reported. The right side y-axis shows the proportion (percentage) and the left y-axis shows the absolute number of specimens reported positive for influenza viruses (influenza A subtypes, pandemic H1N1, and influenza B). SOURCE: Fukuda (2009).

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BOX WO-4 Continued

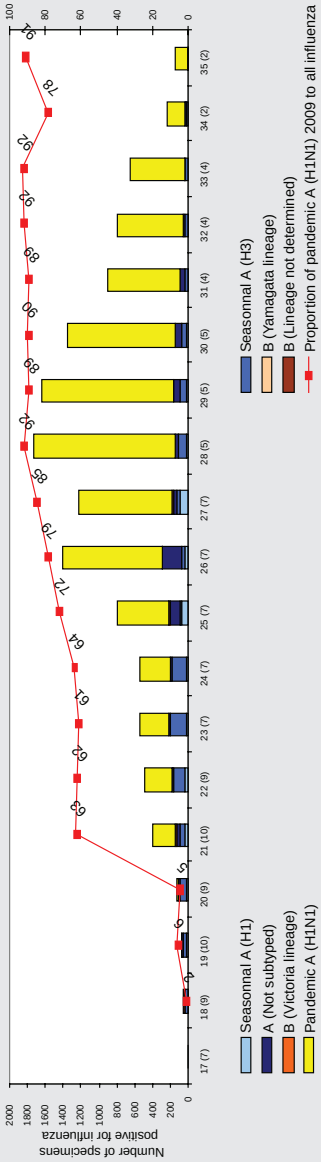

FIGURE WO-13 Number of specimens positive for influenza by subtypes, Southern Hemisphere, April 19 to August 29, 2009 (weeks 17-35). Bars represent the number of specimens reported positive for influenza viruses during the reporting week represented in the x-axis. The x-axis also shows the number of countries that reported to FluNet during the respective week. Example: 17 (7) means that in week 17, 7 countries reported. The right side y-axis shows the proportion (percentage) and the left y-axis shows the absolute number of specimens reported positive for influenza viruses (influenza A subtypes, pandemic H1N1, and influenza B). SOURCE: Fukuda (2009).

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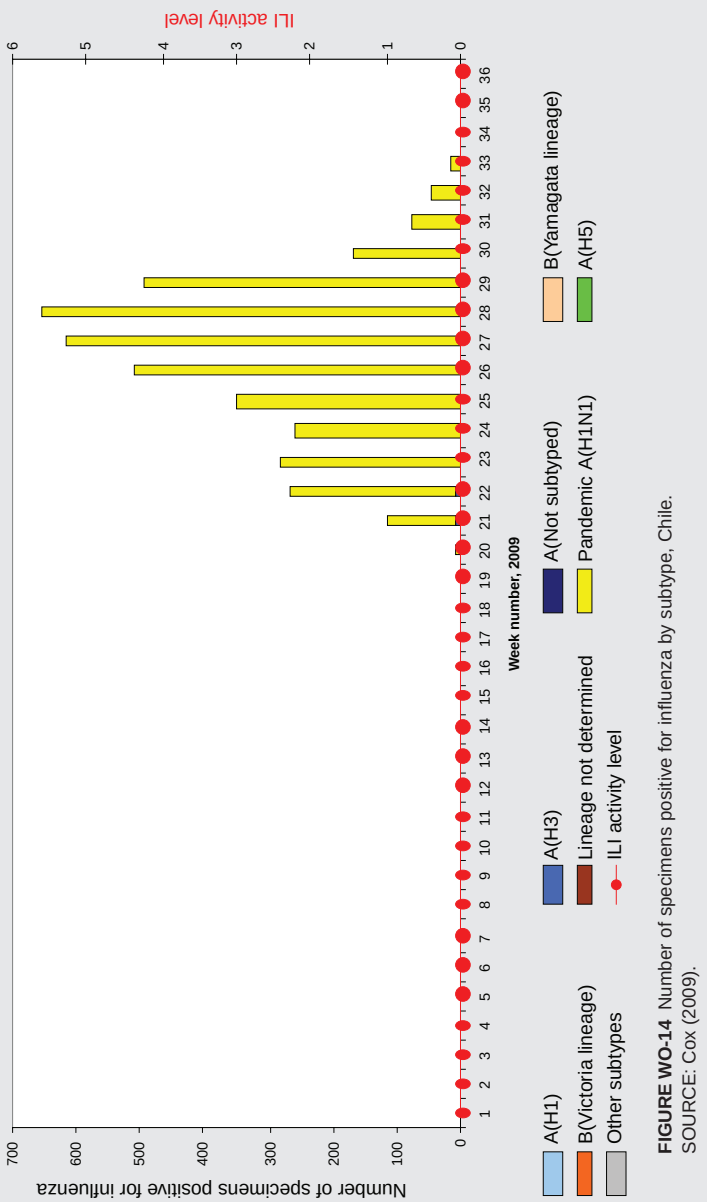

FIGURE WO-14 Number of specimens positive for influenza by subtype, Chile.
SOURCE: Cox (2009).

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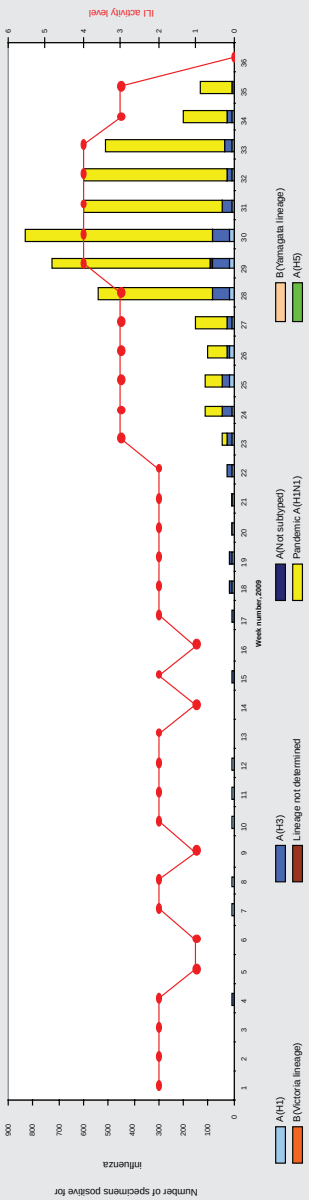

FIGURE WO-15 Number of specimens positive for influenza by subtype, Australia.
SOURCE: Cox (2009).

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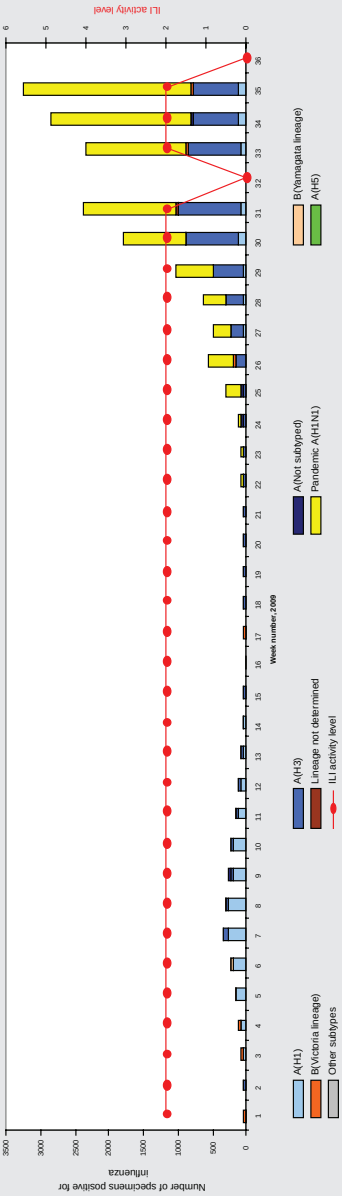

FIGURE WO-16 Number of specimens positive for influenza by subtype, Hong Kong.
SOURCE: Cox (2009).

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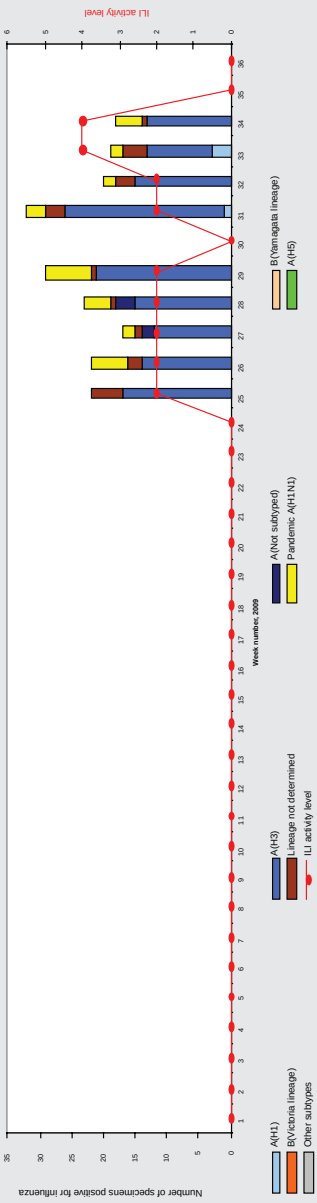

FIGURE WO-17 Number of specimens positive for influenza by subtype, Cambodia.
SOURCE: Cox (2009).

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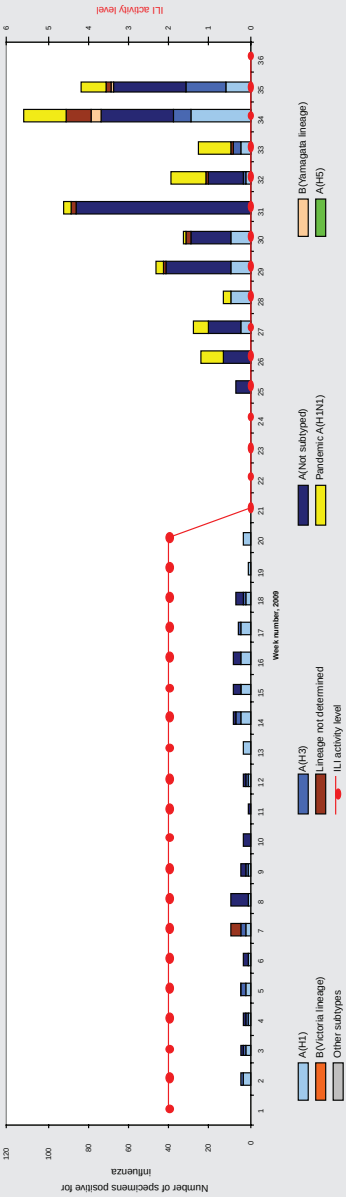

FIGURE WO-18 Number of specimens positive for influenza by subtype, Kenya.
SOURCE: Cox (2009).

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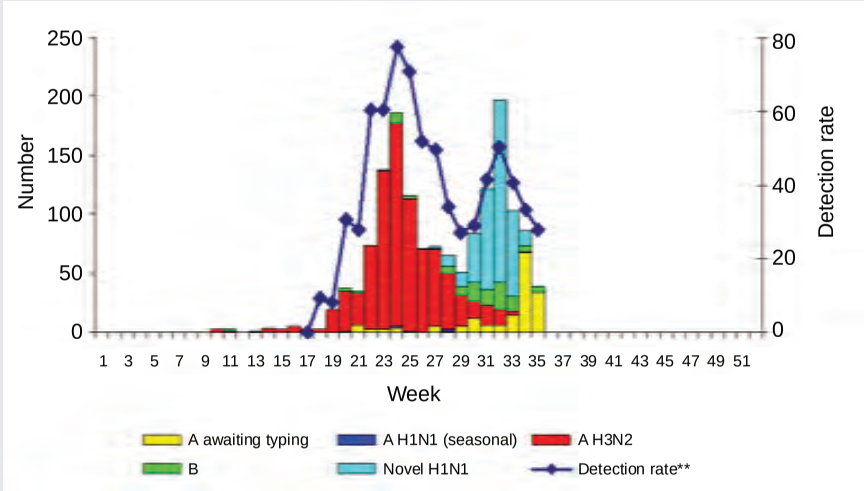

FIGURE WO-19 Influenza viral watch sentinel surveillance,* update to end of week 35 (week ending August 30, 2009). Positive samples by influenza types and subtype, South Africa.
*Virological surveillance at 256 sentinel sites in 9 provinces.
**Detection rate calculated on specimens tested at the National Institute for Communicable Diseases (NICD) only, not shown before onset of season.
SOURCE: Cox (2009).

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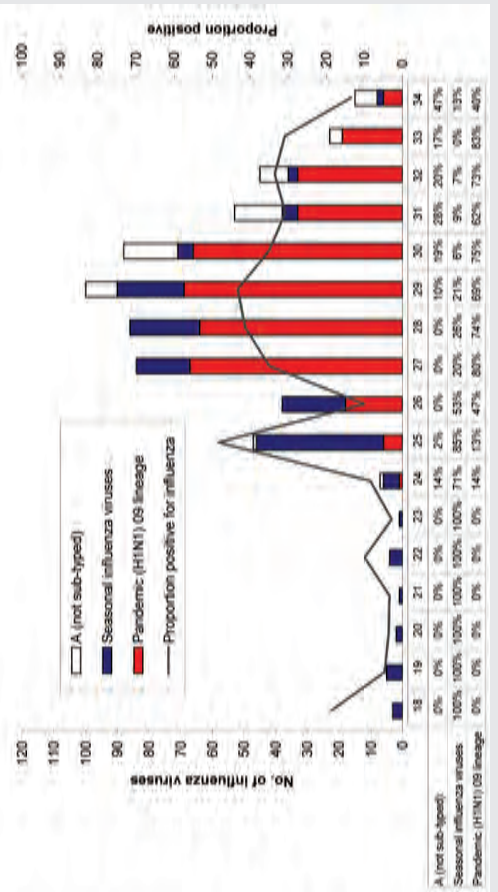

FIGURE WO-20 Total influenza viruses from sentinel surveillance by type and week reported to August 23, 2009, and the total percentage positive from the swabs received, New Zealand.
NOTE: All results of sentinel swabs are received by Environmental Science and Research (ESR). The line shows the proportion of those swabs that test positive for any type of influenza. A low proportion may be due to the swabs not successfully retrieving the virus, or that influenza-like-illness (ILI) presentations to sentinel general practioners (GPs) are due to other viruses.
SOURCE: Reprinted from Lopez and Huang (2009) with permission from the Institute of Environmental Science and Research Limited.

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schools resume session in late July, experienced an unusual late summer increase in ILI that has been attributed to 2009-H1N1 influenza A, Cox reported. This pattern was repeated throughout the country with the opening of most schools in early September, as shown in Figure WO-21, and the cases continue to mount.

Mexico experienced two peaks of viral activity, according to Ruiz-Palacios (Figure WO-22). The first peak began no later than March 2, 2009, the date that a blood sample was obtained from a child hospitalized for a respiratory infection as part of a surveillance program. The child was determined, after the fact, to be the earliest confirmed case of 2009-H1N1 influenza A. As the cases—including severe infections—mounted in the Mexico City area, the Mexican government—in an attempt to slow down the spread of the disease—closed all schools on April 24, 2009, and a few days later halted all nonessential activities (Stern and Markel, 2009). A decline in cases followed these interventions, which continued as schools reopened two weeks later and normal life resumed. However, Ruiz-Palacios continued, in early June, 2009-H1N1 influenza A cases started to appear in large numbers in the southeastern state of Chiapas, which, unlike Mexico City, is in the tropics. Although the population of Chiapas is approximately one-fourth that of Mexico City, the number of cases was similar, indicating a much higher rate of infection in Chiapas compared with Mexico City. Ruiz-Palacios attrib-

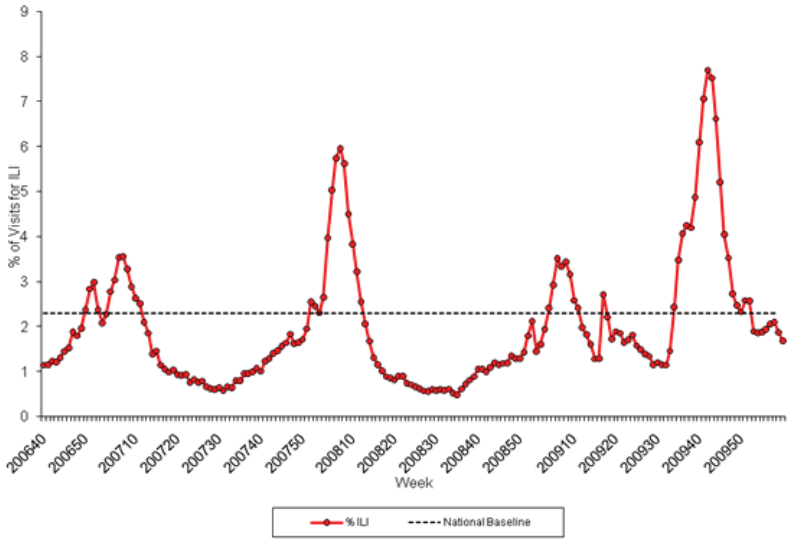

FIGURE WO-21 Percentage of visits for ILI reported by the U.S. Outpatient ILI Surveillance Network (ILINet) weekly national summary, October 1, 2006, to February 27, 2010.
SOURCE: CDC (2010).

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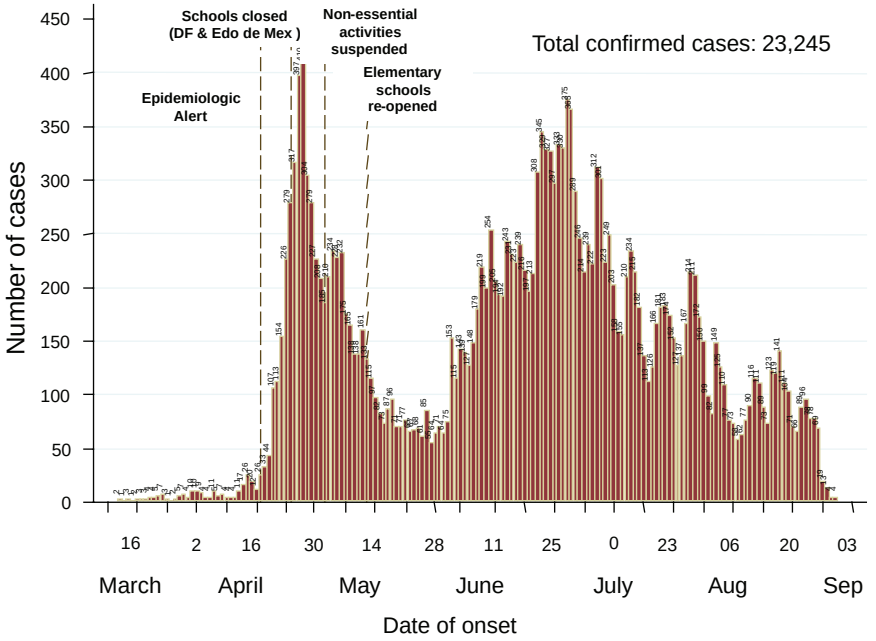

FIGURE WO-22 Epidemic curve in Mexico, cumulative through early September 2009. SOURCE: Ruiz-Palacios (2009).

uted this to the extreme poverty in Chiapas, and the associated lack of access to adequate hygiene or medical care.

Ruiz-Palacios also reported several findings on the topic of viral shedding in 2009-H1N1 influenza A cases, a significant factor in disease transmission, as may be seen in Figure WO-23. In general, he observed, higher viral titers are present early in the course of 2009-H1N1 influenza A infection. While high titers persisted in some severe cases, he found no relationship between disease severity and viral concentration. In most patients who received antiviral treatment early in the course of disease, viral shedding persisted for no more than two days, he said. By contrast, patients who presented after several days to weeks following the onset of symptoms continued to shed virus for several days following antiviral treatment and, in these cases, the virus was shed not only from the nasopharyngeal and endotracheal tissues[20] of these patients, as is typical, but also in their stool and urine. This phenomenon may have contributed to the high rates of 2009-H1N1 influenza A transmission reported in Chiapas and other places where clean water and sanitation are not widely available. In addition, Ruiz-Palacios noted, standard doses

[20]This refers to PCR positive findings, not isolation of viable virus.

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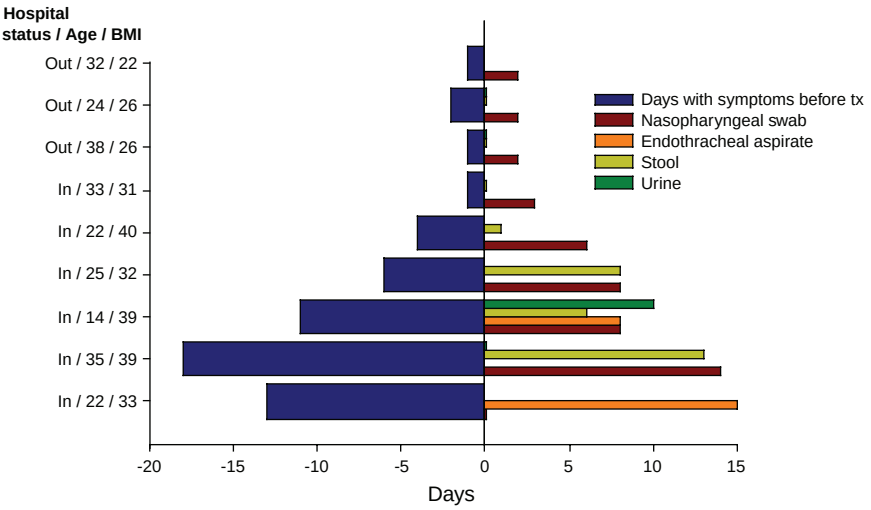

FIGURE WO-23 Viral shedding prior to and following treatment.
SOURCE: Ruiz-Palacios (2009).

of antiviral medications proved insufficient to reduce viral shedding in morbidly obese patients—who were disproportionately affected by severe disease—but that higher doses efficiently halted shedding in this subset of patients.

South America

Speaker and Forum member Eduardo Gotuzzo, of the Universidad Peruana Cayetano Heredia in Lima, Peru, discussed recent experiences and the current status of the 2009-H1N1 influenza A pandemic in South America, with special emphasis on his home country (see Munayco et al., 2009). Following the first confirmed case of 2009-H1N1 influenza A in Peru on May 14, the virus quickly spread among school students (Figure WO-24). Individual schools began to close within days, and a nationwide school closure took place between July 22 and August 1. In order to manage the 2009-H1N1 influenza A pandemic with Peru's limited resources, only "high-risk" patients received antiviral treatment and no prophylaxis was provided, Gotuzzo said; instead, they relied on behavioral interventions such as stressing the importance of hand washing and mask use (in healthcare settings) to reduce viral transmission. The public health response to the 2009-H1N1 influenza A pandemic in Peru was based on, and supported by, the country's pandemic influenza plan, which had been established five years earlier, he added. However, as the 2009-H1N1 influenza A pandemic unfolded, Gotuzzo and his colleagues quickly found that the plan "had to be continuously reviewed and updated."

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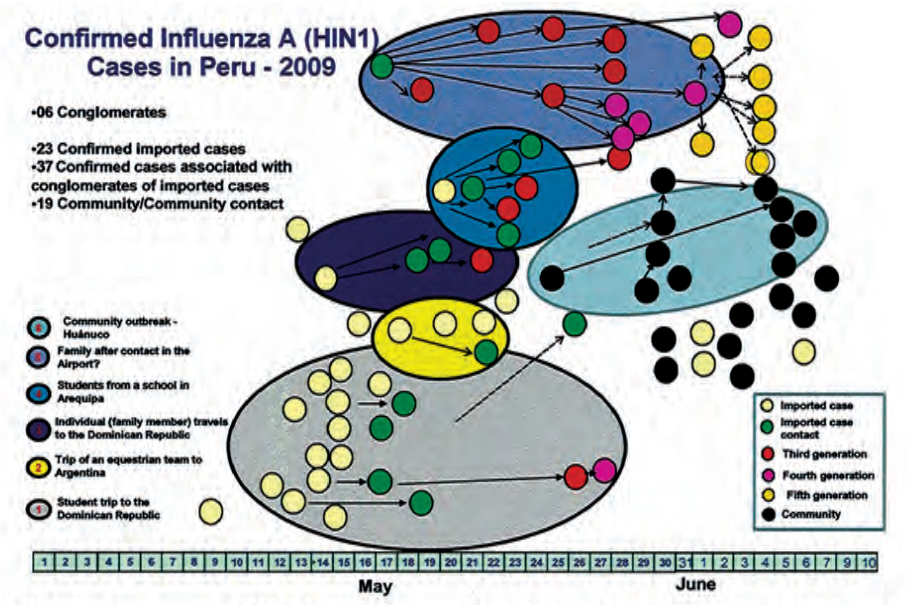

FIGURE WO-24 Confirmed 2009-H1N1 influenza A cases in Peru, 2009.
SOURCE: Dr. Luis Suarez-DGA/Peru.

Gotuzzo also considered an important variable among South American countries' experiences with 2009-H1N1 influenza A: mortality. Mortality rates associated with infection by the 2009-H1N1 influenza A virus varied widely, raising many questions about the course and treatment of influenza, as well as surveillance and monitoring practices, that have yet to be answered (personal communication, Thais dos Santos, PAHO, January 27, 2010). The striking example of the 2009-H1N1 influenza A pandemic in Argentina—where vastly different mortality rates occurred in different regions—however, offers insights on factors that may contribute to such discrepancies.

Despite the Argentine government's late April 2009 decision to suspend flights from Mexico, the 2009-H1N1 influenza A pandemic arrived in Argentina in late April/early May with an infected citizen of that country returning from a Mexican vacation (Bustamante, 2009). Speaker Osvaldo Uez, of Argentina's Instituto Nacional de Epidemiologia, observed that the 2009-H1N1 influenza A virus spread quickly in Buenos Aires, and then throughout the country, after the first case was identified on April 26. By July 22, 2009, the 2009-H1N1 influenza

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A pandemic in Argentina caused the second highest number of deaths in the world, just behind that of the United States (ProMED-mail, 2009a). A health emergency was declared in mid-July when the 2009-H1N1 influenza A virus was detected in the Argentinean swine population.[21] Schools were closed and citizens of Argentina were advised to avoid crowded areas (*Buenos Aires Herald*, 2009; ProMED-mail, 2009b). Estimates suggest that over a million people in Argentina became infected with the virus (see Uez in Appendix A13). Because provincial officials in Buenos Aires delayed school closures, and hospitals there initially provided antiviral treatment only to patients with severe respiratory symptoms, mortality rates were high, Uez reported: at least 29 deaths occurred among a population of approximately 259,000 in health region 2 of the Province of Buenos Aires. "It was like seeing the disease in its natural course, if you will; an experiment in nature," he said. By contrast, he noted, in Argentina's southernmost province, Tierra del Fuego, schools were closed quickly, public gatherings such as sports events were canceled, and patients with influenza-like symptoms consistently received antiviral treatment. There, in a population of 130,000, only one confirmed death due to 2009-H1N1 influenza A occurred.

Asia and Australasia: Implications of Co-Infections

The example of Argentina illustrates that while the epidemiological profile of 2009-H1N1 influenza A pandemic remained stable through the Southern Hemisphere's influenza season, its impact varied widely within and between countries. In an article (Bertozzi et al., 2009) that appeared in *Nature* days before the workshop describing scientific and public health challenges in affected countries, interviews with representatives of Australia, Vietnam, and India revealed very different experiences with the 2009-H1N1 influenza A pandemic. In Australia, which as of January 15, 2010, has reported 191 deaths out of more than 37,680 confirmed 2009-H1N1 influenza A cases (Australian Government, Department of Health and Aging, 2010), influenza was particularly hard on the indigenous population, which suffered disproportionate rates of severe disease (Bertozzi et al., 2009). In Vietnam, where the virus arrived relatively late in their influenza season and where past experiences with SARS and H5N1 encouraged pandemic preparation (Bertozzi et al., 2009), 58 deaths have been reported among the 11,186 confirmed 2009-H1N1 influenza A cases, as of February 10, 2010 (WHO Representative Office in Viet Nam, 2009). In India, where the virus was transmitted in city clusters, it was predicted that even if the pandemic remained moderate in its intensity, it would have a severe impact on the population due to its high

[21]Servicio Nacional de Sanidad y Calidad Agroalimentaria (SENASA) officials suspect that in early July, pig farm workers in Buenos Aires transmitted the 2009-H1N1 influenza A virus to swine. The Argentinean government implemented a contingency plan at this time, which allowed increased funding for H1N1 surveillance at pig farms and in swine slaughterhouses.

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density, youthful demographic (half of all Indians are younger than 25 years of age), and low awareness of the pandemic (Bertozzi et al., 2009). As of March 4, 2010, 1,385 confirmed deaths due to 2009-H1N1 influenza A have been reported in India (WHO/SEARO, 2010).

Workshop speakers Cox and Shortridge addressed another important feature of the recent Southern Hemisphere influenza season in Asia, as well as in New Zealand: the arrival of multiviral influenza epidemics involving 2009-H1N1 influenza A (see Box WO-4 on page 34). In certain parts of Asia, Cox reported, the 2009-H1N1 influenza A virus has failed to replace the H3N2 viruses. In both northern and southern China, H3N2 continues to represent about half of all isolated influenza viruses according to Cox of the CDC. "We're watching H3N2 circulation very carefully," said Cox. Shortridge observed that the "amalgam" of co-circulating 2009-H1N1 influenza A and seasonal H1N1 and H3N2 viruses poses an important question for vaccine production: will the 2009-H1N1 influenza A virus become the dominant influenza A virus, or will all three strains continue to coexist? And what about influenza B viruses? "There's going to be a hell of a job for the vaccine manufacturers if we have this collection of viruses year after year," he concluded (see Shortridge in Appendix A12).

Shortridge also noted the potential implications of the co-circulation of 2009-H1N1 influenza A with the H5N1 avian influenza A virus. This is bound to occur in parts of southern Asia, where H5N1 is endemic in domestic and wild birds and occasionally infects humans. "We're getting terribly carried away and so we should be with [2009-H1N1 influenza A]," he said, "but don't forget there are other viruses around to reassort with." H5N1 viruses have recently been isolated in humans in mainland China, and in poultry and wild birds in several Asian countries, he reported.

Shortridge's concerns about the potential for viral reassortment stem from his long experience as a public health researcher in mainland China and Hong Kong, where, he said, "as soon as you go to the villages, the feeling is palpable and you know that this is a place for pandemics and has been for a long time." He noted that the Chinese character for home depicts a roof with a pig underneath, and the long tradition of pigs—as well as poultry—sharing human dwellings continues to this day (Figure WO-25). He characterized these circumstances as "a wonderful alchemy for the emergence of pandemic influenza virus." Shortridge believes (though, he acknowledged, this belief is not universal) that the 1918 H1N1 pandemic virus emerged in humans in China, and—in addition to traveling through Europe to America—was transmitted from humans into pigs in China. By contrast, he observed, there have been no reported cases of humans infecting pigs with the 2009-H1N1 influenza A virus,[22] and rates of disease in mainland

[22]As of October 2009, a growing list of countries had detected 2009-H1N1 influenza A in pigs. In early May, the virus was found for the first time in pigs in Alberta, Canada. Though an infected worker was thought to have spread the virus to the pigs, the connection was never confirmed. Other

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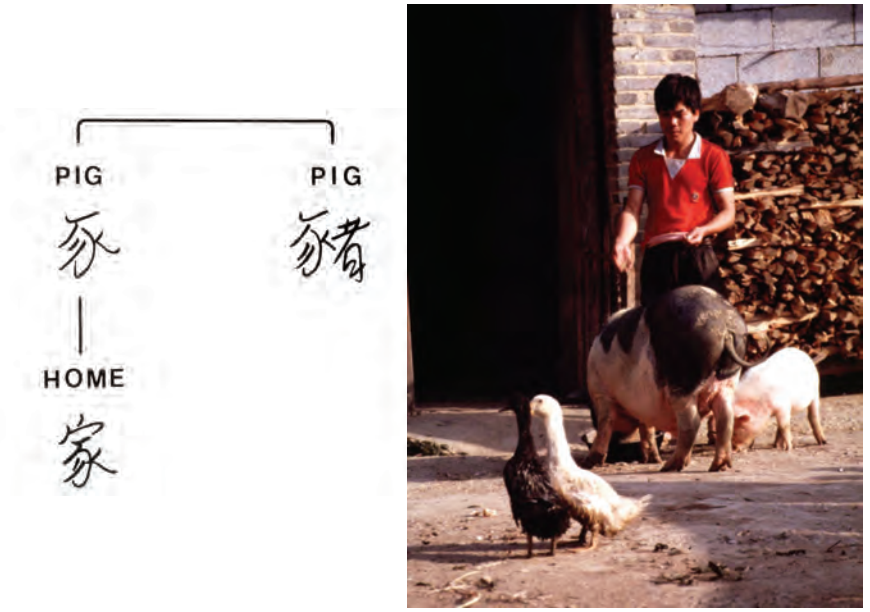

FIGURE WO-25 The long tradition of pigs and poultry sharing human dwellings in China.
SOURCE: Shortridge (2009).

China have been relatively low compared with Hong Kong and other countries in the region.

Africa

Low rates of reported 2009-H1N1 influenza A cases and deaths in Africa probably result from a combination of two factors, according to speaker Barry Schoub of the National Institute for Communicable Diseases, South Africa: a comparatively low volume of tourism, and a dearth of infectious disease surveillance (see Schoub in Appendix A10). He pointed out, however, that South Africa experienced a significant outbreak during the Southern Hemisphere influenza season,

countries—such as Australia, Ireland, and most recently Norway—have more definitively linked infections in pig herds to infected workers (Schnirring, 2009). The U.S. Department of Agriculture (USDA) confirmed the first U.S. case of 2009-H1N1 influenza A in a pig on October 19. The pig was tested at the Minnesota State Fair as part of a University of Iowa and University of Minnesota cooperative agreement research project, funded by the CDC, which documents influenza viruses where humans and pigs interact (USDA, 2009). The first case of human-to-swine transmission of the H1N1 influenza A virus in China was reported on November 6, 2009 (Yuk-hang and Chung, 2009).

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during which 2009-H1N1 influenza A overtook seasonal H2N3 to become the dominant influenza virus circulating in that country, as illustrated in Box WO-3.

The 2009-H1N1 influenza A pandemic did not reach South Africa—where it had sparked what Schoub called an "intensive search" for the virus propelled by public demand—until June 13th. A 16-year-old boy who had visited Texas introduced the 2009-H1N1 influenza A virus to South Africa; additional imported cases came primarily from the United States, Australia, and the United Kingdom. The pandemic is now established in South Africa with sustained community transmission occurring in most major cities. As of March 10, 2010, more than 12,640 laboratory-confirmed cases of 2009-H1N1 influenza A, and 93 deaths, have been reported in all 9 provinces, with the majority in Gauteng and Western Cape provinces (WHO/AFRO, 2010). The highest incidence rates of the 2009-H1N1 influenza A pandemic occurred in provinces that receive the majority of international travelers and which are also crowded urban areas, he reported.

Preliminary epidemiological findings in South Africa track closely with those reported from the initial Northern Hemisphere wave, Schoub said. Most cases (66 percent) have appeared in people 10-24 years of age. He noted, however, that these data highlighted two particular risk groups that sustained higher mortality rates compared to the rest of the population: pregnant women and people co-infected with HIV. Although pregnancy is a well-recognized risk factor in 2009-H1N1 influenza A (Jamieson et al., 2009; Mangtani et al., 2009), this preliminary study found an unusually high number of confirmed deaths among women in late pregnancy. Both pregnant and non-pregnant HIV-positive individuals died at considerably higher rates from 2009-H1N1 influenza A infection than HIV-negative individuals, he reported.

The Scientific Response

Several workshop presentations and considerable discussion focused on the rapid, multipronged scientific response to the emergence of 2009-H1N1 influenza A, which was primed by global anticipation of an H5N1 avian influenza pandemic and strengthened by increased—though still inadequate—scrutiny of emerging zoonotic diseases, as several workshop participants observed. Influenza surveillance ramped up as the pandemic unfolded, as did questions about how to improve and expand these efforts to address future emergent threats and inform the global public health response to 2009-H1N1 influenza A. Nevertheless, many critical decisions, such as those relating to the manufacture and distribution of the 2009-H1N1 influenza A vaccine, had to be made based on incomplete data. Under these circumstances, mathematical models provided a rational basis for decision making, and a means to reconsider and refine strategies as both the pandemic and the models evolved. At the same time, the pandemic offered investigators an important opportunity to analyze an emerging disease in real time and, thereby, inform public health policy.

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This section describes the interdependent pursuits of surveillance, modeling, and research on influenza biology and epidemiology during the early months of the 2009-H1N1 influenza A pandemic. Workshop participants described key findings and challenges encountered in each of these fields and noted their significance to present and future efforts to address emerging infectious diseases.

Surveillance

U.S. efforts before and after 2009-H1N1 influenza A The first U.S. cases of 2009-H1N1 influenza A were quickly diagnosed, and the viral genome was sequenced and published online, according to Cox, thanks to recent surveillance initiatives to detect and investigate swine influenza cases in humans. "Novel influenza of humans has been a notifiable disease in the United States for a number of years," she stated, "and there have been increasing efforts ongoing at state health departments, at [the] CDC, and in conjunction with our [U.S. Department of Agriculture (USDA)] partners to investigate these human cases of swine influenza and try to determine the extent of spread of swine influenza in humans when these instances arose."

The CDC also moved quickly to develop vaccine candidates, Cox said, making the decision to do so on April 18, the day after the second viral isolate was identified. "We did that because there was absolutely no evidence that the first two patients had had any contact with livestock [and] we also had heard that there was influenza-like illness activity in contacts of these two individuals, and so we thought it was better to be safe than sorry," she explained.

At the same time, the CDC amplified surveillance efforts directed at the 2009-H1N1 influenza A virus; these included enhanced detection, testing, virologic and epidemiologic surveillance, case reporting through ILInet,[23] and mortality surveillance. The agency also developed diagnostic RT-PCR[24] pandemic H1N1 kits, which—having been granted an Emergency Use Authorization by the

[23]ILInet is a nationwide surveillance program for influenza-like illness (ILI) conducted by the CDC in collaboration with state health departments. More than 2,700 physicians in all 50 states were enrolled in this network during the 2008–2009 influenza season, during which they reported the total number of patient visits each week and number of patient visits for ILI by age group (0-4 years, 5-24 years, 25-49 years, 50-64 years, >65 years). These data are transmitted once a week to a central data repository at CDC via the Internet or fax (http://www.health.state.ny.us/diseases/communicable/influenza/recruits.htm, accessed January 6, 2010).

[24]Reverse transcription polymerase chain reaction (RT-PCR) is a variant of polymerase chain reaction (PCR), a laboratory technique commonly used in molecular biology to generate many copies of a DNA sequence, a process termed "amplification." In RT-PCR, however, the RNA strand is first reverse transcribed into its DNA complement (*complementary DNA*, or *cDNA*) using the enzyme reverse transcriptase, and the resulting cDNA is amplified using traditional or real-time PCR. Reverse transcription PCR is not to be confused with real-time polymerase chain reaction (Q-PCR/qRT-PCR), which is also sometimes (incorrectly) abbreviated as RT-PCR (http://en.wikipedia.org/wiki/Reverse_transcription_polymerase_chain_reaction, accessed November 6, 2009).

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FDA—were provided in less than 3 weeks to state health departments and Department of Defense (DOD) laboratories, as well as to laboratories in 140 countries. As of early September, Cox reported, more than 1,000 such kits had been distributed to more than 100 labs domestically, 15 DOD labs, and to more than 250 labs in 140 countries.

As Cox and Worobey noted previously, however, a period of "unsampled diversity" in swine influenza viruses (SIVs) preceded the emergence of the pandemic strain of the 2009-H1N1 influenza A virus. "There's lots of room for improvement in our surveillance of swine flu in pigs," said Worobey, who advocated for global sequence-based surveillance of influenza-like disease in humans and animals. "If we had been doing that kind of thing, we may have picked up on this new flu strain a month or two or three earlier than we did," he speculated. "We can take a lot of lessons from this example . . . [for] the next time a virus runs into humans, perhaps one that has a higher virulence." While acknowledging that a comprehensive sampling of SIVs might not permit identification of strains that could jump to humans and cause a pandemic, "it would be great to actually be able to at least try to do that," he said. Influenza surveillance in humans is even more crucial, he noted: "It's a very rare event, but [when] any new flu strain jumps into humans and does anything more than sporadic transmission . . . we need to be bracing ourselves for the possibility that it's going to be the next pandemic."

"We've really tried to close this gap in surveillance for SIVs among swine and swine workers," Cox said of the CDC. However, she noted, there is no existing systematic surveillance for SIV in the United States, nor is there a global effort. Reporting of SIV is not required by the World Organization for Animal Health (OIE). Cox further characterized recent requirements imposed with the emergence of 2009-H1N1 influenza A (which now presents a risk to swine) as "loose." In September 2008, Cox reported, the CDC provided the USDA with $1.5 million to initiate a pilot project to conduct more systematic SIV surveillance, after increased numbers of triple-reassortant SIVs were detected in humans. Cox noted that additional potential benefits to increased SIV surveillance (on either a regional or a global basis) include improved vaccine strain selection and better SIV diagnostics for swine and other mammalian species.

As the 2009-H1N1 influenza A pandemic continues through the Northern Hemisphere's influenza season, the CDC plans to maintain its enhanced epidemiologic and virologic surveillance, Cox said. Focus on the diagnosis of severe cases, hospitalizations, and deaths due to the 2009-H1N1 influenza A virus will continue, but—much as the WHO advised in July—there will be no attempt to count cases. The CDC will also conduct syndromic surveillance for ILI and pursue new sources of surveillance data, she added. "We expect that seasonal influenza viruses will co-circulate with [2009-H1N1 influenza A]," Cox stated, "but the timing, spread, and severity of the 2009-2010 influenza season are unpredictable."

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Investigations of outbreaks in healthcare settings In his presentation on challenges for controlling the transmission of the 2009-H1N1 influenza A virus in healthcare facilities, Michael Bell of the CDC described a series of case studies conducted in May designed to examine disease transmission patterns among healthcare workers. At that time, he observed, this group did not appear to be overrepresented among 2009-H1N1 influenza A cases. Among 81 confirmed cases of 2009-H1N1 influenza A among healthcare personnel in 25 states, Bell and coworkers found that about 40 percent were community infections, and that more than half of infections that workers might have acquired from patients occurred in outpatient settings. Most disturbing of the study's findings was "a tremendous lack of adherence to even basic infection control recommendations," Bell observed (these recommendations are discussed in a subsequent section entitled "The Public Health Response"). Many of these healthcare personnel were apparently unaware that they should be taking precautions when evaluating patients with undiagnosed 2009-H1N1 influenza A infection, and that most reported that they had worked while ill.

To illustrate the varied impact of the 2009-H1N1 influenza A pandemic in healthcare settings, Bell offered the following examples:

- In an Ohio location where no prior community transmission of the 2009-H1N1 influenza A virus had occurred, a surgical resident returned from a rodeo show at which he had apparently become infected with the virus, exposing 166 coworkers before he became ill. About two-thirds of them received antiviral prophylaxis, although many discontinued treatment due to the gastrointestinal side effects associated with the antiviral medication. None of the exposed individuals became symptomatically ill.
- Upon investigation of a 2009-H1N1 influenza A infection cluster in a Chicago hospital where patients with unrecognized infections had not been isolated, it was determined that transmission had occurred in equal parts among the general community, between hospital workers, and between hospital workers and patients.
- None of the 721 elderly residents of a long-term care facility in Boston became infected with the 2009-H1N1 influenza A virus from two healthcare personnel who were working while ill with influenza. However, 18 more staff members—7 of whom had contact with residents—reported ILI that could have been contracted from their coworkers.

Monitoring outbreaks on the Internet The near ubiquity of the Internet, and the voluminous information it carries, makes it an ideal platform for a variety of surveillance strategies (Brownstein et al., 2009; IOM, 2007b). As speaker Lawrence Madoff of the University of Massachusetts explained, informal sources—such as blogs, chat rooms, and analyses of Web searches—provide considerable information on disease outbreaks and their impacts that can be gathered and

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assessed quickly. He contrasted that with the traditional "ground-up" flow of public health information from healthcare practitioners and laboratories through multiple administrative layers to national or international governmental bodies (and then back down the same chain in the form of health policy guidance or recommendations).

Focusing on the International Society for Infectious Diseases' Program for Monitoring Emerging Diseases, known as ProMED-mail, and its performance during the 2009-H1N1 influenza A pandemic, Madoff (who has served as a ProMED-mail editor since 2002) described a range of informal surveillance programs, as well as efforts under way to measure and improve their performance. Founded in 1994, ProMED-mail has grown into a large, publicly available reporting system with more than 55,000 subscribers in nearly every country, he said. ProMED-mail posts information on outbreaks and case reports, including many provided by or gleaned from readers. Many of these readers first became aware of ProMED-mail during the SARS pandemic, which ProMED tracked from an early rumor about an unusual disease outbreak in south China (Morse, 2007). "We expect our readers to write to us and tell us what they know," Madoff said, adding that "ProMED frequently publishes press reports from non-health media. ProMED moderators screen all posted reports and attempt to limit releases to about seven reports per day in order to prevent 'information overload.'"

ProMed emphasizes the concept of One Health®,[25] which places human health within a larger ecological context, Madoff said. Recognizing the importance of the animal–human health interface, ProMed tracks animal diseases of agricultural importance in livestock, as well as reports of zoonotic diseases. A significant number of ProMED staff members are veterinary specialists. Another key principle of the ProMED culture is transparency, because, he noted, "we can't predict who's going to need to know" the information ProMED provides. "Who would have guessed," he wondered, "that doctors in an emergency room in Toronto were going to be seeing cases of SARS within days of ProMED's initial post on the disease?"

The volume of potential surveillance information available on the Internet quickly grew beyond the capacity of individuals to search for it, leading to the

[25]Health experts from around the world met on September 29, 2004, for a symposium focused on the current and potential movements of diseases among human, domestic animal, and wildlife populations, which was organized by the Wildlife Conservation Society and hosted by The Rockefeller University. Using case studies on Ebola, avian influenza, and chronic wasting disease as examples, the assembled expert panelists delineated priorities for an international, interdisciplinary approach for combating threats to the health of life on Earth. The product—called the "Manhattan Principles" by the organizers of the "One World, One Health®" event—lists 12 recommendations for establishing a more holistic approach to preventing epidemic/epizootic disease and for maintaining ecosystem integrity for the benefit of humans, their domesticated animals, and the foundational biodiversity that supports us all. For more information, see http://www.oneworldonehealth.org/ (accessed July 16, 2009).

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creation of automated web crawlers such as the Global Public Health Information Network (GPHIN), operated by the Public Health Agency of Canada (IOM, 2007b; Mawudeku et al., 2007). Available on a paid subscription basis system, GPHIN provides early warning of disease outbreaks to public health officials at all levels of government, as well as to agencies such as the CDC and the WHO, who use GPHIN reports to detect and track emerging diseases. HealthMap, based at the Children's Hospital in Boston, combines an automated surveillance system with a geographical interface, producing maps of disease outbreaks. HealthMap reports are freely available online.[26] A more recent addition to the automated surveillance approach is the monitoring of Internet search term usage, which is the strategy employed by Google Flu Trends[27] (Ginsberg et al., 2009). Its premise, Madoff explained, is that people with influenza or their family members will search the Internet for information on such topics as "flu," "fever," or "Tamiflu®." This approach has detected some local influenza peaks before other surveillance methods were able to do so, he said.

Human-based Internet surveillance systems—including the CDC's Epi-X,[28] the International Society for Tropical Medicine's GeoSentinel,[29] and the WHO's Global Outbreak Alert and Response Network (GOARN)[30]—provide equally valuable information that often complements or reinforces intelligence from automated systems, Madoff said. Because each Internet surveillance system picks up different signals, having a variety of approaches in operation maintains overall balance and fills information gaps. Madoff concluded that "redundancy in this setting is a good thing." Moreover, he added, these surveillance systems complement traditional public health reporting. "We certainly don't see [informal source surveillance systems] replacing the traditional public health [surveillance] system," he concluded.

[26]See http://www.healthmap.org.

[27]See www.google.org/flutrends.

[28]CDC's web-based communications solution for public health professionals. Through Epi-X, CDC officials, state and local health departments, poison control centers, and other public health professionals can access and share preliminary health surveillance information—quickly and securely. Users can also be actively notified of breaking health events as they occur. For more information, see http://www.cdc.gov/epix/ (accessed November 5, 2009).

[29]A worldwide communication and data collection network for the surveillance of travel-related morbidity. It was initiated in 1995 by the International Society of Travel Medicine (ISTM) and the CDC as a network of ISTM member travel/tropical medicine clinics. GeoSentinel is based on the concept that these clinics are ideally situated to effectively detect geographic and temporal trends in morbidity among travelers, immigrants, and refugees. For more information, see http://www.istm.org/geosentinel/main.html (accessed November 5, 2009).

[30]A technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification of, confirmation of, and response to outbreaks of international importance. GOARN provides an operational framework to link this expertise and skill to keep the international community constantly alert to the threat of outbreaks and ready to respond. For more information, see http://www.who.int/csr/outbreaknetwork/en/ (accessed November 5, 2009).

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One of the earliest reports of the 2009-H1N1 influenza A pandemic-to-be appeared on HealthMap on April 1, marking the outbreak of pneumonia that occurred in the small town of La Gloria, Veracruz, Mexico. Madoff acknowledged, however, that informal surveillance played "a relatively minor role" in the early detection of the emergence of the 2009-H1N1 influenza A virus. Rather, he observed, the "traditional public health system actually worked quite well in this outbreak," particularly systems put in place in anticipation of an H5N1 avian influenza pandemic. Today, he added, informal sources play an important role in monitoring the pandemic's progress. Workshop participants suggested that informal surveillance systems might also be employed prior to a 2009-H1N1 influenza A immunization campaign to identify and quash inaccurate information on vaccine risks, as well as to provide an alternative means to monitor for adverse vaccine event allegations.

Madoff described several approaches that he and colleagues are developing for evaluating and improving early outbreak detection by informal source surveillance systems. This is the goal of a collaboration between HealthMap and ProMED, which will convert ProMED's archive of more than 40,000 reports into a structured database. Careful analysis of its content will permit the identification of gaps in surveillance systems by disease type, geography, or language, Madoff explained. Such content analysis may suggest timely indicators of disease outbreaks that distinguish them from background "noise." For example, he observed, outbreaks of pneumonia (such as the one in early April in La Gloria, Veracruz) are common; what are the "unique" traits that would mark it as a disease emergence event? Often, the information that is needed to recognize an emerging disease must be obtained from official sources, so ProMED frequently issues requests for the verification of information they have received, he said.

Because areas of the Southern Hemisphere are not well represented in its collection of informal sources, Madoff said, ProMED is developing regional surveillance programs with such partners as the Asociación Panamericana de Infectología (API or Pan American Association of Infectious Diseases) in South America and the Mekong Basin Disease Surveillance Group,[31] and creating new networks in Africa. ProMED is also looking for new ways to monitor diseases, including surveys of social networking sites such as Facebook and Twitter.

Smart surveillance Introducing his workshop presentation, entitled "Ecological Factors to Understanding Influenza Risk," Peter Daszak of the Wildlife Trust emphasized the profound influence of human activity—travel, trade, agriculture, land use, and animal domestication—on infectious disease emergence (see

[31]The Mekong Basin is home to six countries: Cambodia, China, Laos, Myanmar, Vietnam, and Thailand. In 1999, delegates from these countries agreed to start disease surveillance collaborations under the name Mekong Basin Disease Surveillance (MBDS). For more information, see http://www.mbdsoffice.com/ (accessed November 17, 2009).

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Daszak in Appendix A2; Daszak, 2009b). Having examined these influences in relation to a variety of emerging pathogens, including Nipah virus, West Nile virus, and SARS, Daszak and colleagues conceive of disease emergence as a series of discrete events. Rarely is the series completed, leading to the global spread of a new pathogen, he explained. Instead, zoonotic diseases that spill over into human populations tend to die out, hitting an evolutionary "dead end." If we were really good at surveillance, he observed, we could develop predictive strategies based on interactions between wildlife and livestock and conduct our surveillance in a "smarter" way. These predictive strategies, it is hoped, would enable us to recognize when a pathogen was likely to emerge into human populations and we could respond accordingly.

In the course of pursuing this goal, Daszak and coworkers have examined several emerging diseases and, through detailed ecological analyses, have attempted to predict subsequent transmission routes and future geographic spread. The results could be used to target surveillance efforts, making them more cost-effective, or "smarter." In the case of H5N1 avian influenza, Daszak's group considered whether the disease was likeliest to reach the United States through the poultry trade, through wild bird migrations, or through wild birds imported by the pet trade. First, they determined the pathways by which H5N1 had spread through Asia, Europe, and North Africa (Kilpatrick et al., 2006a). "The poultry trade within southeast Asia was the prime driver of the spread of H5N1 in the first few years," Daszak said. "Then once [H5N1] got out of Asia and across into Eastern Europe, there was a rapid spread, most likely due to wild birds." Although the importation of birds from countries where H5N1 had been detected had been banned in the United States, Daszak's group predicted that the virus would nonetheless enter the country through the "back door," via birds that were first imported into Mexico and Canada, rather than with migratory birds on the Alaska flyway, which had been a focus of U.S. H5N1 surveillance efforts.

When they attempted to apply similar analyses to 2009-H1N1 influenza A after the early outbreaks in order to determine how and why it emerged in Mexico, Daszak's group found their model was "pretty useless" due to the lack of surveillance for influenza in swine, as previously discussed. Trade in swine is vast in both volume and geography, he explained. He estimated that, in the past decade, up to 1.5 million hogs moved to Mexico from the United States and Canada, and they in turn could have been bred in Australia, Latin America, Asia, or Europe. Without rigorous surveillance for SIVs in these widely mixing swine herds, he said, "it's impossible to say anything else about the origin of that virus from an ecological perspective other than that huge trade in pigs and poultry is going to lead to this sort of event."

Daszak and coworkers then tried to devise a predictive model to anticipate where the next 2009-H1N1 influenza A outbreaks were likeliest to occur—a tool that could be used to target intervention efforts to minimize the global impact of an infectious disease. They began by examining direct and secondary airline

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flights originating from Mexico, which gave a reasonable prediction of where outbreaks actually occurred. When they included an additional variable—such as national healthcare spending over the previous year—that accounted for the likelihood that a particular country would report an outbreak, the model predicted outbreaks with "incredibly rigorous probability," Daszak reported. When the next virus with pandemic potential emerges, he continued, the WHO should target resources to countries that receive a high volume of travelers, and particularly those that spend relatively little on healthcare (which could be approximated by gross domestic product, or GDP), where cases are unlikely to be detected or reported quickly (Daszak, 2009a).

An even "smarter" surveillance program would actually predict where the next zoonosis would emerge. To approach this daunting task, Daszak's group created an emerging disease database by identifying as closely as possible the point origin of every emerging disease between 1940 and 2004 (Jones et al., 2008). These spatial patterns in emerging infectious disease (EID) events, when corrected for geography and timing of discovery, Daszak said, revealed "hot spots" for infectious disease emergence in places where the animal–human interface is particularly active. As it turns out, the area in Mexico where 2009-H1N1 influenza A appears to have emerged occupies one of these hot spots, he added (Figure WO-26).

Daszak's group continues to refine this general model and adapt it to predict geographic transmission patterns for specific pathogens, including West Nile virus (Kilpatrick et al., 2006b) and the H5N1 virus (Gilbert et al., 2008). In the

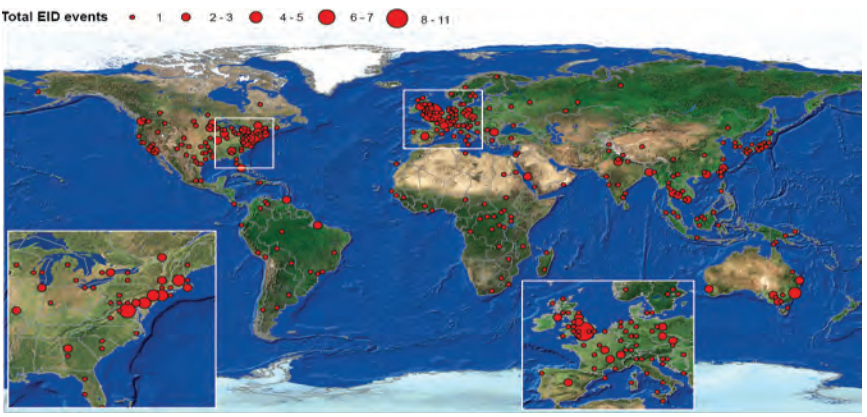

FIGURE WO-26 Spatial pattern in emerging infectious disease events. Main hotspots are in high latitude, developed countries.
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case of influenza, this process involves determining viral transfer rates between all involved species, locating geographic hot spots for emergence, and examining viral reassortment events. They also hope to use the model to determine the drivers of disease spillover from wildlife into livestock and from livestock into people, and in particular to compare the extent to which intensive production of livestock and backyard farming contribute to this process.

Modeling

A timely response to an incipient pandemic results from decisions based on uncertain data and assumptions regarding the nature of the threat at hand, according to speaker Marc Lipsitch of Harvard University (Lipsitch et al., 2009). As the 2009-H1N1 influenza A pandemic unfolded, Lipsitch and coworkers created models to estimate parameters of infection and to inform the public health response—an experience, he said, that highlights inherent assumptions and uncertainties and also suggests ways to increase both the accuracy and timeliness of impact estimates (see Lipsitch in Appendix A7).

Estimating severity Several assumptions regarding the severity of 2009-H1N1 influenza A derived from analyses of H5N1, Lipsitch observed. A community mitigation strategy devised to address the threat posed by H5N1 influenza, developed by the U.S. government in 2007, included a pandemic scale based on attack rate and case fatality rate (CFR)—the number of deaths divided by the total number of infections—coupled with tailored interventions, as shown in Figure WO-27 (HHS, 2007). Early CFRs that could be calculated based on early data on 2009-H1N1 influenza A were inconsistent, however, ranging from 4 percent in Mexico to 0.1 percent in the United States, he recalled. Subsequent analyses, based on larger pools of data, continued to produce varied estimates of the CFR, ranging from a low of 0.0004 percent (Wilson and Baker, 2009) to a high of 1.2 percent (Garske et al., 2009). Estimates of the reproduction number (R_0)—a measure of transmissibility reflecting the average number of secondary infections caused by each primary infection in the early part of an outbreak—for 2009-H1N1 influenza A have been less variable, Lipsitch noted, with many close to 1.5.[32] When his group incorporated corrections for missing data and variable reporting over the course of the pandemic into their calculations, they obtained a higher estimate of R_0 for the spread of the 2009-H1N1 influenza A virus, between 1.7 and 1.8 (White et al., 2009).

In an attempt to obtain better estimates of the severity of the 2009-H1N1 influenza A pandemic in the United States, Lipsitch and coworkers examined

[32]By comparison, estimates for the median R_0 for 1918 H1N1 in the United States range from 1.8 to 2.0 (Ferguson et al., 2005; Mills et al., 2004); some researchers think it may have been far higher at certain stages and locations of the pandemic, Lipstich noted (Andreasen et al., 2008).

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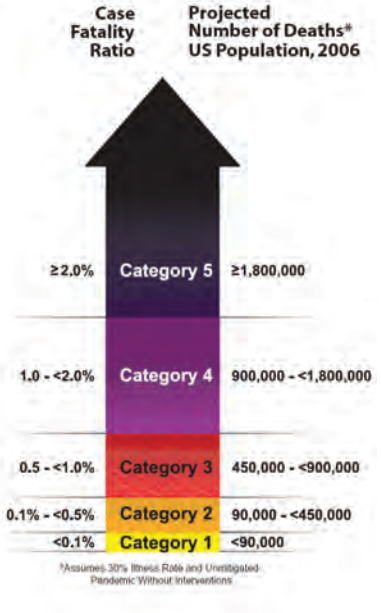

Interventions* by Setting	Pandemic Severity Index 1	2 and 3	4 and 5
Home **Voluntary isolation** of ill at home (adults and children); combine with use of antiviral treatment as available and indicated	Recommend†§	Recommend†§	Recommend†§
Voluntary quarantine of household members in homes with ill persons¶ (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient	Generally not recommended	Consider**	Recommend**
School **Child social distancing**			
-dismissal of students from schools and school based activities, and closure of child care programs	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
-reduce out-of-school social contacts and community mixing	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
Workplace / Community **Adult social distancing**			
-decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)	Generally not recommended	Consider	Recommend
-increase distance between persons (e.g., reduce density in public transit, workplace)	Generally not recommended	Consider	Recommend
-modify, postpone, or cancel selected public gatherings to promote social distance (e.g., postpone indoor stadium events, theatre performances)	Generally not recommended	Consider	Recommend
-modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended	Consider	Recommend

FIGURE WO-27 The pandemic severity scale developed by the U.S. government for planning and response.
SOURCE: HHS (2007).

several stages of the so-called "severity pyramid" depicted in Figure WO-28, using data on influenza cases and deaths from three different sources, each of which represented the most precise measure of a particular parameter of severity. Because the number of serologically-infected people is unknown, Lipsitch's group could not calculate a true CFR, but instead determined a symptomatic case fatality ratio (sCFR), or the number of deaths divided by the number of symptomatic cases. Their first estimate of sCFR for this data set, 0.045 percent, was ten times lower than an estimate based on data from New Zealand (Wilson and Baker, 2009). The lack of correspondence between these calculations was largely due to differences in estimates of the percentage of symptomatic patients who sought medical attention and the corresponding estimates of how many symptomatic cases had occurred. Using an alternate methodology, Lipsitch and coworkers considered the possibility that 12 percent of the population of New York City had experienced symptomatic H1N1 infection during the spring (corresponding to the proportion who had experienced ILI, as self-reported in a New York City phone survey during a period of high 2009-H1N1 influenza A activity). This methodology resulted in a lower estimated sCFR of 0.007 percent, closer to the

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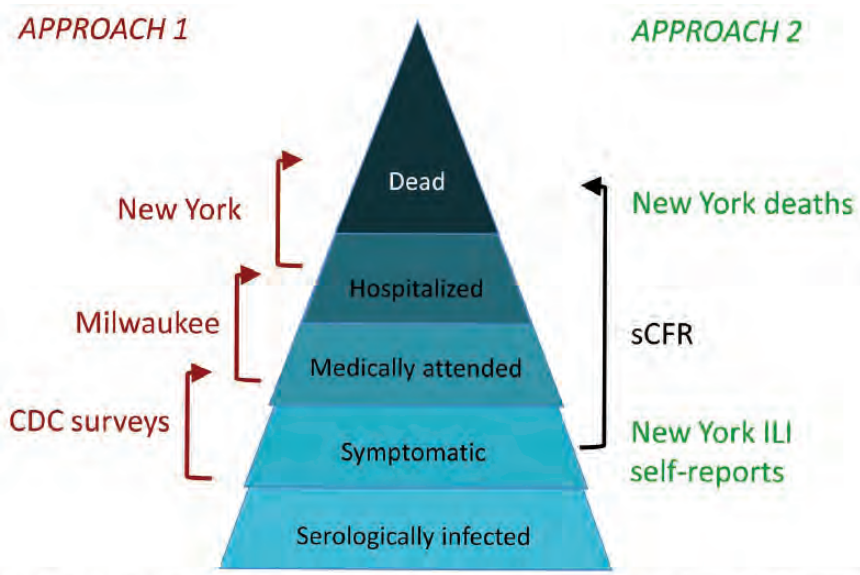

FIGURE WO-28 Severity pyramid.
SOURCE: Reprinted from Presanis et al. (2009).

New Zealand estimate of 0.005 percent (Table WO-2). The "true" ratio probably lies between these [two] numbers, Lipsitch said.

The most striking feature of the data presented in Table WO-2 is the range of severity estimates among the four age classes and, in particular, the disproportionate impact of the 2009-H1N1 influenza A pandemic on nonelderly adults (aged 18 to 64 years). This distinction from seasonal influenza—in which approximately 90 percent of the deaths are in people over 65, mainly due to complications rather than to the direct effect of influenza infection—makes comparisons between the potential impact of 2009-H1N1 influenza A infections with that of seasonal influenza challenging. Lipsitch noted, moreover, that the pandemic's severity will increase if the 2009-H1N1 influenza A virus evolves greater virulence; if secondary infections became more prevalent; or even if more elderly people become infected, as they would likely die in greater proportions due to comorbid conditions. "Barring any changes in the virus, I think we can say we're in a Category 1 pandemic (according to the scale in Figure WO-26) . . . [and] we're certainly under the 0.1 percent case fatality ratio," Lipsitch concluded. "That's really become clear in the last month or so."

However, as Forum member Michael Osterholm of the University of Minnesota pointed out, impact comparisons based on overall death rates tell only part of the story. If large numbers of people between the ages of 20 and 30 die, he

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TABLE WO-2 Age-Specific Severity Estimates

		sCHR: Ratio of Hospitalizations to Symptomatic Cases	sCIR: ratio of ICU Admissions to Symptomatic Cases	sCFR: Ratio of Deaths to Symptomatic Cases
Self-reported ILI denominator (NYC data only)	0-4 yr	0.33% (0.21-0.63)	0.044% (0.026-0.078)	0.004% (0.001-0.011)
	5-17 yr	0.11% (0.08-0.18)	0.019% (0.013-0.027)	0.002% (0.000-0.004)
	18-64 yr	0.15% (0.11-0.25)	0.029% (0.021-0.040)	0.010% (0.007-0.016)
	65+ yr	0.16% (0.10-0.30)	0.030% (0.016-0.055)	0.010% (0.003-0.025)
	Total	0.16 % (0.12-0.26)	0.028% (0.022-0.035)	0.007% (0.005-0.009)
Self-reported frequency of seeking care (NYC/Milw/CDC data)	0–4 yr	2.19% (0.85-5.73)	0.275% (0.097-0.777)	0.022% (0.005-0.088)
	5–17 yr	0.53% (0.27-1.34)	0.088% (0.043-0.240)	0.009% (0.003-0.030)
	18–64 yr	2.66% (1.35-5.56)	0.458% (0.230-1.019)	0.136% (0.065-0.311)
	65+ yr	0.57% (0.11-12.78)	0.100% (0.016-2.185)	0.028% (0.003-0.0672)
	Total	1.37% (0.68-2.52)	0.222% (0.022-0.035)	0.045% (0.020-0.081)

NOTE: These estimates have changed slightly following revision of the work, and updated numbers will be available at the following website and in the published version of the paper.
SOURCE: Reprinted from Presanis et al. (2009).

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observed, influenza will assume the role of a major global killer, and it will produce untold "collateral damage." "Nobody is thinking what might happen to U.S. or global supply chains when pandemic flu hits [developing] countries, where the primary workforce are the young, who are most affected by the virus," Osterholm told *Nature* (Bertozzi et al., 2009). Despite the dire predictions of many about the mortality associated with the 2009-H1N1 influenza A pandemic, it is proving to be the mildest influenza pandemic on record (Presanis et al., 2009).

Lessons for surveillance Notwithstanding the extraordinary international effort to address 2009-H1N1 influenza A, Lipsitch observed that epidemiological data remain inadequate in terms of both quality and completeness. With severity measures still uncertain to an order of magnitude, public health is limited to general approaches, rather than precise ones, to optimizing interventions, he said. Improvements in influenza surveillance will be needed in order to reduce uncertainty and support a rapid, precise, evidence-based response.

When asked by a workshop participant whether it might be possible to establish a system to generate high-quality epidemiological data in the event of disease emergence, Lipsitch replied that, having given this possibility considerable thought, it is most important to be able to determine how many people become infected during an epidemic. "We don't know how many people really had influenza-like illness, and I think part of the problem is that we don't have any kind of centralized way to track that," he explained. Various approaches have been suggested for establishing such a capacity, he added. They include repeated, routine, telephone surveys to gauge ILI and care-seeking behavior, and, calculating a population-based estimate of medically-attended cases, as is done in New Zealand and the United Kingdom (cases are typically reported as a percent of visits in the United States). Lipsitch added that he was encouraged by the CDC's significant expansion of surveillance capacity to address 2009-H1N1 influenza A, but wondered aloud whether this momentum could be sustained once the pandemic passes.

Research in Real Time

In a commentary published in *Science* in early May 2009, Fineberg and Wilson (2009) recalled the 1976 swine flu outbreak at Fort Dix and reminded readers that "scientists and policy-makers have often failed to take advantage of the opportunity to learn and adjust policy in real time." Decision makers at that time failed to consider—and investigate—additional information that might have led them to a different course of action, the authors observed. Thus, they urged the pursuit of "real-time answers" to scientific questions in five areas critical to policy making regarding 2009-H1N1 influenza A: pandemic risk, vulnerable populations, available interventions, implementation possibilities and pitfalls, and public understanding. Similarly, Forum chair David Relman, of Stanford Univer-

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sity, advocated the practice of something he called "as you go science," which he defined as "applied science in the true sense of designing experiments with imperfect information, with hastily formulated hypotheses . . . and then incorporating the results into rational decision making that is well communicated."

Scientists, as well as decision makers, must fight their tendency to react to the most recent threat—which, prior to the emergence of 2009-H1N1 influenza A, was considered to be H5N1 influenza, observed speaker Jesse Goodman, Chief Scientist of the FDA. Instead, they must continually assess the current situation and identify the assumptions under which they operate, he advised. In his remarks to the workshop concerning the scientific research agenda for the 2009-H1N1 influenza A virus, Goodman recognized the many-pronged effort to produce, evaluate, and improve vaccines, and the potential of this work to answer current questions, such as, "Why is one dose sufficient, and why do people without preexisting immunity respond so well?" He also noted the need to conduct "practical science," which he defined as research that produces clinical guidance, on such topics as respiratory protection (as discussed in the next section, "The Public Health Response"). He further contended that there is not enough investment in such "mundane but crucial" research that benefits public health.

Shortridge, at the conclusion of his presentation on the epidemiology of 2009-H1N1 influenza A in Asia, defined four sets of pressing scientific questions raised by the pandemic. First, he said, what we know about the virus so far should lead us to further investigate the H1 subtype, the swine "mixing vessel" hypothesis, and the question as to whether 2009-H1N1 influenza A can act as a "third-party" virus to carry important genes to prevailing seasonal influenza viruses. It should also focus surveillance efforts on viral emergence "hot spots" in order to detect reassortment events involving 2009-H1N1 influenza A, he said, echoing a comment made by Peter Daszak in his prepared remarks.

Second, because the virus's evolutionary origins suggest patterns of HA antigen "recycling," Shortridge said, "it's about time for H2 to come back if it's going to come back, so we ought to be looking out for H2 antibodies." To do so, he advocated a systematic global serological study of those born after 1957—a project he acknowledged was "a bit of a tall order" as it would require "a massive, well-structured, well-organized system using one diagnostic technique so that results could be compared."

Third, Shortridge encouraged comparative structure-function analyses of pandemic viruses in order to determine factors that result in global transmission (and which answer the question, given ecological conditions in China and in other hot spots for emergence, "Why don't we have a new pandemic every year?"). These studies would include analysis of HA antigenic epitopes, escape mutants, antigenic characteristics associated with persistence in the host, and "non-receptor factors," such as pathogenesis or the three-dimensional conformation of the HA molecule, that might provide the boost in transmission efficiency that turns a virus into a pandemic strain.

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Fourth, given limited supplies of vaccine and antiviral drugs in the event of a pandemic, Shortridge advocated the evaluation of immunomodulatory agents, such as statins, fibrates, and glitazones,[33] as a second line of defense (see the next section for additional discussion of this topic). "My vision is very straightforward," he said, as he concluded his presentation. "It always has been since I went to Hong Kong, and that is no more pandemics. That's the only way I see flu. It's quite simple. No pussyfooting around with the niceties; no more pandemics."

The Public Health Response

As Fukuda observed in his keynote address, the first five months of the first pandemic of the twenty-first century were extraordinarily productive. Much was learned about the 2009-H1N1 influenza A virus and the disease it causes (as described in the previous two sections) and about approaches to controlling it, which will be discussed next. Paramount among these approaches is immunization. As of early 2010, the H1N1 influenza A vaccine is now becoming available to the general public. At the time of the workshop, several technical decisions related to vaccine production and distribution remained under consideration. Fukuda noted, however, that the most fundamental issue to be resolved—one that is far too complex and fraught to be settled before this pandemic runs its course—is how much access developing countries will have to a pandemic vaccine as well as to antiviral medications and other means of mitigating a pandemic's impact. This issue, which Fukuda framed as one of "global solidarity," galvanized workshop discussions regarding global and national public health responses to the 2009-H1N1 influenza A pandemic.

Workshop participants also considered smaller-scale impacts of the 2009-H1N1 influenza A pandemic: on cities and their public health departments, on hospitals and their staffs, and on individual patients and their family members. Much has been learned about the public health response to pandemic influenza in these settings and the challenges and opportunities to be met as the 2009-H1N1 influenza A virus returned to the Northern Hemisphere after a not-so-quiet summer. Fukuda's description of the global stage, set for 2009-H1N1 influenza A's next act, is therefore equally descriptive at the local scale: "I think it's fair to say that as difficult as the first several months have been, in a lot of ways it's the easier part of the pandemic," he observed. "We're entering into a period where the issues are now becoming much more complex and difficult to deal with."

Infection Control

Infection control practices are focused on hospitals, which tend to be amplification centers for infectious diseases, noted Bell of the CDC. Consider emerg-

[33]Also known as Thiazolidinediones, a class of antidiabetes drugs that promote cell sensitivity to insulin and increase glucose uptake by cells (San Francisco AIDS Foundation, 2009).

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ing infectious disease such as SARS or Ebola hemorrhagic fever, he said: such diseases may smolder in a population for months or years before a hospital case produces a noticeable outbreak. To prevent or control such threats, Bell noted, several levels of infection control are practiced in hospitals. *Standard precautions*, such as gloves, gown, and mask, prevent infections due to direct contact with pathogens. *Universal precautions*, originally developed to prevent transmission of the HIV virus, treat all body fluids as infectious. *Transmission-based practices* protect against infection by specific diseases known to be spread either through the air, by droplets, or by direct contact.

The distinction between airborne and droplet-borne diseases has important implications for infection control, Bell explained. Droplets, spread by coughing, are generally thought to spread in an arc over distances of three to six feet; masks and other means to block droplets from contact with the mucosa are recommended for infection protection. To protect against the airborne pathogens that cause diseases such as chickenpox, tuberculosis, and measles—which can remain viable, suspended in the air, for hours—requires special air handling procedures such as negative pressure rooms, which protect people in a building from an infected occupant of one room by preventing airborne particles generated in the room of an infected patient from escaping the sickroom into the surrounding environment.

Current recommendations for infection control for seasonal influenza include standard plus droplet precautions, Bell said. However, since initial 2009-H1N1 influenza A precautions were based on pandemic plans designed for H5N1 influenza (expected to be a much greater threat than seasonal influenza), they included single patient rooms (though without special air handling); standard and contact precautions; wearing a respirator when entering a patient room; isolating patients for seven days from onset of symptoms; negative pressure isolation in addition to respiratory protection for aerosol-generated procedures such as bronchoscopy; and encouraging hospitals to increase monitoring and to furlough healthcare personnel who become ill.

Now, having found that the vast majority of 2009-H1N1 influenza A cases do not require hospitalizations—and particularly since some infected patients are asymptomatic—it is clear that infection control alone is insufficient to prevent the virus from being imported into hospitals and other healthcare settings, Bell said. “There’s a huge challenge to be dealt with when individuals are becoming infected by their kids at home, by their fellow commuters, by simply being a member of the population,” he observed. Instead of coming in with recognized, symptomatic patients, 2009-H1N1 influenza A arrives in hospitals through multiple portals, one of which is the front door. “Logistically speaking, the needs for healthcare protection with [2009-H1N1 influenza A] are substantially different from what we’ve seen in the past,” he acknowledged.

It remains to be determined where the pandemic strain of the 2009-H1N1 influenza A and other influenza viruses lie along the transmission continuum between droplet and airborne, and this has a bearing on infection precautions,

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Bell continued. The epidemiology of a pathogen transmitted by droplets would be difficult to distinguish from one transmitted by very short distance inhalation, he observed, leaving open the question as to whether a respirator is needed or not (Loeb et al., 2009). He noted that some researchers, using personal samplers for particulates, have detected airborne influenza viruses in clinical settings, but the viability of the viruses was not tested, nor were samples taken "in the community, in the parking lot, or anywhere else," for comparison. Animal studies demonstrate the transmission of the 2009-H1N1 influenza A virus, presumably by inhalation, over two to three meters (Itoh et al., 2009). Epidemiological studies such as a recent description of 2009-H1N1 influenza A virus transmission within a Chinese tour group (Han et al., 2009) suggests that speaking with an infected person (as opposed to sitting close by in a bus for several hours) significantly raises one's risk for infection.

To study the "gray zone" between droplet and airborne transmission, Bell and coworkers are building a system that will allow them to aerosolize infectious organisms and measure their loss of viability over hours or days, as a basis for infection control practices. "I don't want to have a different set of recommendations for every pathogen," he added, "but for a handful of important ones, maybe we do want [to be] specific. We do it for tuberculosis, so this is a [further] step in that direction." In the meantime, Bell said, the CDC recommends respiratory protection and special air handling for aerosol-generated procedures involving patients infected with 2009-H1N1 influenza A virus—a practice he would like to see as a standard precaution for all procedures, as it is in autopsies. Bell also suggested that surgical and respirator masks should be improved, possibly by combining them to produce a single product used throughout medical care, and that better-ventilated clinical facilities would make the environment less risky for staff members. He outlined the following goals for an "ideal approach" to infection control which would

- reduce risk for healthcare personnel;
- minimize negative effects on patient care;
- be acceptable to healthcare personnel (i.e., adherence likely);
- be implementable by healthcare facilities;
- be consistent with public health approaches in other settings; and
- be appropriate for demonstrated severity of infection.

Nonpharmaceutical Interventions

Nonpharmaceutical interventions against infectious diseases are intended to slow the spread of infection. They include isolating ill people and quarantining their suspected contacts, closing schools and businesses, and canceling public gatherings (Markel et al., 2007). Unlike medical interventions against pandemic disease, which by reducing illness and death also reduce the likelihood of social

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disruption, nonpharmaceutical interventions are undeniably socially disruptive. They must be carefully tuned to maximize their health benefits and minimize the problems they cause for individuals and communities, according to speaker Martin Cetron of the CDC (see Appendix A1). Nonpharmaceutical strategies cannot "stop a pandemic in its tracks," he said, but they can spread a surge in cases over a longer period of time, which relieves peak burden on healthcare and other critical infrastructures. Such interventions may also reduce attack rates, and thereby, reduce the attendant morbidity and mortality associated with a highly communicable disease.

Cetron described his recent work with Howard Markel and colleagues, of the University of Michigan, that compared the apparent effectiveness of nonpharmaceutical interventions undertaken singly and in various combinations in 43 different U.S. cities during the influenza pandemic of 1918-1919 (Markel et al., 2007). Most of the cities used a combination of strategies, and some applied them in a more timely way than others, resulting in a widespread difference in mortality among them, Cetron said. "The variability that we saw in 1918, I think we will continue to see with this much less severe pandemic in the United States," he predicted.

Cetron and his colleagues found that *no single intervention* effectively slowed transmission of infection in the 1918 pandemic but that when several interventions were used together—and particularly when they were instituted early on in the infection's course in a community and sustained—they appeared to mitigate the impact of the pandemic (an effect Cetron likened to layering slices of Swiss cheese until every hole is covered). Timely, sustained, layered interventions were associated with reduced and delayed peak transmission, and also with reduced morbidity and mortality, Cetron reported. Twenty-three of the cities essentially served as their own controls, he added, for they relaxed the interventions when the first wave of disease subsided (most often, this meant reopening schools), only to succumb to a second, more intense, outbreak of illness and death. Several other studies have noted significant reductions in pandemic impact associated with school closings, Cetron noted. For example, he said, Cauchumez and colleagues (2009) suggested that closing schools could reduce the total number of influenza cases by 15 percent, and peak attack rates by 40 to 50 percent.

Focusing on schools, Cetron noted their uniquely high "social density," with an average of less than four feet between people (Stern et al., 2009). During the spring wave of the 2009-H1N1 influenza A pandemic, he and colleagues monitored school closures during the brief period (April 27 to May 2) during which the CDC recommended the dismissal of schools with confirmed cases, affecting at least 600,000 students; a 5-day closure followed by reassessment was recommended. "It wasn't going to stop this pandemic from moving," he acknowledged, but at that stage, school closure could plausibly protect school-age children and their families, particularly if they included vulnerable individuals, from high rates of infection. To this end, Cetron said, school closures

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appear to work if they are undertaken early, before absenteeism begins to climb to 25 percent or more.

However, he added, one also needs to ask whether closure is justified on the basis of the severity of the disease, not just the number of cases, and whether it is truly feasible. "There are many unintended consequences that have to be addressed and offset for this tool to be considered seriously for future use in a more severe event," he concluded. He noted that several studies have been initiated (and many are ongoing) to examine the costs and benefits of school closure (Cauchemez et al., 2009). These include a comparison of Dallas, where schools closed for seven days during the spring wave of 2009-H1N1 influenza A, and neighboring Tarrant County, Texas, where schools remained open. The CDC also conducted household surveys in areas where schools closed in order to gauge the level of social disruption, which in many areas was less than expected, Cetron observed. Given the mildness of the illness, "if things had gone on much longer, it would have been much more challenging," he speculated. On the other hand, he noted how quickly the number of cases declined in areas as school dismissed for the summer, and again how quickly cases mounted as school returned to session.

Clearly there were many adverse effects of school closures, he continued; these were highlighted in the CDC's guidance document on school closure (CDC, 2009a) and in a Harvard public opinion poll conducted in June (Harvard School of Public Health, 2009). In the latter, 51 percent of respondents said they would have to miss some work if schools closed and as a result would experience loss of pay or worse, of their job or business. Based on these findings, and deliberations over the summer, CDC revised its school closure guidance for the fall, Cetron said. Updated guidance for schools, daycare centers, and colleges and universities, along with a series of checklists and toolkits, are available online.[34]

Communicating the strategies and goals—and the uncertainties—of pandemic mitigation practices and guidance to the public is a challenging task, as Cetron and many other workshop participants noted, and doubly so for nonpharmaceutical interventions. "There is clearly a preference for 'magic bullet' interventions over these traditional public health ones," the toughest being for adults and children to stay home when they are ill. The timing and duration of nonpharmaceutical interventions are also critical to their success, he added, and they must be continually evaluated and adjusted to maintain a positive benefit-to-risk ratio. Early overreactions can be "dialed back," as happened in the United States once the severity of the disease—or lack thereof—became apparent. This, he argued, was a far better scenario than if initial indications of severity were accurate and no early actions were taken.

[34]See http://www.cdc.gov/h1n1flu/groups.htm.

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Antiviral Drugs

The WHO has recently issued guidance (WHO, 2009g) on the use of antiviral drugs for influenza that includes a consideration of the current susceptibility patterns of pandemic H1N1 virus, situations in which viruses with different susceptibility types might co-circulate, and where there is potential for sporadic zoonotic infections, according to speaker Frederick Hayden of the University of Virginia. The 2009-H1N1 influenza A virus is susceptible to the neuraminidase inhibitors oseltamivir and zanamivir but resistant to the M2 inhibitors amantadine and rimantadine—in contrast to the seasonal H1N1 virus, which is resistant to oseltamivir and sensitive to amantadine and rimantadine (with the exception of a few resistant isolates). The possibility of multiply-resistant pandemic H1N1 viruses might result from reassortment among these two H1N1 viruses or emergence of a transmissible, oseltamivir-resistant pandemic H1N1 strain. Sporadic instances of oseltamivir resistance have been found in pandemic H1N1 viruses; however, without evidence of community transmission to date. In addition, there has been no evidence of reassortment of the neuraminidase or other genes between the pandemic and the seasonal H1N1 viruses.

Both the WHO and the CDC (2009g) had recently updated their guidelines for antiviral use for the treatment and prevention of influenza, Hayden reported, and both focused on early, empiric treatment of persons in risk groups including pregnancy, people (both at-risk and otherwise healthy individuals) with clinical evidence of severe or progressive disease (those showing warning signs of lower respiratory tract involvement), and hospitalized patients. In countries with sufficient antiviral supplies, treatment is also an option for previously healthy persons with apparently uncomplicated illness. Oseltamivir was clearly identified as the pharmaceutical drug of choice by the WHO in patients with serious lower respiratory infections (as occurs in severe cases of 2009-H1N1 influenza A) due to its availability and the dearth of data regarding both tolerability and activity of inhaled zanamivir. Such patients, Hayden added, require high doses and prolonged antiviral therapy. The WHO recommendations were made primarily on the basis of *in vitro* susceptibility studies with the pandemic virus and of experiences in management of seasonal and H5N1 influenza illness, he said. They are supported, however, by more recent data, including the results of animal studies by Kawaoka's group (Itoh et al., 2009), described earlier in this summary, and emerging clinical experience in pandemic H1N1 patients.

A study conducted in Viet Nam followed 300 patients with confirmed mild to moderate 2009-H1N1 influenza A infections who were given a standard dose of oseltamivir then sampled for viral RNA or infectious virus to examine how long the virus survived (van Doorn, 2009). Viral RNA was uncommonly detected in the upper respiratory tract in these patients following antiviral treatment. Among the small number of individuals with a detectable a viral RNA signal up to 12 days after starting oseltamivir treatment, none were culture positive or found

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to carry oseltamivir-resistant virus. Hayden noted, however, that other patient populations—particularly those with severe infections—did not show such robust responses to oseltamivir. For example, from informal reports he had learned of several patients with severe disease who carried infectious virus for weeks following oseltamivir treatment. These cases highlight the importance of developing more effective antiviral therapies for influenza, Hayden observed, particularly for severely ill patients.

Poor outcomes and fatalities in hospitalized patients (e.g., pregnant women) with severe cases of 2009-H1N1 influenza A have been strongly associated with delayed antiviral treatment (Jain et al., 2009; Jamieson et al., 2009; Louie et al., 2009a; Napolitano et al., 2009; Shannon et al., 2009)—thus the recommendation to treat such high-risk persons as soon as possible after the appearance of symptoms. Some patient studies in seasonal influenza and H5N1 suggest that even late antiviral intervention can be beneficial as long as viral replication is ongoing, Hayden said. In seasonal influenza, three retrospective studies found significant reductions in all-cause mortality in hospitalized patients treated with oseltamivir within about 96 hours after symptom onset (Hanshaoworakul et al., 2009; Lee et al., 2008; McGeer et al., 2007).

A recent modeling study by Lipsitch and colleagues (Goldstein et al., 2009) suggests that predispensing of up to 20 percent of the antiviral stockpile to high-risk patients during an influenza pandemic would likely result in a net savings of life, and this strategy to ensure early access to treatment for high-risk patients warrants further discussion.

Prophylaxis with oseltamivir appears to be effective against pandemic 2009-H1N1 influenza A illness, according to Hayden, but it also appears to be associated with a higher frequency of gastrointestinal complaints (Wallensten et al., 2009) and prophylaxis failure due to resistance than that observed in older studies in seasonal influenza. For example, the first report of likely pandemic H1N1 oseltamivir resistance transmission occurred in close cases at a North Carolina camp where the antiviral was used prophylactically (CDC, 2009c). There was no evidence, however, for further person-to-person spread of resistance beyond cabin mates within the camp. Indeed, between September 1, 2009, and January 2, 2010, there have been only about 42 (CDC, 2009i) sporadic, mostly geographically dispersed detections of oseltamivir-resistant cases of 2009-H1N1 influenza A reported, all of which have had one common neuraminidase mutation (His 275 Tyr) that confers high-level oseltamivir resistance in N1-containing viruses, as well as the two isolates identified in the North Carolina cluster that shared a second mutation in the neuraminidase, Hayden noted. While the majority of these oseltamivir-resistant viruses were detected in treated persons, particularly immunocompromised hosts with prolonged replication of virus and associated oseltamivir treatment, instances were also detected in several persons without drug exposure and more often among persons failing post-exposure prophylaxis. Most instances of oseltamivir resistance resulted in mild, self-limiting illness, except for complications in sev-

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eral children and serious disease in immunocompromised patients (Englund et al., 2009). Intravenous zanamivir has been used as salvage therapy[35] in several severely ill patients with proven or suspected oseltamivir resistance (Englund et al., 2009; Kidd et al., 2009).

In this regard, the August 7th PCAST report on U.S. preparations for 2009-H1N1 influenza A includes two key recommendations regarding antiviral drug development: to expedite the licensing of intravenous formulations of antivirals and to stimulate the development of new drugs with novel mechanisms of action against influenza in order to reduce the potential for antiviral resistance (PCAST, 2009).

Hayden described several anti-influenza agents currently under investigation:

- intravenous formulations of neuraminidase inhibitors, zanamivir, peramivir, and oseltamivir. Intravenous peramivir recently became available by Emergency Use Authorization (CDC, 2009h) for hospitalized patients and intravenous zanamivir is available through an emergency Investigational New Drug (IND) process in the United States;
- a long-acting neuraminidase inhibitor designated CS-8958, under study for use by inhalation;
- agents directed against other targets involved in influenza virus replication, including T-705, a polymerase inhibitor, and DAS181, an attachment inhibitor; and
- combination therapies with currently available and investigational agents, which have appeared promising in animal models but which have received limited clinical study (Hayden, 2009). The combination of T-705 and oseltamivir has appeared to be especially promising in murine models (Severson et al., 2009).

Hayden also described several proposals for immunomodulatory therapies, including the use of:

- convalescent blood products, which were used with apparent success to treat pneumonia patients during the 1918–1919 influenza epidemic (Luke et al., 2006) and have been used in individual patients with severe H5N1 illness and which have been proposed for use in the event of a pandemic;
- heterosubtypic neutralizing monoclonal antibodies recovered from human IgM memory cells (Throsby et al., 2008), which are active against multiple group 1 hemagglutinin subtypes (e.g., H1, 2, 5, and 9 viruses); and

[35]A final treatment for people who are nonresponsive to or cannot tolerate other available therapies for a particular condition and whose prognosis is often poor (http://www.medterms.com/script/main/art.asp?articlekey=9380, accessed December 15, 2009).

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- immunomodulatory therapy with agents such as statins, fibrates, in glitazones (Fedson, 2009), and cyclooxygenase 2 inhibitors (Zheng et al., 2008). Controlled studies of statins as adjunctive therapy are planned in patients with influenza-associated acute lung injury. However, Hayden stressed that some immunomodulators like corticosteroids could have deleterious effects on viral replication as well as other adverse effects, that immunomodulators should be studied in conjunction with effective antiviral therapy, and that a much better understanding of pathogenesis of severe disease secondary to pandemic H1N1 is needed to guide selection of the best interventions to study.

Vaccines

Following the identification of 2009-H1N1 influenza A viruses in California children in mid-April (2009), an intense effort produced vaccine candidate viruses by May 27, 2009, according to the CDC's Cox. "We were able to get them out the door even before the safety testing was done by working globally with all of our partners in a very efficient way," she recalled. By June 9, the WHO had completed safety studies of the vaccine candidate viruses in ferrets. Additional candidate viruses have been produced since then, she said, because the initial isolates proved inadequate for vaccine manufacture.

Several studies undertaken by the CDC and other agencies determined that seasonal influenza vaccine provides no protection against 2009-H1N1 influenza A. However, Cox added, people who received the 1976 swine influenza vaccine did develop a robust antibody response to the 2009-H1N1 influenza A viruses, as determined by in vitro studies of stored serum. "We feel that it's really nearly impossible to study those who had the vaccine in 1976 and look at their antibody levels now," she said. "Most people don't even remember if they had the vaccine or not, and it would be probably more trouble than it would be worth because we wouldn't make recommendations that those individuals should not receive vaccine." As previously noted, the CDC cross-reactivity study (among others) found that about 30 percent of adults born before 1950 had preexisting cross-reactive antibodies to 2009-H1N1 influenza A, and that cross-reactive antibody levels increased slightly in these older adults following vaccination with seasonal influenza vaccine (Hancock et al., 2009).

At the time of the workshop, Treanor calculated that the "enormous profusion" of 2009-H1N1 influenza A vaccine clinical trials listed on clinicaltrials.gov included 38 studies, with a planned enrollment of more than 30,000 subjects. All of the studies were evaluating two-dose schedules, reflecting the reasonable assumption that, due to the antigenic divergence of 2009-H1N1 influenza A from the seasonal H1N1 virus, a priming and boosting dose would be needed to generate sufficient immunity in the population, Treanor explained. However, evidence emerged over the summer that most people, regardless of age, mounted a vigor-

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ous immune response to a single dose of unadjuvanted 2009-H1N1 influenza A vaccine (Greenberg et al., 2009). Studies in the United States also showed that, within 14 days of a single dose, subjects generated antibody titers comparable to those achieved with seasonal influenza vaccine, he added. Given this response, Treanor observed, adjuvants might not provide significant dose-sparing for the 2009-H1N1 influenza A vaccine (Greenberg et al., 2009).

Of the vigorous immune response to 2009-H1N1 influenza A vaccine, Treanor said, "I think the only conclusion you can reach from this is that seasonal H1N1 exposure primes for a rapid antibody response to novel H1N1." He and coworkers are therefore investigating the putative mechanism for H1 priming, trying to determine the features that control it, whether shared epitopes are important to priming, and whether priming can be predicted by measurement of baseline immunity.[36] Treanor noted that studies conducted in the 1970s found that prior exposure to H3 and H2 do not prime for a response to H1.

At the time of the workshop, Treanor reported that 2009-H1N1 influenza A vaccines currently licensed in the United States included inactivated subvirion vaccines, manufactured by CSL Limited,[37] Sanofi Pasteur, and Novartis, and live attenuated vaccine, manufactured by MedImmune. Licensure for these vaccines followed the same process as the annual updating of the seasonal influenza vaccine, he said, although clinical data continue to be collected on the 2009-H1N1 influenza A vaccine. In children, live influenza vaccines are more efficacious as compared with inactivated vaccines, Treanor said. Children need two doses of either type, but for different reasons: in the case of live vaccines, two-dose schedules were developed to eliminate interference between vaccine components, he explained, rather than to prime and boost, as is the case in inactivated vaccines administered to children and other naïve patients.

Regarding the question of whether the 2009-H1N1 influenza A vaccine should be administered before, after, or in conjunction with the seasonal vaccine, Treanor observed that there is little evidence on which to base such a recommendation, although he noted that individuals in a multivariate analysis who reported having received seasonal vaccine had statistically significantly lower responses to the H5 antigen, which has led to concerns that receiving the seasonal vaccine first will somehow diminish response to the 2009-H1N1 influenza A vaccine. "Some of the studies that NIH is doing are directly addressing that question," he said.

The CDC has taken several steps to address concerns about the 2009-H1N1 influenza A vaccine arising from the association of GBS with the 1976 swine influenza vaccine, according to Cox. First, they compared the HA and NA antigens of the New Jersey 1976 virus with those of the 2009-H1N1 influenza A

[36]Xing and Cardona (2009) note that "it is rational to expect that CMI does provide a protective role, and cross-reactive CMI to pandemic (H1N1) 2009 virus through conserved MHC class I-restricted epitopes may exist in persons previously vaccinated for or exposed to seasonal influenza."

[37]CSL Limited; Parkville, Victoria, 3052, Australia.

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vaccine candidate at the nucleotide and the amino acid level, which they determined to differ by 11 and 8 percent, respectively. This is a significant difference, exceeding the genetic distance between the currently circulating H3N2 viruses and their 1975 predecessors, she said. More important, she noted that the CDC plans to conduct enhanced surveillance for GBS as well as for other adverse events associated with the 2009-H1N1 influenza A vaccine. "We certainly don't want to focus exclusively on GBS," Cox emphasized, "but we want to be able to capture adverse events [and] we want to know what the background rate is for the adverse events that we might expect, including other neurologic adverse events that are potentially associated with vaccines." Thus, she continued, the CDC has coordinated with the FDA, the WHO, and other partners to enhance surveillance for adverse events temporally associated with vaccination. "We are trying to put in place plans to very rapidly investigate whether there might be a causal association if a signal is detected," she explained.

In addition, Cox said, the CDC is "working very, very hard on communications, because we know how absolutely essential clear, transparent communications are to the public in order for us to have a successful vaccination campaign." Nevertheless, as she and several other participants acknowledged, there will inevitably be fallout from the temporal association of the 2009-H1N1 influenza A immunization campaign with a variety of poor—but statistically insignificant—health outcomes, as has occurred for several effective vaccines in current use.

Treanor considered several technological innovations under investigation that could speed development of future pandemic vaccines. For example, he said, the 2009-H1N1 influenza A vaccine virus is currently being grown in experimental cell cultures, as well as in eggs. Treanor's group has explored the expression of HA in insect cells under the control of a recombinant baculovirus in order to generate a subunit vaccine, which he said has properties similar to inactivated vaccine. An Australian company is currently testing a 2009-H1N1 influenza A subunit vaccine, according to Treanor, and they have also reported very vigorous responses to a single dose of recombinant hemagglutinin vaccine against 2009-H1N1 influenza A. It is also possible to express both the HA and the NA antigens along with M antigen[38] in insect cells, to produce highly immunogenic virion-like particles, he said; similar approaches involve the decoration of phages with multiple antigens. HA can also be expressed, linked to flagellin in *E. coli*, to generate a functional antibody response, he reported. "The potential emergence of pandemic viruses has stimulated an enormous amount of product development," Treanor concluded, including "an incredible number of ways of delivering vaccine antigens."

[38]M antigen: An antigen found in the cell of *Streptococcus pyogenes*; associated with virulence.

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Political, Legal, Ethical, and Public Considerations

Several workshop presentations and discussions addressed the social context of the public health response to the 2009-H1N1 influenza A pandemic, which extend from the global perspective of international law and politics to the ethics of clinical practice and its effects on individual patients, their families, and their care providers.

Pandemic influenza and global health governance In his keynote address, Fukuda observed that the International Health Regulations (IHR) provided a solid framework for global discussions of the 2009-H1N1 influenza A pandemic, which began with the detection of the first cases. This was an important goal of the IHR, the legal framework for global cooperation on infectious disease surveillance,[39] following its fundamental revision in the aftermath of the SARS pandemic (IOM, 2007b; Stern and Markel, 2004; WHO, 2005a).

The 2009-H1N1 influenza A pandemic also arrived on the heels of a major challenge to the IHR, and to global public health governance in general. In 2006, Indonesia refused to share samples of the H5N1 avian influenza virus, collected within the country, with the WHO's H5N1 influenza surveillance team (IOM, 2010). The Minister of Health pointed out that developing countries were not in a position to be able to access benefits from such viruses, such as vaccines, in the same way as developed countries and that this situation was inherently unfair and unacceptable. This general perspective was shared by many other countries. Claiming "viral sovereignty" over these samples, the country announced that it would not share them until the WHO and developed countries established an equitable means of sharing the benefits (e.g., vaccines and antiviral drugs) that could derive from viruses collected within its borders. Indonesia criticized the WHO's practice of distributing influenza viruses it received for surveillance to pharmaceutical companies, which would make patented vaccines from such samples—vaccines that were often too costly for developing countries to purchase.

Proposals to use the IHR as a means to force Indonesia to share H5N1 virus samples for global surveillance purposes failed, because the IHR do not (1) require the sharing of biological samples, and (2) address inequitable access to the benefits derived from such samples, according to speaker David Fidler of Indiana University. Instead, WHO member states passed a resolution at the World Health Assembly in 2007 to initiate a series of intergovernmental meetings to discuss, debate, and develop a new framework for the sharing of influenza viruses and benefits derived from them. Fukuda reported that this intergovernmental process ended in 2009 without complete agreement due to the complexity and

[39]Article 2 of the IHR (2005) states that the primary purpose of the IHR (2005) is to "prevent, protect against, control, and provide a public health response to the international spread of disease commensurate with public health risks, and which avoid unnecessary interference with international traffic and trade" (WHO, 2005a).

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fundamental nature of the issues surrounding this controversy. Nevertheless, he contended, it is both possible and essential to complete a framework to resolve these issues in a socially just and equitable way.

"In many ways this pandemic we are going through right now is the best case scenario," Fukuda observed, noting its relative mildness and its onset in developed countries. "I don't think this is the kind of situation that we can count on in the future." He went on to observe that not only must the virus-sharing dispute be settled in order to promote global equity, justice, and solidarity, but also from a practical standpoint: when a severe pandemic emerges, the world needs to be ready to address it as a global public health threat, not a political conflict. If a worse scenario were to develop with higher rates of mortality and social disruption, it is less likely that developed countries would be willing to distribute vaccines to others as ad hoc donations, and any negotiations would likely be very time consuming, potentially reducing the attention given to ameliorating the pandemic. In the interim, the WHO will respond to the current pandemic by sharing the 150 million to 200 million doses of vaccine pledged to it by member countries and manufacturers. Fukuda reported that the WHO is actively engaged in ongoing negotiations to secure more vaccine and that the WHO plans to distribute vaccine first to health workers in the least-developed countries. The first shipments of vaccine donated by drug manufacturers to developing countries arrived in Mongolia on January 7, 2010, followed a few days later by shipments to Azerbaijan and Afghanistan. However, while the vaccine supply in developed countries is beginning to catch up with or exceed demand, none of the countries that pledged to donate vaccine have fulfilled that promise, including the United States (PBS, 2010).

Fidler, who presented a detailed analysis of the process and incentives for creating a global framework to share viruses and their benefits, observed that this endeavor faces many serious obstacles (see Fidler in Appendix A4). First among these are the skeptical views of such a framework that arise among foreign policy makers who wonder why—given global disparities in just about every other kind of health resources including clean water and adequate food—influenza vaccines and antiviral drugs should receive greater priority in terms of global equity, solidarity, and justice. Foreign policy makers may also worry that even if developing countries are given access to these medical resources, they will be wasted because of weak infrastructures in developing countries, or worse, misused, encouraging antiviral resistance.

Overcoming such skepticism and building an effective global access framework demands careful attention to political and legal considerations, Fidler stressed. On the legal side, he analyzed existing international health agreements and regimes (e.g., the IHR, the International Vaccine Institute) and how they might contribute to this goal, as well as other efforts that have increased access to vaccines and drugs for other diseases (e.g., the United Nations Children's Fund [UNICEF]). According to Fidler, none of these approaches offered useful

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models for a global network on increasing access to influenza vaccines. Turning to the creation and allocation of resources under international law more generally, Fidler noted that the main principle of resource allocation—sovereignty—presents a problem for strategies to share vaccines and drugs, which must address claims of sovereignty by parties in as many as three locations: where the virus strains are isolated, where vaccines or drugs are manufactured, and where vaccines and drugs are sold or exported.

Strategies and policies to create and share resources between countries are strongest, Fidler observed, when they serve the national interests of each state involved. However, Fidler observed that in a mild influenza pandemic, the incentive to share vaccine and antiviral medications is weak; conversely, in a severe pandemic, the incentive to hoard these resources is strong. Similarly, short-term epidemiological uncertainty—as has occurred during the present pandemic—creates incentives for states that likely will have access to vaccines and antivirals to preserve the status quo rather than risk losing resources they may need if the pandemic worsens.

In the face of long political and legal odds, under the "dark cloud" of the H5N1 virus-sharing controversy, and in recognition of the fact that a global access framework would need to be built "from the ground up," Fidler offered the following components as a basis for constructing such a framework:

- increased and geographically diversified global influenza vaccine production capacities;
- increased and sustained interpandemic demand for seasonal influenza vaccines;
- improved preparedness and response capabilities—perhaps through strengthened emphasis on IHR implementation;
- accelerated research collaboration on new vaccine manufacturing techniques and other scientific issues (such as the use of adjuvants); and
- clear "triggers" for pandemic alert levels.

The best model for constructing this framework is to use the IHR, which were recently revised to address emerging infectious diseases, Fidler said. He added, however, that "compared to the problem of equitable access to vaccines and antivirals, what was done with the IHR was picking the low-hanging fruit, [in the form of] information sharing." The foundation of information sharing—which extends to an obligation to build surveillance and response capacity among all states party to the IHR—must underlie any global access framework, he insisted.

Forum member Terence Taylor emphasized that the breadth of the IHR represents an important strength that should not be compromised. In the case of virus sharing, Taylor stated, "we are being driven by a single disease category, which may not be necessarily helpful in trying to design the long-term, standing global framework." Instead of basing global benefit sharing on influenza alone,

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he continued, it might be better to construct a "network of networks" from existing regional agreements that address such public health issues as foodborne and waterborne diseases and drug distribution. Countries involved in regional efforts "have already bought into cooperation," Fidler agreed. "You should take advantage of that."

Asserting that benefit access is "really more a political issue than it is a legal framework issue," Fukuda observed that improving global access to viruses and their products should permit swift action to decrease uncertainty as to whether a potential pandemic will be mild or severe. "The enlightened self-interest is what do you do to reduce that uncertainty, because everyone needs it reduced to move quickly enough to keep up with fast moving disease events," he said, which involves concrete steps—such as acquiring information necessary to predicting a pandemic's impact—to reduce the harm to one's country. "Before you get to any legal framework, you have to have the political interests lined up," Fidler responded. "The deal here obviously is the continued flow of information in return for response capacities, whether that is vaccines themselves or whether it is technology." In the case of the H5N1 negotiations, such a deal has yet to be made for lack of political incentives, he concluded, which demonstrates the difficulties of constructing the broader global framework for access to influenza vaccines envisioned by Fukuda.

Ethical issues in clinical care The ethical principles guiding clinical care during public health emergencies also underlie the granting of extraordinary powers to government officials under the same circumstances, according to speaker Bernard Lo of the University of California, San Francisco (see Appendix A8). Several extraordinary things can happen during public health emergencies, he observed: critical medical resources are in short supply; essential services, such as public safety, are threatened; core social needs, such as the provision of adequate food and shelter, are not adequately met. In the aftermath of Hurricane Katrina, when such conditions led to chaos in New Orleans, many states granted public health officials emergency powers in an attempt to avoid a similar fate, he noted.

Lo articulated the following basic, ethical principles that govern actions during emergencies by public health officials:

- Provide benefit to the population as whole, not to individual patients; allocate resources prudently.
- When individual liberty and autonomy must be overridden, choose the least restrictive alternatives and ensure procedural due process.
- Create fair policies and procedures that treat people in similar situations similarly, without favoritism or discrimination; distribute benefits and burdens fairly (e.g., protect those whose work benefits society but puts them at risk).
- Maintain duty to care to the extent possible; accept personal risk.

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Lo also observed that these principles differ significantly from those of the allocation of scarce resources in the absence of critical shortages: "first come, first served;" the ability to pay; and patients' informed choices.

When health care resources are severely limited—for example, as ventilators might be in a severe influenza pandemic—they might be triaged, or rationed, with highest priority, as defined by Lo, going to one of the following groups:

- Those in greatest need. This rationale is used in emergency departments (EDs), but it means resources will be used on patients with poor prognoses; when applied to immunization, 2009-H1N1 influenza A vaccines would go first to pregnant women and infants; for antiviral medications, post-exposure prophylaxis for people with compromised immunity and/or living in residential settings.
- Those who would benefit most from care. This would maximize the number of lives saved.
- Those whose work is of instrumental value to the community. This would favor medical and public safety personnel, who would risk seeming self-serving if they made such a decision.
- Those whose work puts them at increased risk for infection.

The dilemma public officials face in choosing among these potentially conflicting priorities, and applying one of them in an emergency, might be further complicated by a lack of belief in government's trustworthiness and competence that is widespread in the United States, Lo observed. This may be accompanied to a large extent by distrust of scientific expertise as well.

Lo offered several pragmatic suggestions for developing policies to address ethical issues in an emergency, such as the allocation of life support measures (White et al., 2009). Such policies should be established in advance of need and in consultation with the public, he said. It is particularly important to include vulnerable populations in these discussions, he added, and to ensure that all stakeholders understand the risks of an uncoordinated response to an emergency. Emergency policies should reflect a shared vision of the kind of nation we aspire to be, Lo continued, expressing values we hold in common and embodying the proper role of government. Once established, ethical policies for emergencies should be supported by a focused, consistent media campaign that clarifies both the reasoning behind the policies and the expectations they engender, and which anticipates and responds to public concerns and objections.

When asked how these general principles and suggestions might be translated into specific guidance for hospitals and public health officials at the local level, Lo insisted that robust guidance is founded on a broad understanding of the role of government and the notion of placing public good ahead of any individual's welfare. People will object to making personal sacrifices in emergencies unless

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they grasp this broader vision, he said; when they do, extraordinary heroism often happens. We need to be able to tap into that generosity and altruism first, he said, then build policies around it.

Allocation of healthcare resources is very likely to occur in some U.S. communities during this pandemic, Osterholm said. "I think that if we see even a 20 percent increase in severe cases in many of our communities, we may outstrip our intensive care capabilities and allocation of critical medical equipment and supplies will be necessary," he predicted. "I don't think people yet get that because 2009-H1N1 influenza A infection isn't a severe disease for most of the population." With hospitals operating at near-full capacity, a shortage in ventilators during a severe influenza pandemic is a likely scenario, Lo agreed. "This situation of a dire shortage of ventilators . . . is the most poignant and dramatic case, because you have an individual who is critically ill and who without ventilatory support is highly likely to die," he said. Some have argued that these "identified victims" create dilemmas too painful to be resolved publicly, Lo observed. But, he insisted, such decisions must be public, and predicated on full explanations, or public support for emergency health measures will be severely undermined.

Public communication Cetron, Cox, Lo, and several other workshop participants observed that keeping the public informed about the 2009-H1N1 influenza A pandemic as it developed was one of the most difficult tasks they faced. Goodman cautioned that polarized, "black and white" thinking—"2009-H1N1 influenza A is a scourge or it's nothing"; "vaccines are perfect or dangerous"—stood in the way of clear communication. Goodman went on to stress that finding ways to get past such polarizing ideas and transparently explain uncertainties to the public was essential for establishing the credibility of science and the government in these matters, and thereby gaining public confidence in the pandemic response.

One aspect of this polarized thinking concerned the pandemic scale adopted by the WHO, which was based solely on the geographic spread of disease but was frequently misinterpreted as indicating disease severity. Recent pandemic plans reflected the severity of the threat posed by H5N1, which was appropriate, Fukuda observed, but it was difficult for countries to adjust to a pandemic influenza that was milder than expected. It was especially problematic to communicate this situation to the public without either overstating or understating the significance of 2009-H1N1 influenza A to public health, he noted. "In retrospect, it is very clear that [progressing] from three to four to five and then six was not seen as changes in levels of preparedness . . . [but instead as] . . . going up the scale in terms of severity and alarm," Fukuda observed. "This is something that I do regret that we could not make this clear enough, and it is something that we'll have to revisit."

In the meantime, Goodman of the FDA urged, it is important to prepare for "worst-case" pandemic scenarios, while responding only to what is actually happening—and for the public to recognize and support these efforts. Over the

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long term, he said, this will require greater capacity and expertise in scientific communication. Ultimately, the truth must be told, and uncertainties must be identified as such, he continued. Likening false rumors—such as those that circulate on the Internet regarding vaccine safety—to PCR false positives, Goodman observed that both amplified quickly and led to bad decisions. "How we monitor and respond [to these situations] is critical," he concluded.

Local Perspectives

Speakers Jeffrey Duchin, of the Seattle-King County Department of Health, and Annie Fine, of the New York City Department of Health, reflected on their experiences and those of their departments and cities during the spring wave of the 2009-H1N1 influenza A pandemic and discussed their preparations for the anticipated fall upsurge of influenza activity. Their accounts featured several common elements, as well as a common theme: an under-supported, overloaded public health system. Duchin and Fine reported that:

- Their departments quickly shifted from case-counting to syndromic surveillance of ILI (along with population surveillance, in New York City).
- They received conflicting and confusing clinical guidance from the CDC, the WHO, and professional organizations.
- Their EDs were overwhelmed with the mildly and severely ill, along with the "worried well."
- Supply chains for antivirals and N95 masks were fragile and unpredictable.
- School closures proved of limited use in reducing the surge in illness.
- Public messaging was a daunting challenge that will only become more difficult with the arrival of the 2009-H1N1 influenza A vaccine.

Duchin provided a detailed description of public health under siege, due to the near-simultaneous arrival of pandemic influenza and economic recession (see Duchin in Appendix A3). "We needed over 200 staff and 40 volunteers for our outbreak response," he recalled. "On our epi team alone, we required . . . 41 unique surge staff and 2,500 hours of work. We received about 1,600 calls from healthcare providers alone, not including the public, over the first six weeks," he continued. "Of course we don't have enough staff for shift work like most emergency operation centers, and this resulted in a lot of stress on our staff," he said, many of whom subsequently received layoff notices, withheld during the outbreak, due to budget cuts.

However, he said, some things did go right. "We certainly had a better response than we did during SARS," he observed, adding that facilities that had made a pandemic plan found it to be useful in managing the 2009-H1N1 influenza A. A regional healthcare coalition expedited the surge response in large healthcare facilities and enabled good communication among hospitals and

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between the hospitals and the public health department, he said. "We were at least able to help the hospitals manage their scarce resources by loaning to one another, and they were coordinated with the public health response," Duchin concluded. He also described Tamiflu® clinics and a call center as particularly useful elements of the public health response.

In New York City, Fine reported that, based on their experience during the spring, the public health department modified several aspects of their surge strategy in order to better manage the anticipated return of 2009-H1N1 influenza A in the fall of 2009. The New York City Department of Health and Mental Hygiene (NYCDOH) would not conduct case-based surveillance but would, instead, continue syndromic surveillance; monitor trends in overall incidence, clinical and epidemiological risk factors, and pathogens; conduct monthly population surveys by telephone; use sentinel hospitals and a primary care network for limited intensive in-patient surveillance; and match laboratory-confirmed cases with registered deaths to determine the number of confirmed influenza deaths.

After hospitals coped with a series of problems not anticipated in their surge plans, her department instituted a series of changes, Fine said. They have reviewed all hospital surge plans and have provided hospitals with guidance on suggested practices in addressing the resurgence of 2009-H1N1 influenza A. After localized shortages occurred during the spring wave, antiviral medications have been made more accessible. Hospitals were requested to activate their incident command systems in mid-September, as schools returned to session. Protocols for using Medical Reserve Corps volunteers remained under consideration but could involve training and preselecting volunteers to work if needed.

To ease pressure on EDs, New York City has established about 100 flu diagnostic and treatment centers that will treat all patients, regardless of their usual source of care or insurance status, Fine said. The clinics will be open evenings and weekends, and will offer seasonal and pandemic vaccines as well as antivirals, should they become unavailable through the commercial sector. Local physicians and health care workers will also receive guidance encouraging them to discuss and prescribe antivirals early for their high-risk patients, in order to ensure access.

Based on his experience during the spring wave of the H1N1 influenza pandemic Duchin called for more vigorous efforts to get antivirals to high-risk individuals. "With the sudden rise and the rapid transmission you can't expect patients to get to their physicians, get diagnosed, get to the pharmacy, and get their drug in the time frame that you really want that to happen," he asserted. Moreover, he stated, pharmacies do not maintain their stocks, so even if in theory there is no shortage, there are times when antivirals are locally unavailable. "I think we have to be very aggressive about getting the message out that high-risk patients, pregnant women for example, should have Tamiflu® . . . now, not wait until they need it when the outbreak is hitting in the community," he concluded, adding that he would extend that recommendation to other high-risk people.

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The tireless efforts demonstrated by Duchin, Fine, and their departments in the face of this pandemic should not obscure the fact that "local public health capacity to respond to H1N1 and other large-scale health emergencies is tenuous and unstable," as Duchin has observed. Indeed, perhaps the most important lesson learned from the domestic and international public health community's experiences with the 2009-H1N1 influenza A pandemic is, in his words, that "inadequate long-term sustainable funding for both core public health and health emergency preparedness undermines the ability of local communities to adequately prepare for and respond to large scale health emergencies of any type."

WORKSHOP OVERVIEW REFERENCES

Andreasen, V., C. Viboud, and L. Simonsen. 2008. Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. *Journal of Infectious Diseases* 197(2):270-278.

Australian Government, Department of Health and Aging. 2010. *Australian influenza surveillance 2010—latest report*, http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/ozflucurrent.htm (accessed January 14, 2010).

Bertozzi, S., A. Kelso, M. Tashiro, V. Savy, J. Farrar, M. Osterholm, S. Jameel, and C. P. Muller. 2009. Pandemic flu: from the front lines. *Nature* 461(7260):20-21.

Bridges, C. B., W. Lim, J. Hu-Primmer, L. Sims, K. Fukuda, K. H. Mak, T. Rowe, W. W. Thompson, L. Conn, X. Lu, N. J. Cox, and J. M. Katz. 2002. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. *Journal of Infectious Diseases* 185(8):1005-1010.

Brownstein, J. S., C. C. Freifeld, and L. C. Madoff. 2009. Digital disease detection—harnessing the Web for public health surveillance. *New England Journal of Medicine* 360(21):2153-2155, 2157.

Buenos Aires Herald. 2009. *Nationwide alert: Argentina declares health emergency, flu found in pigs*, http://www.buenosairesherald.com/BreakingNews/View/6666 (accessed August 21, 2009).

Bustamante, J. 2009. *Argentina confirms first H1N1 flu case*, http://www.reuters.com/article/latestCrisis/idUSN07423083 (accessed August 21, 2009).

Cauchemez, S., N. M. Ferguson, C. Wachtel, A. Tegnell, G. Saour, B. Duncan, and A. Nicoll. 2009. Closure of schools during an influenza pandemic. *Lancet Infectious Diseases* 9(8):473-481.

CDC (Centers for Disease Control and Prevention). 2009a. *CDC guidance for state and local public health officials and school administrators for school (K-12) responses to influenza during the 2009-2010 school year*, http://www.cdc.gov/h1n1flu/schools/schoolguidance.htm (accessed November 3, 2009).

———. 2009b. *Novel H1N1 flu: facts and figures*, http://www.cdc.gov/h1n1flu/surveillanceqa.htm (accessed November 3, 2009).

———. 2009c. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis—North Carolina, 2009. *Morbidity and Mortality Weekly Report* 58(35):969-972.

———. 2009d. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. *Morbidity and Mortality Weekly Report* 58(19):521-524.

———. 2009e. Swine influenza A (H1N1) infection in two children—Southern California, March-April 2009. *Morbidity and Mortality Weekly Report* 58(15):400-402.

———. 2009f. Update: novel influenza A (H1N1) virus infection—Mexico, March-May, 2009. *Morbidity and Mortality Weekly Report* 58(21):585-589.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

———. 2009g. *Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season*, http://www.cdc.gov/h1n1flu/recommendations.htm (accessed November 3, 2009).

———. 2009h. *Antiviral treatment options, including intravenous peramivir, for treatment of influenza in hospitalized patients for the 2009-2010 season*, http://www.cdc.gov/H1N1flu/EUA/Peramivir_recommendations.htm (accessed November 18, 2009).

———. 2009i. *2009-2010 influenza season week 52 ending January 2, 2010*, http://www.cdc.gov/flu/weekly/ (accessed January 14, 2010).

———. 2010. 2009-2010 influenza season week 8 ending February 27, 2010. *FluView*, http://www.cdc.gov/flu/weekly/weeklyarchives2009-2010/weekly08.htm (accessed March 15, 2010).

Childs, R. A., A. S. Palma, S. Wharton, T. Matrosovich, Y. Liu, W. Chai, M. A. Campanero-Rhodes, Y. Zhang, M. Eickmann, M. Kiso, A. Hay, M. Matrosovich, and T. Feizi. 2009. Receptor-binding specificity of pandemic influenza A (H1N1) 2009 virus determined by carbohydrate microarray. *Nature Biotechnology* 27(9):797-799.

CIDRAP (Center for Infectious Disease Research and Policy). 2009. *Pandemic influenza*, http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/biofacts/panflu.html (accessed November 3, 2009).

Cox, N. 2009. *Detection and characterization of and response to the emergence of 2009 H1N1 viruses*. Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

Daszak, P. 2009a. A call for "smart surveillance": a lesson learned from H1N1. *EcoHealth* 6(1):1-2.

———. 2009b. *Ecological factors to understanding influenza risk*. Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

Ely, B. 1999. Infectious salmon anaemia. *Mill Hill Essays*. National Institute for Medical Research, http://www.nimr.mrc.ac.uk/MillHillEssays/1999/isa.htm (accessed November 18, 2009).

Englund, J., D. Zerr, J. Heath, S. Pergam, J. Kuypers, J. Yager, M. Boeckh, D. Mattson, N. Whittington, E. Whimbey, J. Duchin, T. Uyeki, V. Deyde, M. Okomo-Adhiambo, T. Sheu, A. Trujillo, A. Klimov, L. Gubareva, and M. Kay. 2009. Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients—Seattle, Washington, 2009. *Morbidity and Mortality Weekly Report* 58(32):893-896.

Fedson, D. S. 2009. Confronting the next influenza pandemic with anti-inflammatory and immunomodulatory agents: why they are needed and how they might work. *Influenza and Other Respiratory Viruses* 3(4):129-142.

Ferguson, N. M., D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn, and D. S. Burke. 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 437(7056):209-214.

Fineberg, H. V., and M. E. Wilson. 2009. Epidemic science in real time. *Science* 324(5930):987.

Fukuda, K. 2009. *2009 (H1N1) pandemic lessons for going forward*. Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

Garske, T., J. Legrand, C. A. Donnelly, H. Ward, S. Cauchemez, C. Fraser, N. M. Ferguson, and A. C. Ghani. 2009. Assessing the severity of the novel influenza A/H1N1 pandemic. *British Medical Journal* 339:b2840.

Gilbert, M., X. Xiao, D. U. Pfeiffer, M. Epprecht, S. Boles, C. Czarnecki, P. Chaitaweesub, W. Kalpravidh, P. Q. Minh, M. J. Otte, V. Martin, and J. Slingenbergh. 2008. Mapping H5N1 highly pathogenic avian influenza risk in Southeast Asia. *Proceedings of the National Academy of Sciences* 105(12):4769-4774.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Ginsberg, J., M. H. Mohebbi, R. S. Patel, L. Brammer, M. S. Smolinski, and L. Brilliant. 2009. Detecting influenza epidemics using search engine query data. *Nature* 457(7232):1012-1014.

Goldstein, E., J. C. Miller, J. O'Hagan, and M. Lipsitch. 2009. Predispensing of antivirals to high-risk individuals in an influenza pandemic. Version 4. *PLoS Currents Influenza*, http://knol.google.com/k/edward-goldstein/predispensing-of-antivirals-to-high/1uji2pldf66z5/1# (accessed November 3, 2009).

Greenberg, M. E., M. H. Lai, G. F. Hartel, C. H. Wichems, C. Gittleson, J. Bennet, G. Dawson, W. Hu, C. Leggio, D. Washington, and R. L. Basser. 2009. Response after one dose of a monovalent influenza A (H1N1) 2009 vaccine—preliminary report. *New England Journal of Medicine* 361(25):2405-2413.

Gubler, D. J. 1998. Resurgent vector-borne diseases as a global health problem. *Emerging Infectious Diseases* 4(3):442-450.

Han, K., X. Zhu, F. He, L. Liu, L. Zhang, H. Ma, X. Tang, T. Huang, G. Zeng, and B.-P. Zhu. 2009. Lack of airborne transmission during outbreak of pandemic (H1N1) 2009 among tour group members, China, June 2009. *Emerging Infectious Diseases* 15(10):1578-1581.

Hancock, K., V. Veguilla, X. Lu, W. Zhong, E. N. Butler, H. Sun, F. Liu, L. Dong, J. R. Devos, P. M. Gargiullo, T. L. Brammer, N. J. Cox, T. M. Tumpey, and J. M. Katz. 2009. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *New England Journal of Medicine* 361(20):1945-1952.

Hanshaoworakul, W., J. M. Simmerman, U. Narueponjirakul, W. Sanasuttipun, V. Shinde, S. Kaewchana, D. Areechokechai, J. Levy, and K. Ungchusak. 2009. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS One* 4(6):e6051.

Harvard School of Public Health. 2009. *National survey finds six in ten Americans believe serious outbreak of influenza A (H1N1) likely in fall/winter*, http://www.hsph.harvard.edu/news/press-releases/2009-releases/national-survey-americans-influenza-a-h1n1-outbreak-fall-winter.html (accessed November 3, 2009).

Hayden, F. 2009. Developing new antiviral agents for influenza treatment: what does the future hold? *Clinical Infectious Diseases* 48(Suppl 1):S3-S13.

Henderson, D. A., B. Courtney, T. V. Inglesby, E. Toner, and J. B. Nuzzo. 2009. Public health and medical responses to the 1957-58 influenza pandemic. *Biosecurity and Bioterrorism* 7(3):265-273.

HHS (Department of Health and Human Services). 2007. *Community strategy for pandemic influenza mitigation*, http://www.flu.gov/professional/community/commitigation.html (accessed November 6, 2009).

Hufnagel, L., D. Brockmann, and T. Geisel. 2004. Forecast and control of epidemics in a globalized world. *Proceedings of the National Academy of Sciences* 101(42):15124-15129.

IOM (Institute of Medicine). 2003. *Microbial threats to health: emergence, detection, and response*. Washington, DC: The National Academies Press.

———. 2004. *Learning from SARS*. Washington, DC: The National Academies Press.

———. 2005. *The threat of pandemic influenza*. Washington, DC: The National Academies Press.

———. 2007a. *Ethical and legal considerations in mitigating pandemic disease.* Washington, DC: The National Academies Press.

———. 2007b. *Global infectious disease surveillance and detection*. Washington, DC: The National Academies Press.

———. 2010. *Infectious disease movement in a borderless world.* Washington, DC: The National Academies Press.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Itoh, Y., K. Shinya, M. Kiso, T. Watanabe, Y. Sakoda, M. Hatta, Y. Muramoto, D. Tamura, Y. Sakai-Tagawa, T. Noda, S. Sakabe, M. Imai, Y. Hatta, S. Watanabe, C. Li, S. Yamada, K. Fujii, S. Murakami, H. Imai, S. Kakugawa, M. Ito, R. Takano, K. Iwatsuki-Horimoto, M. Shimojima, T. Horimoto, H. Goto, K. Takahashi, A. Makino, H. Ishigaki, M. Nakayama, M. Okamatsu, D. Warshauer, P. A. Shult, R. Saito, H. Suzuki, Y. Furuta, M. Yamashita, K. Mitamura, K. Nakano, M. Nakamura, R. Brockman-Schneider, H. Mitamura, M. Yamazaki, N. Sugaya, M. Suresh, M. Ozawa, G. Neumann, J. Gern, H. Kida, K. Ogasawara, and Y. Kawaoka. 2009. *In vitro* and *in vivo* characterization of new swine-origin H1N1 influenza viruses. *Nature* 460(7258):1021-1025.

Jain, S., L. Kamimoto, A. M. Bramley, A. M. Schmitz, S. R. Benoit, J. Louie, D. E. Sugerman, J. K. Druckenmiller, K. A. Ritger, R. Chugh, S. Jasuja, M. Deutscher, S. Chen, J. D. Walker, J. S. Duchin, S. Lett, S. Soliva, E. V. Wells, D. Swerdlow, T. M. Uyeki, A. E. Fiore, S. J. Olsen, A. M. Fry, C. B. Bridges, L. Finelli, and 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. 2009. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *New England Journal of Medicine* 361(20):1935-1944.

Jamieson, D. J., M. A. Honein, S. A. Rasmussen, J. L. Williams, D. L. Swerdlow, M. S. Biggerstaff, S. Lindstrom, J. K. Louie, C. M. Christ, S. R. Bohm, V. P. Fonseca, K. A. Ritger, D. J. Kuhles, P. Eggers, H. Bruce, H. A. Davidson, E. Lutterloh, M. L. Harris, C. Burke, N. Cocoros, L. Finelli, K. F. MacFarlane, B. Shu, and S. J. Olsen. 2009. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 374(9688):451-458.

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, and P. Daszak. 2008. Global trends in emerging infectious diseases. *Nature* 451(7181):990-993.

Jones, L. D., and P. A. Nuttall. 1989. Non-viraemic transmission of Thogoto virus: influence of time and distance. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 83(5):712-714.

Kawaoka, Y. 2009. *Influenza pandemic 2009.* Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

Khan, K., J. Arino, W. Hu, P. Raposo, J. Sears, F. Calderon, C. Heidebrecht, M. Macdonald, J. Liauw, A. Chan, and M. Gardam. 2009. Spread of a novel influenza A (H1N1) virus via global airline transportation. *New England Journal of Medicine* 361(2):212-214.

Kidd, I. M., J. Down, E. Nastouli, R. Shulman, P. R. Grant, D. C. Howell, and M. Singer. 2009. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet* 374(9694):1036.

Kilpatrick, A. M., A. A. Chmura, D. W. Gibbons, R. C. Fleischer, P. P. Marra, and P. Daszak. 2006a. Predicting the global spread of H5N1 avian influenza. *Proceedings of the National Academy of Sciences* 103(51):19368-19373.

Kilpatrick, A. M., L. D. Kramer, M. J. Jones, P. P. Marra, and P. Daszak. 2006b. West Nile virus epidemics in North America are driven by shifts in mosquito feeding behavior. *PLoS Biology* 4(4):e82.

Lee, N., C. S. Cockram, P. K. S. Chan, D. S. C. Hui, K. W. Choi, and J. J. Y. Sung. 2008. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clinical Infectious Diseases* 46(8):1323-1324.

Lipsitch, M. 2009. *Epidemiology of pH1N1: narrowing the uncertainty.* Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

Lipsitch, M., S. Riley, S. Cauchemez, A. C. Ghani, and N. M. Ferguson. 2009. Managing and reducing uncertainty in an emerging influenza pandemic. *New England Journal of Medicine* 361(2):112-115.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Loeb, M., N. Dafoe, J. Mahony, M. John, A. Sarabia, V. Glavin, R.Webby, M. Smieja, D. J. D. Earn, S. Chong, A. Webb, S. D. Walter. 2009. Surgical mask vs N95 respirator for preventing influenza among health care workers: a randomized trial. *Journal of the American Medical Association* 302(17):1865-1871.

Lopez, L., and S. Huang. 2009. *Influenza weekly update*, http://www.surv.esr.cri.nz/PDF_surveillance/Virology/FluWeekRpt/2009/FluWeekRpt200934.pdf (accessed December 17, 2009).

Louie, J., K. Winter, K. Harriman, D. Vugia, C. Glaser, B. Matyas, D. Schnurr, H. Guevara, C. Y. Pan, E. Saguar, R. Berumen, E. Hunley, S. Messenger, C. Preas, D. Hatch, G. Chavez, P. Kriner, K. Lopez, D. Sunega, D. Rexin, S. Roach, J. Kempf, R. Gonzalez, L. Morgan, N. Barnes, L. Berman, S. Emery, B. Shu, K. H. Wu, J. Villanueva, S. Lindstrom, D. Sugarman, M. Patel, J. Jaeger, E. Meites, and N. Dharan. 2009a. Hospitalized patients with novel influenza A (H1N1) virus infection—California, April-May, 2009. *Morbidity and Mortality Weekly Report* 58(19):536-541.

Louie, J., C. Jean, T.- H. Chen, S. Park, R. Ueki, T. Harper, E. Chmara, J. Myers, R. Stoppacher, C. Catanese, N. Farley, E. Leis, C. DiAngelo, A. M. Fry, L. Finelli, M. G. Carvalho, B. Beall, M. Moore, C. Whitney, and D. M. Blau. 2009b. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1)—United States, May-August 2009. *Morbidity and Mortality Weekly Report* 58(early release):1-4.

Luke, T. C., E. M. Kilbane, J. L. Jackson, and S. L. Hoffman. 2006. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Annals of Internal Medicine* 145(8):599-609.

Mangtani, P., T. K. Mak, and D. Pfeifer. 2009. Pandemic H1N1 infection in pregnant women in the USA. *Lancet* 374(9688):429-430.

Markel, H., H. B. Lipman, J. A. Navarro, A. Sloan, J. R. Michalsen, A. M. Stern, and M. S. Cetron. 2007. Nonpharmaceutical interventions implemented by US cities during the 1918-1919 influenza pandemic. *Journal of the American Medical Association* 298(6):644-654.

Mawudeku, A., M. Ruben, and B. Lemay. 2007. Global public health surveillance: the role of non-traditional surveillance tools. In *Global infectious disease surveillance and detection: assessing the challenges, finding solutions*, S. M. Lemon, M. A. Hamburg, P. F. Sparling, E. R. Choffnes, and A. Mack, rapporteurs. Washington, DC: The National Academies Press.

McGeer, A., K. A. Green, A. Plevneshi, A. Shigayeva, N. Siddiqi, J. Raboud, and D. E. Low. 2007. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clinical Infectious Diseases* 45(12):1568-1575.

Mills, C. E., J. M. Robins, and M. Lipsitch. 2004. Transmissibility of 1918 pandemic influenza. *Nature* 432(7019):904-906.

Morens, D. M., J. K. Taubenberger, and A. S. Fauci. 2009. The persistent legacy of the 1918 influenza virus. *New England Journal of Medicine* 361(3):225-229.

Morse, S. S. 2007. Global infectious disease surveillance and early warning systems: ProMED and ProMED-mail. In *Global infectious disease surveillance and detection: assessing the challenges, finding solutions*, S. M. Lemon, M. A. Hamburg, P. F. Sparling, E. R. Choffnes, and A. Mack, rapporteurs. Washington, DC: The National Academies Press.

Munayco, C. V., J. Gomez, V. A. Laguna-Torres, J. Arrasco, T. J. Kochel, V. Fiestas, J. Garcia, J. Perez, I. Torres, F. Condori, H. Nishiura, and G. Chowell. 2009. Epidemiological and transmissibility analysis of influenza A(H1N1)v in a Southern Hemisphere setting: Peru. *Eurosurveillance* 14(32), http://www.eurosurveillance.org/images/dynamic/EE/V14N32/art19299.pdf (accessed November 3, 2009).

Munster, V. J., E. de Wit, J. M. van den Brand, S. Herfst, E. J. Schrauwen, T. M. Bestebroer, D. van de Vijver, C. A. Boucher, M. Koopmans, G. F. Rimmelzwaan, T. Kuiken, A. D. Osterhaus, and R. A. Fouchier. 2009. Pathogenesis and transmission of swine-origin 2009 A(H1N1) influenza virus in ferrets. *Science* 325(5939):481-483.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Napolitano, L. M., P. K. Park, K. C. Sihler, T. Papadimos, C. Chenoweth, S. Cinti, C. Zalewski, R. Sharangpani, P. Somsel, E. Wells, A. M. Fry, A. E. Fiore, J. M. Villanueva, S. Lindstrom, and T. M. Uyeki. 2009. Intensive-care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. *Morbidity and Mortality Weekly Report* 58(27):749-752.

Nelson, M. I., L. Simonsen, C. Viboud, M. A. Miller, and E. C. Holmes. 2007. Phylogenetic analysis reveals the global migration of seasonal influenza A viruses. *PLoS Pathogens* 3(9):1220-1228.

Nelson, M. I., C. Viboud, L. Simonsen, R. T. Bennett, S. B. Griesemer, K. St George, J. Taylor, D. J. Spiro, N. A. Sengamalay, E. Ghedin, J. K. Taubenberger, and E. C. Holmes. 2008. Multiple reassortment events in the evolutionary history of H1N1 influenza A virus since 1918. *PLoS Pathogens* 4(2):e1000012.

Neumann, G., T. Noda, and Y. Kawaoka. 2009. Emergence and pandemic potential of swine-origin H1N1 influenza virus. *Nature* 459(7249):931-939.

Neustadt, R. E., and H. V. Fineberg. 1978. *The swine flu affair: decision-making on a slippery disease.* Honolulu, HI: University Press of the Pacific.

Noble, G. R. 1982. Epidemiological and clinical aspects of influenza. In *Basic and applied influenza research*, edited by A. S. Beare. Boca Raton, FL: CRC Press. Pp. 11-50.

Pandemic Plan. 2005. *H5N1 history: emergence of the influenza A H5N1 subtype (1997-2005)*, http://reports.typepad.com/pandemic_plan/2005/12/h5n1_history.html (accessed November 4, 2009).

PBS (Public Broadcasting System). 2009. *Introduction: Influenza 1918*, http://www.pbs.org/wgbh/americanexperience/influenza/introduction (accessed January 11, 2010).

———. 2010. *H1N1 vaccine reaching poorer nations as flu fears continue to wane*, http://www.pbs.org/newshour/updates/north_america/jan-june10/flu_01-07.html (accessed January 27, 2010).

PCAST (President's Council of Advisors on Science and Technology). 2009. *Report to the President on U.S. preparations for 2009-H1N1 influenza*. Washington, DC: Office of Science and Technology Policy.

Pourbohloul, B., A. Ahued, B. Davoudi, R. Meza, L. A. Meyers, D. M. Skowronski, I. Villasenor, F. Galvan, P. Cravioto, D. J. Earn, J. Dushoff, D. Fisman, W. J. Edmunds, N. Hupert, S. V. Scarpino, J. Trujillo, M. Lutzow, J. Morales, A. Contreras, C. Chavez, D. M. Patrick, and R. C. Brunham. 2009. Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. *Influenza and Other Respiratory Viruses* 3(5):215-222.

Presanis, A. M., D. De Angelis, The New York City Swine Flu Investigation Team, A. Hagy, C. Reed, S. Riley, B. S. Cooper, L. Finelli, P. Biedrzycki, and M. Lipsitch. 2009. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. *PLoS Medicine* 6(12):e1000207.

Presti, R. M., G. Zhao, W. L. Beatty, K. A. Mihindukulasuriya, A. P. A. Travassos da Rosa, V. L. Popov, R. B. Tesh, H. W. Virgin, and D. Wang. 2009. Quaranfil, Johnston Atoll, and Lake Chad viruses are novel members of the family orthomyxoviridae. *Journal of Virology* 83(22):11599-11606.

ProMED-mail. 2009a. *Influenza pandemic (H1N1) 2009 (16): Argentina, Sequencing*, http://www.promedmail.org/pls/otn/f?p=2400:1001:298185261489014::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1004,78457 (accessed August 21, 2009).

———. 2009b. *Influenza pandemic (H1N1) 2009 (07): Argentina, swine, alert*, http://www.promedmail.org/pls/otn/f?p=2400:1001:57555::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1400,78398 (accessed August 21, 2009).

Raynard, R. S., A. G. Murray, and A. Gregory. 2001. Infectious salmon anaemia virus in wild fish from Scotland. *Diseases of Aquatic Organisms* 46(2):93-100.

Ruiz-Palacios, G. M. 2009. *Ground zero: the origins of a pandemic?* Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Russell, C. A., T. C. Jones, I. G. Barr, N. J. Cox, R. J. Garten, V. Gregory, I. D. Gust, A. W. Hampson, A. J. Hay, A. C. Hurt, J. C. de Jong, A. Kelso, A. I. Klimov, T. Kageyama, N. Komadina, A. S. Lapedes, Y. P. Lin, A. Mosterin, M. Obuchi, T. Odagiri, A. D. Osterhaus, G. F. Rimmelzwaan, M. W. Shaw, E. Skepner, K. Stohr, M. Tashiro, R. A. Fouchier, and D. J. Smith. 2008. The global circulation of seasonal influenza A (H3N2) viruses. *Science* 320(5874):340-346.

Salomon, R., and R. Webster. 2009. The influenza virus enigma. *Cell* 136(3):402-410.

San Francisco AIDS Foundation. 2009. *Glossary of HIV/AIDS terms*, http://www.sfaf.org/custom/glossary.aspx?l=en&a=G (accessed December 15, 2009).

Schnirring, L. 2009. *USDA confirms first pandemic H1N1 finding in US pigs*, http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/oct1909pig-br.html (accessed November 3, 2009).

Sencer, D. J., and J. D. Millar. 2006. Reflections on the 1976 swine flu vaccination program. *Emerging Infectious Diseases* 12(1):29-33.

Severson, W. X., Chen, J. Maddry, Y.-K. Chu, C. Jonsson, A. McBrayer, R. Tapp, D. Smee, C. Maddox, S. Ananthan, J. Noah, L. Black, B. Moore, M. Sosa, L. White, and L. Rasmussen. 2009. Discovery of new inhibitors of the influenza H5N1 virus. *Antiviral Research* 82(2):A36-A37.

Shannon, S., J. Louie, A. Siniscalchi, E. Rico, D. Richter, R. Hernandez, R. Lynfield, L. McHugh, C. Waters, E. Lee, A. Stoute, K. Landers, U. Bandy, N. Pascoe, V. Vernon, T. Haupt, C. Moore, L. Schieve, G. Peacock, C. Boyle, M. Honein, M. Yeargin-Allsopp, E. Trevathan, L. Finelli, T. Uyeki, R. Dhara, A. Fowlkes, D. Christensen, and V. Jarquin. 2009. Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection—United States, April-August 2009. *Morbidity and Mortality Weekly Report* 58(34):941-947.

Shinya, K., M. Ebina, S. Yamada, M. Ono, N. Kasai, and Y. Kawaoka. 2006. Avian flu: influenza virus receptors in the human airway. *Nature* 440(7083):435-436.

Shortridge, K. F. 2009. *Southern Hemisphere, Northern Hemisphere: a global influenza world*. Presentation given at the September 15-16, 2009 public workshop "The domestic and international impacts of the 2009 influenza A H1N1 pandemic: global challenges, global solutions," Forum on Microbial Threats, Institute of Medicine, Washington, DC.

Simonsen, L. D., R. Olson, C. Viboud, E. Heiman, R. J. Taylor, M. A. Miller, and T. A. Reichert. 2005. Pandemic influenza and mortality: past evidence and projections for the future. In *The threat of pandemic influenza*. Washington, DC: The National Academies Press.

Smith, D. J., A. S. Lapedes, J. C. de Jong, T. M. Bestebroer, G. F. Rimmelzwaan, A. D. Osterhaus, and R. A. Fouchier. 2004. Mapping the antigenic and genetic evolution of influenza virus. *Science* 305(5682):371-376.

Smith, G. J. D., D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghwani, S. Bhatt, J. S. Malik Peiris, Y. Guan, and A. Rambaut. 2009. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* 459(7250):1122-1125.

Soundararajan, V., K. Tharakaraman, R. Raman, S. Raguram, Z. Shriver, V. Sasisekharan, and R. Sasisekharan. 2009. Extrapolating from sequence—the 2009 H1N1 "swine" influenza virus. *Nature Biotechnology* 27(6):510-513.

Stein, R. 2009 (August 10). Preparing for swine flu's return: new wave expected after virus flourished in Southern Hemisphere. *The Washington Post*: A1.

Stern, A. M., and H. Markel. 2004. International efforts to control infectious diseases, 1851 to the present. *Journal of the American Medical Association* 292(12):1474-1479.

———. 2009. What Mexico taught the world about pandemic influenza preparedness and community mitigation strategies. *Journal of the American Medical Association* 302(11):1221-1222.

Stern, A. M., M. S. Cetron, and H. Markel. 2009. Closing the schools: lessons from the 1918-19 U.S. influenza pandemic. *Health Affairs* 28(6):w1066-w1078.

Taubenberger, J. K., and D. M. Morens. 2006. 1918 Influenza: the mother of all pandemics. *Emerging Infectious Diseases* 12(1):15-22.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Thompson, W. W., D. K. Shay, E. Weintraub, L. Brammer, N. Cox, L. J. Anderson, and K. Fukuda. 2003. Mortality associated with influenza and respiratory syncytial virus in the United States. *Journal of the American Medical Association* 289(2):179-186.

Throsby, M., E. van den Brink, M. Jongeneelen, L. L. Poon, P. Alard, L. Cornelissen, A. Bakker, F. Cox, E. van Deventer, Y. Guan, J. Cinatl, J. ter Meulen, I. Lasters, R. Carsetti, M. Peiris, J. de Kruif, and J. Goudsmit. 2008. Heterosubtypic neutralizing monoclonal antibodies cross-protective against H5N1 and H1N1 recovered from human IgM+ memory B cells. *PLoS One* 3(12):e3942.

Treanor, J. J. 2010. Influenza virus. In *Principles and Practice of Infectious Diseases*, 7th Edition, edited by G. L. Mandell, J. E. Bennett, and R. Dolin R. Chapter 165.

University of California Museum of Paleontology. 2009. *Founder effect*, http://evolution.berkeley.edu/evosite/glossary/glossary_browse.shtml (accessed December 15, 2009).

USDA (U.S. Department of Agriculture). 2009. *USDA confirms 2009 pandemic H1N1 influenza virus present in Minnesota fair pig sample*, http://www.usda.gov/wps/portal/!ut/p/_s.7_0_A/7_0_1OB?contentidonly=true&contentid=2009/10/0514.xml (accessed November 3, 2009).

van Doorn, R. 2009. *Influenza pandemic (H1N1) 2009 (27): Viet Nam, patient data update, August 8, 2009*, http://www.promedmail.org/pls/otn/f?p=2400:1202:2994427309200284::NO::F2400_P1202_CHECK_DISPLAY,F2400_P1202_PUB_MAIL_ID:X,78714 (accessed November 3, 2009).

van Riel, D., V. J. Munster, E. de Wit, G. F. Rimmelzwaan, R. A. Fouchier, A. D. Osterhaus, and T. Kuiken. 2006. H5N1 virus attachment to lower respiratory tract. *Science* 312(5772):399.

Wallensten, A., I. Oliver, D. Lewis, and S. Harrison. 2009. Compliance and side effects of prophylactic oseltamivir treatment in a school in south west England. *Eurosurveillance* 14(30):1-4.

Webby, R. J., K. Rossow, G. Erickson, Y. Sims, and R. Webster. 2004. Multiple lineages of antigenically and genetically diverse influenza A virus co-circulate in the United States swine population. *Virus Research* 103(1-2):67-73.

Webster, R. 2009. *Evolution of the novel H1N1 influenza virus of swine origin*. Remarks to the Forum on Microbial Threats Discussion Meeting, June 16, 2009, Washington, DC.

White, D. B., M. H. Katz, J. M. Luce, and B. Lo. 2009. Who should receive life support during a public health emergency? Using ethical principles to improve allocation decisions. *Annals of Internal Medicine* 150(2):132-138.

White, L. F., J. Wallinga, L. Finelli, C. Reed, S. Riley, M. Lipsitch, and M. Pagano. 2009. Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. *Influenza and Other Respiratory Viruses* 3(6):267-276.

White House. 2009. *Declaration of a national emergency with respect to the 2009 H1N1 influenza pandemic*, http://www.whitehouse.gov/THE-PRESS-OFFICE/DECLARATION-A-NATIONAL-EMERGENCY-WITH-RESPECT-2009-H1N1-INFLUENZA-PANDEMIC-0 (accessed November 17, 2009).

WHO (World Health Organization). 2005a. *International Health Regulations*, http://www.who.int/ihr/en/ (accessed November 3, 2009).

———. 2005b. *Avian influenza: assessing the pandemic threat, the pandemic threat*. Geneva, Switzerland: World Health Organization.

———. 2009a. *Avian influenza frequently asked questions*, http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html#isthere (accessed November 3, 2009).

———. 2009b. *Changes in reporting requirements for pandemic (H1N1) 2009 virus infection*, http://www.who.int/csr/disease/swineflu/notes/h1n1_surveillance_20090710/en/index.html (accessed November 3, 2009).

———. 2009c. *Pandemic (H1N1) 2009 update 69*, http://www.who.int/csr/don/2009_10_09/en/index.html (accessed November 3, 2009).

———. 2009d. *Situation updates—pandemic (H1N1) 2009*, http://www.who.int/csr/disease/swineflu/updates/en/index.html (accessed November 3, 2009).

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

———. 2009e. *Timeline (22 July 2009 onwards) pandemic (H1N1) 2009 laboratory confirmed cases and number of deaths as reported to WHO*, http://gamapserver.who.int/h1n1/cases-deaths/h1n1_casesdeaths.html (accessed January 6, 2010).

———. 2009f. *Clinical features of severe cases of pandemic influenza: pandemic (H1N1) 2009 briefing note 13*, http://www.who.int/csr/disease/swineflu/notes/h1n1_clinical_features_20091016/en/print.html (accessed November 4, 2009).

———. 2009g. *Antiviral use and the risk of drug resistance*, http://www.who.int/csr/disease/swineflu/notes/h1n1_antiviral_use_20090925/en/index.html (accessed November 5, 2009).

———. 2010a. *Pandemic (H1N1) 2009 update 91*, http://www.who.int/csr/don/2010_03_12/en/index.html (accessed March 15, 2010).

———. 2010b. *Pandemic (H1N1) 2009 update 76*, http://www.who.int/csr/don/2009_11_27a/en/index.html (accessed January 7, 2010).

WHO/AFRO (Regional Office for Africa). 2010. *Pandemic (H1N1) 2009 in the African region: update 65*, http://www.afro.who.int/ddc/influenzaa/index.html (accessed January 22, 2010).

WHO Representative Office in Viet Nam. 2009. *Overview of the current pandemic H1N1 2009 situation*, http://www.wpro.who.int/vietnam/sites/dcc/h1n1/ (accessed January 7, 2010).

WHO/SEARO. 2010. *Pandemic H1N1 2009*, http://www.searo.who.int/EN/Section10/Section2562_15050.htm (accessed January 22, 2010).

Wikipedia. 2007. *Virus replication*, http://en.wikipedia.org/wiki/File:Virus_Replication_large.svg (accessed November 18, 2009).

———. 2009. *Influenza*, http://en.wikipedia.org/wiki/Influenza#Replication (accessed November 18, 2009).

Wilson, M. E. 2003. The traveller and emerging infections: sentinel, courier, transmitter. *Journal of Applied Microbiology* 94(Suppl):1S-11S.

Wilson, N., and M. G. Baker. 2009. The emerging influenza pandemic: estimating the case fatality ratio. *Eurosurveillance* 14(26).

Xing, Z., and C. J. Cardona. 2009. Preexisting immunity to pandemic (H1N1) 2009. *Emerging Infectious Diseases* 15(11):1847-1849.

Yuk-hang, N., and L. Chung. 2009 (November 6). Virus passes from humans to pigs in City. *South China Morning Post*.

Zheng, B. J., K. W. Chan, Y. P. Lin, G. Y. Zhao, C. Chan, H. J. Zhang, H. L. Chen, S. S. Wong, S. K. Lau, P. C. Woo, K. H. Chan, D. Y. Jin, and K. Y. Yuen. 2009. Delayed antiviral plus immunomodulator treatment still reduces mortality in mice infected by high inoculum of influenza A/H5N1 virus. *Proceedings of the National Academy of Sciences* 105(23):8091-8096.

Zimmer, S. M., and D. S. Burke. 2009. Historical perspective—emergence of influenza A (H1N1) viruses. *New England Journal of Medicine* 361(3):279-285.

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Appendix A

Contributed Manuscripts

A1

TECHNICAL REPORT FOR STATE AND LOCAL PUBLIC HEALTH OFFICIALS AND SCHOOL ADMINISTRATORS ON CDC GUIDANCE FOR SCHOOL (K-12) RESPONSES TO INFLUENZA DURING THE 2009-2010 SCHOOL YEAR[1]

CDC Community Mitigation Task Force

CDC is releasing new guidance[2] to help decrease the spread of flu among students and school staff during the 2009-2010 school year. The guidance expands upon earlier school guidance documents by providing a menu of tools that school and health officials can choose from based on conditions in their area. It recommends actions to take this school year, suggests strategies to consider if CDC finds that the flu starts causing more severe disease than during the spring 2009 outbreak, and provides a checklist for making decisions at the local level. Based on the severity of 2009 H1N1 flu-related illness thus far, this guidance also recommends that students and staff with influenza-like illness remain home until 24 hours after resolution of fever without the use of fever-reducing medications. For the purpose of this document, "schools" will refer to both public and private institutions providing grades K-12 education to children and adolescents in group

[1]Reprinted from http://www.cdc.gov/h1n1flu/schools/technicalreport.htm (accessed November 10, 2009).

[2]See http://www.cdc.gov/h1n1flu/schools/schoolguidance.htm.

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settings. The guidance applies to such schools in their entirety, even if they provide services for younger or older students. Guidance for child care settings and institutions of higher education will be addressed in separate documents.

This Technical Report includes detailed information on the reasons for the strategies presented in the *CDC Guidance for School (K-12) Responses to Influenza During the 2009-2010 School Year*[3] and suggestions on how to use them. The guidance is designed to decrease exposure to regular seasonal flu and 2009 H1N1 flu while limiting the disruption of day-to-day activities and the vital learning that goes on in schools. CDC will continue to monitor the situation and update the current guidance as more information is obtained on 2009 H1N1.

About 55 million students and 7 million staff attend the more than 130,000 public and private schools in the United States each day. By implementing these recommendations, schools and health officials can help protect one-fifth of the country's population from flu. In addition to their central mission of educating children and adolescents, schools meet other basic needs: feeding students and providing needed child care, health and mental health services, and safe and stable routines. It is crucial not to interrupt the learning process without due cause. Although illness may be such a cause, schools and their communities have a responsibility to balance the risks of illness among students and staff with the benefits of keeping students in school.

The decision to dismiss students should be made locally and should balance the goal of reducing the number of people who become seriously ill or die from influenza with the goal of minimizing social disruption and safety risks to children sometimes associated with school dismissal. Based on the experience and knowledge gained in jurisdictions that had large outbreaks in spring 2009, the potential benefits of preemptively dismissing students from school are often outweighed by negative consequences, including students being left home alone, health workers missing shifts when they must stay home with their children, students missing meals, and interruption of students' education. Still, although the situation in fall 2009 is unpredictable, more communities may be affected, reflecting wider transmission. The overall impact of 2009 H1N1 should be greater than in the spring, and school dismissals may be warranted, depending on the disease burden and other conditions.

CDC is continually monitoring the spread of flu, the severity of the illness it is causing (including hospitalizations and deaths), and whether the virus is changing; CDC will provide periodic updates of these assessments. If this information indicates that flu is causing more severe disease than during the spring 2009 outbreak, or if other developments might require more aggressive mitigation measures, CDC might recommend preemptive, or early, school dismissals.

[3]See http://www.cdc.gov/h1n1flu/schools/schoolguidance.htm.

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Recommended School Responses to Influenza for the 2009–2010 School Year

Basic foundations of infection control in school settings should always be promoted and facilitated, not only during an influenza pandemic. During flu season, schools should be particularly vigilant about keeping sick students and staff home. Schools should be proactive, develop contingency plans to cover key positions (for example, school nurses) when staff are home ill, and regularly remind parents and staff of the exclusion recommendations. Plans should focus on protecting people at high risk for influenza complications as these groups are frequently found in schools. For example, asthma alone affects nearly one in ten school-aged youth. For a list of groups at high risk for influenza complications, see Novel H1N1 Flu and You.[4]

For general guidance on infection control in schools, see the American Academy of Pediatrics' *Managing Infectious Diseases in Child Care and Schools: A Quick Reference Guide, 2nd Edition*[5] (2009).

Recommended Responses Under Conditions with Similar Severity as in Spring 2009

Stay Home When Sick

CDC recommends that individuals with influenza-like illness remain at home until at least 24 hours after they are free of fever (100° F [37.8° C] or greater), or signs of a fever, without the use of fever-reducing medications.

This recommendation is based on epidemiologic data about the overall risk of severe illness and death and attempts to balance the risks of severe illness from influenza and the potential benefits of decreasing transmission through the exclusion of ill persons with the goal of minimizing social disruption.

Decisions about extending the exclusion period should be made at the community level, in conjunction with local and state health officials. More stringent guidelines and longer periods of exclusion – for example, until complete resolution of symptoms – may be considered for people returning to settings where high numbers of high-risk people may be exposed.

Epidemiologic data collected during spring 2009 found that most people with 2009 H1N1 flu who were not hospitalized had a fever that lasted 2 to 4 days; this would require an exclusion period of 3 to 5 days in most cases. Those with more severe illness are likely to have fever for longer periods of time. Although fever is a component of the case definition of influenza-like illness, the epidemiologic data collected during spring 2009 found that a minority

[4]See http://www.cdc.gov/h1n1flu/qa.htm.

[5]See http://aapredbook.aappublications.org/resources/midsheets.dtl.

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of patients infected with 2009 H1N1 flu with respiratory symptoms did not have a fever.

Sick individuals should stay at home until the end of the exclusion period, to the extent possible, except when necessary to seek required medical care. Sick individuals should avoid contact with others. Keeping people with a fever at home may reduce the number of people who get infected since elevated temperature is associated with increased shedding of influenza virus. CDC recommends this exclusion period whether or not antiviral medications are used. People on antiviral treatment may shed influenza viruses that are resistant to antiviral medications.

Many people with influenza illness will continue shedding influenza virus 24 hours after their fevers go away, but at lower levels than during their fever. Shedding of influenza virus, as detected in laboratory tests, can be detected for 10 days or more in some cases. Therefore, when people who have had influenza-like illness return to school they should continue to practice good respiratory etiquette and hand hygiene when they return to school and avoid close contact with people they know to be at increased risk of influenza-related complications.

Because some people may shed influenza virus before they feel ill, and because some people with influenza will not have a fever, it is important that all people cover their cough and wash hands often. To lessen the chance of spreading influenza viruses that are resistant to antiviral medications, adherence to good respiratory etiquette and hand hygiene is as important for people taking antiviral medications as it is for others.

Fever-reducing medications, that is, medications containing acetaminophen or ibuprofen, are appropriate for use in individuals with influenza-like illness. Aspirin (acetylsalicylic acid) should not be given to children or teenagers who have influenza; this can cause a rare but serious illness called Reye's syndrome. The determination of readiness to return to school should be made when at least 24 hours have passed since the ill person's temperature first remained normal without the use of these medications.

For more information on caring for sick persons in the home, see Taking Care of a Sick Person in Your Home.[6]

Separate Ill Students and Staff

Sick students and staff should always be required to stay home. *CDC recommends that students and staff who appear to have an influenza-like illness at arrival or become ill during the day be promptly separated from other students and staff and sent home*. Schools should regularly update contact information for parents so that they can be contacted more easily if they need to pick up their ill child. Recognizing that space is often in short supply, early planning on the location for a sick room is essential. This room should not be one commonly used for

[6]See http://www.cdc.gov/h1n1flu/guidance_homecare.htm.

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other purposes for example, the lunchroom during non-meal times. Nor should it be a space through which others regularly pass. It is not necessary for this room to have a separate air supply (HVAC) system. Ill persons should be placed in well ventilated areas and placed in areas where at least 6 feet of distance can be maintained between the ill person and others.

A limited number of staff should be designated to care for ill persons until they can be sent home. When possible, these should be people with limited interactions with other students and staff and therefore decreased risk of spreading influenza. These persons should not be at increased risk of influenza complications (for example, pregnant women) and they should be familiar with infection control recommendations to prevent spread of influenza. When possible and if the sick person can tolerate it, he or she should wear a surgical mask when near other persons.

School nurses, and other staff who act in this capacity, are likely to come into close contact with students and staff with influenza-like illness. *CDC recommends that staff who provide care for persons with known, probable or suspected influenza or influenza-like illness use appropriate personal protective equipment.*

For more information on caring for sick persons in the home, see Taking Care of a Sick Person in Your Home.[7]

See Interim Recommendations for Facemask and Respirator Use to Reduce Novel Influenza A (H1N1) Virus Transmission[8] or www.flu.gov for more information on personal protective equipment and how to recommend it to employees.

Hand Hygiene

Influenza may spread via contaminated hands or inanimate objects that become contaminated with influenza viruses. *CDC recommends that students and staff be encouraged to wash their hands often with soap and water, especially after coughing or sneezing.* Alcohol-based hand cleaners are also effective at killing flu germs, but may not be allowed in all schools. If soap and water are not available, and alcohol-based products are not allowed in the school, other hand sanitizers that do not contain alcohol may be useful however, there is less evidence on their effectiveness compared to that on hand washing and alcohol-based sanitizers.

Schools should provide the time needed for all students and staff to wash their hands whenever necessary, especially after coughing or sneezing into hands, before eating, and after using the restroom. Soap, paper towels and sanitizers are critical for proper hand hygiene and should be readily available in schools. If it is necessary to provide supervision to students as they wash hands in rest rooms, schools should consider timing and staffing as they plan for the fall. Schools also

[7]See http://www.cdc.gov/h1n1flu/guidance_homecare.htm.
[8]See http://www.cdc.gov/h1n1flu/masks.htm.

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should educate families, students and staff about the importance of good hand hygiene and proper methods for cleaning hands.

Visit Clean Hands Save Lives[9] for more information on hand hygiene.

Respiratory Etiquette

Influenza viruses are thought to spread mainly from person to person in respiratory droplets of coughs and sneezes. This can happen when droplets from a cough or sneeze of an infected person are propelled through the air and deposited on the mouth or nose or are inhaled by people nearby. *CDC recommends covering the nose and mouth with a tissue when coughing or sneezing and throwing the tissue in the trash after use.* Wash hands promptly after coughing or sneezing. If a tissue is not immediately available, coughing or sneezing into one's arm or sleeve (not into one's hand) is recommended. To encourage respiratory etiquette, students and staff should have access to tissues and must be educated about the importance of respiratory etiquette, including keeping hands away from the face.

Visit Cover Your Cough[10] for more information on respiratory etiquette.

Routine Cleaning

The American Academy of Pediatrics provides guidance for school cleaning and sanitizing which is appropriate for influenza. *Schools should regularly clean all areas and items that are more likely to have frequent hand contact* (for example, keyboards or desks) and also clean these areas immediately when visibly soiled. Use the cleaning agents that are usually used in these areas.

Some states and localities have laws and regulations mandating specific cleaning products be used in schools. School officials should contact their state health department or department of environmental protection for additional guidance. Schools should ensure that custodial staff and others (such as classroom teachers) who use cleaners or disinfectants read and understand all instruction labels and understand safe and appropriate use. Instructional materials and training should be provided in languages other than English as locally appropriate**.** CDC does not believe any additional disinfection of environmental surfaces beyond the recommended routine cleaning is required.

See the American Academy of Pediatrics' *Managing Infectious Diseases in Child Care and Schools: A Quick Reference Guide, 2nd Edition* (2009)[11] for guidance on cleaning and sanitizing in schools.

The EPA provides a list of EPA-registered products effective against flu.[12]

[9]See http://www.cdc.gov/cleanhands/.

[10]See http://www.cdc.gov/flu/protect/covercough.htm.

[11]See http://aapredbook.aappublications.org/resources/midsheets.dtl.

[12]See http://www.epa.gov/oppad001/influenza-disinfectants.html.

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Early Treatment for High-Risk Students and Staff

People at high risk for influenza complications who become ill with influenza-like illness should speak with their health care provider as soon as possible. Early treatment with antiviral medications is very important for people at high risk because it can prevent hospitalizations and deaths. *CDC recommends that schools encourage ill staff and parents of ill students at higher risk of complications from influenza to seek early treatment.*

High-risk students and staff who have had close contact with others who are sick with an influenza-like illness should contact their health care provider to discuss whether they may need to take influenza antiviral medications that require a prescription in the U.S.

People on antiviral treatment may still shed influenza viruses and therefore may still transmit the virus to others. These influenza viruses may develop resistance to antiviral medications. To lessen the chance of spreading influenza viruses that are resistant to antiviral medications, adherence to good respiratory etiquette and hand hygiene is as important for people taking antiviral medications as it is for others.

For more information on antiviral medications, see Interim Guidance on Antiviral Recommendations for Patients with Novel Influenza A (H1N1) Virus Infection and Their Close Contacts.[13]

Selective School Dismissals

Selective school dismissals may be considered based on the population of an individual school. Although there are not many schools where all or most students are at high risk (for example, a school for medically fragile children or for pregnant students) a community might decide to dismiss such a school to better protect these high-risk children. The decision to selectively dismiss a school should be made locally and should balance the risks of keeping the students in school with the social disruption that school dismissal can cause. School officials should work closely and directly with their local and state public health officials when deciding whether or not to selectively dismiss a school or schools. Selective school dismissals are not likely to have a significant effect on community-wide transmission: Instead, this strategy aims to protect students and staff at high risk of severe illness and death. Information on reactive and preemptive school dismissals is provided in the next section.

[13]See http://www.cdc.gov/h1n1flu/recommendations.htm.

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Recommended Additional Responses During Times of Increased Influenza Severity

CDC will continue to assess the severity of illness caused by 2009 H1N1 flu and disseminate the results of these ongoing assessments. If global or national risk assessments indicate an increased level of severity compared with the spring 2009 H1N1 flu outbreak, CDC will consider the need to recommend additional strategies including preemptive school dismissals.

Decisions to add strategies should be based on information on the severity of illness reported in national and global assessments, local goals, epidemiology, health care system capacity, and feasibility and acceptability of the strategies under consideration. The strategies which follow use a variety of methods for increasing social distance, while attempting to maintain operability of most schools. Feasibility and acceptability of these strategies will vary considerably across communities. Except for school dismissals, the following strategies have not been scientifically tested. But CDC wants communities to have tools to use that may be the right measures for their community and circumstances.

Active Screening for Illness

If influenza severity increases, schools should consider instituting active fever and respiratory infection symptom screening of students and staff when they arrive at school. At the beginning of the school day, all students and staff should be asked about suggestive symptoms such as fever, cough, runny nose, and sore throat during the previous 24 hours. Some persons with laboratory-confirmed influenza do not have a fever (between 10% and 40% of people). Therefore, absence of fever does not indicate absence of infection. In a higher severity situation, schools should send home persons with symptoms of acute respiratory infection (that is, any two of the following: sore throat, cough, runny nose [new and unexplained by allergies], or fever). As always, parents should be aware of their child's health status and monitor them for illness every morning before school.

Throughout the day, staff should be vigilant in identifying students and other staff who appear ill. These students and staff should be further screened by the school nurse, or other school-based health care worker, by taking their temperature and inquiring further about symptoms. Students and staff who develop symptoms of acute respiratory infection at school should be separated from others until sent home. When possible and if the sick person can tolerate it, he or she should wear a surgical mask until sent home.

Permit High-Risk Students and Staff to Stay Home

If influenza severity increases, students and staff at high risk for influenza complications may consider staying home from school while influenza transmis-

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sion is high in their community if they, or their families, are concerned about their ability to avoid influenza at school. The decision about whether to stay home should be made in consultation with their health care provider. People who elect to stay home from school should also attempt to decrease their exposure in other ways for example, by avoiding large public gatherings. Well students should be expected to continue their education while at home as much as possible.

Schools should prepare for discussions with parents about school safety and should consult with school boards and legal counsel about policy accommodations that might be necessary to allow students and staff at high risk for influenza complications to stay home. Local and state laws and policies also might need to be reviewed for applicability. Policies to be reviewed may be official or unofficial, such as school principals' awards for students with perfect attendance. Schools should plan now for ways to continue educating students who stay home through methods such as instructional telephone calls, homework packets, internet-based lessons, and other distance-based learning approaches.

Students With Ill Household Members Stay Home

If influenza severity increases, school-aged children who live with people with influenza-like illness should remain home for 5 days from the day the first household member got sick. This is the time period they are most likely to get sick themselves. The greatest risk of transmission is during the first 5 days of illness of the first ill household member (about 90%), with the largest transmission risk by Day 1 of this person's illness (about 40%). Keeping all the children in the household at home during this time period may also keep the flu virus from being spread to others outside the home. If a household member develops an acute respiratory illness during this time, the recommendations for exclusion of persons with influenza-like illness should be implemented. The five-day period does not need to start again for other well children in the household.

Increase Social Distances Within the School Environment

If influenza severity increases, schools should explore innovative methods for increasing social distances within the school environment. The goal should be to keep distance between people at most times or to cluster students in small, consistent groups. This is not a simple or easy strategy for most schools. Implementing any of the following options would require considerable flexibility and willingness to change among students, staff, and families. Some possible options to increase the amount of space between students or to keep consistent groups of students include:

- rotate teachers between classrooms while keeping the same group of students in one classroom (in middle and high school);

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- cancel classes that bring students together from multiple classrooms (in elementary school);
- postpone class trips that bring students together from multiple classrooms or schools in large, densely-packed groups;
- hold classes outdoors;
- discourage use of school buses and public transit;
- divide classes into smaller groups;
- move desks farther apart; and
- move classes to larger spaces, when available, to allow more space between students.

Extended Exclusion Period

If influenza severity increases, individuals with influenza-like illness should remain at home for at least 7 days, even if symptoms resolve sooner. Individuals who are still sick 7 days after they become ill should continue to stay home until at least 24 hours after symptoms have resolved.

This recommendation is based on viral shedding information. Influenza virus shedding general occurs for 5 to 7 days for seasonal influenza infection. This period may be longer for persons with 2009 H1N1 flu and among young children and people who are immunocompromised. Longer periods of exclusion also may be considered based on setting- and population-specific characteristics. Schools also might prefer a longer period so that students and staff feel able to fully function at school after recovery from their illness.

Sick individuals should stay at home until the end of the exclusion period, to the extent possible, except when necessary to seek required medical care. Sick individuals should avoid contact with others. CDC recommends this exclusion period whether or not antiviral medications are used. People on antiviral treatment may shed influenza viruses that are resistant to antiviral medications.

When people who have had influenza-like illness return to school they should continue to practice good respiratory etiquette and hand hygiene and avoid close contact with people likely to be at increased risk of influenza-related complications. To lessen the chance of spreading influenza viruses that are resistant to antiviral medications, adherence to good respiratory etiquette and hand hygiene is as important for people taking antiviral medications as it is for others.

For more information on caring for sick persons in the home, see Taking Care of a Sick Person in Your Home.[14]

[14]See http://www.cdc.gov/h1n1flu/guidance_homecare.htm.

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School Dismissals: Reactive and Preemptive

In case influenza severity increases, CDC recommends that communities review and prepare to implement their school dismissal plans according to the guidelines outlined below. School and health officials should balance the risks of influenza in their community with the disruption dismissals will cause in both education and the wider community. *School officials should work closely and directly with their local and state public health officials to make sound decisions, based on local conditions, and to implement strategies in a coordinated manner.*

When communities choose to use school dismissal, education and public health officials should clearly state to parents and their communities the reason for dismissing students and the type of school dismissal they are implementing. There are three types of school dismissals: selective (described above), reactive, and preemptive.

Reactive dismissals might be appropriate when schools are experiencing excessive absenteeism among students or staff, a large number of children are visiting the school health office or being sent home from school during the school day with documented fever, the school is not able to keep potentially infectious people out, or for other reasons that decrease the ability to maintain school functioning. Reactive dismissals might reduce the burden on the local health care system.

As with selective dismissals, the decision to dismiss students should be made locally and should balance the goal of reducing the number of people who become seriously ill or die from influenza with the goal of minimizing social disruption. School officials are encouraged to work collaboratively and communicate with neighboring districts or schools to keep others in the region aware of actions that are taken. Officials might decide to dismiss or not dismiss students from their own schools based on the experiences of their neighbors. The risk to students and staff from an ongoing school-based outbreak if potentially infectious individuals cannot be excluded from school may also lead some jurisdictions to decide to close schools. In this case, school-related mass gatherings also should be cancelled or postponed.

Preemptive dismissals can be used to decrease the spread of influenza virus or to reduce demand on the health care system. If global or national risk assessments indicate an increased level of severity compared with the spring 2009 H1N1 influenza outbreak, CDC might recommend preemptive school dismissals. If schools are dismissed, school-related mass gatherings should be cancelled or postponed. This would include sporting events, school dances, performances, rallies, commencement ceremonies, and other events that bring large groups of people into close proximity with one another.

School dismissal is likely to be more effective in decreasing the spread of influenza virus in the community when used **early** in relation to the appearance of the virus in the community and when used in **conjunction** with other strategies (for example, cancellation of community sporting events and other mass gather-

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ings). Cancellation or postponement of community events is a decision of event organizers, local public health officials and other government agencies and should be part of a coordinated community process.

A vaccine for 2009 H1N1 flu will likely become available in fall 2009. For children, at least, protective immunity will require 2 doses of vaccine, separated by at least 3 weeks and an additional 2 weeks for the immune response to develop (that is, approximately 5 weeks after the first vaccination). If an increase in community-wide transmission occurs shortly before vaccine-induced immunity is anticipated, or before a scheduled vacation, some jurisdictions may consider preemptive dismissals.

Resuming Classes After the Dismissal

The length of time students should be dismissed from school will vary depending on the type of school dismissal as well as the severity and extent of illness. *When the decision is made to dismiss students, CDC recommends doing so for 5 to 7 calendar days.* Reactive school dismissals are likely to be of shorter duration than selective or preemptive dismissals. Because the goals of selective dismissals (to protect students and staff at high risk of severe illness or death) and preemptive dismissals (to decrease the spread of influenza virus) are usually different from those of reactive dismissals, the length of time schools are dismissed might be longer.

On a regular basis (for example, weekly) communities that have dismissed students from school should reassess the epidemiology of the disease, the benefits of keeping students home, and the societal repercussions of doing so. Based on this reassessment, communities may decide either to extend the school dismissal or to reopen schools. In the event that CDC recommends preemptive school dismissals, this recommendation also might include a modification to the suggested length of dismissal, based on the severity observed across the nation and globally. Therefore, schools and school boards should plan for more prolonged periods of school dismissal. If schools attempt to continue educational services to all students during a lengthy school dismissal, students with disabilities should receive comparable access to education.

The authority for decision-making regarding school dismissal may reside in multiple sectors of state and local government; these entities must work in a coordinated manner. National, regional, or local data, and the decision-making guidance included in this document, may be useful for determining whether to dismiss schools.

Reducing Adverse Effects from School Dismissal

As part of a community planning process, school dismissal plans should address possible secondary effects on the community. The planning process should include communicating these plans with all community members affected

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by school dismissal. These might include effects on critical infrastructure, parents' job security and income loss, school funding due to funding calculations based on attendance, child nutrition due to the loss of access to the school meals program, loss of access to health services, educational progress, and child safety due to possibly increased unsupervised time. Communities should prepare to address these secondary effects so as to increase the acceptability of and participation in school dismissal. Parents should plan for child care while schools are dismissed, as these decisions may be made very quickly.

Communities should also plan to allow school staff to use school facilities while students are dismissed. Keeping school facilities open may allow teachers to develop and deliver lessons and materials (for example, by using school teleconference lines or other distance-based education delivery systems) and other staff to provide essential services (such as preparation of meals) keeping in mind basic infection control practices.

If school is dismissed, let CDC, the U.S. Department of Education, and your state health and education agencies know by submitting a simple report at ww.cdc.gov/FluSchoolDismissal.[15]

Roles

Collaboration is essential: many different stakeholders have important roles to play in the decision-making process, implementing strategies, and ensuring their effectiveness. To be most effective, these activities must be coordinated at the federal, state, and local levels.

- CDC will continue to monitor the spread and severity of influenza illness, monitor for changes in circulating influenza viruses that may confer increased severity of disease, identify promising methods for reducing morbidity and mortality, assist state and local health and education agencies to implement those methods and evaluate their effectiveness, and provide timely updates on new scientific findings as well as additional guidance as the situation warrants.
- The U.S. Department of Education (ED) will collaborate with federal, state, and local agencies as well as non-governmental entities to disseminate new guidance, provide support to state and local education agencies, and work with states to provide flexibility in regulations around funding.
- ED, state public health and education agencies, and CDC will monitor school dismissals and other related issues.
- State and local public health and education agencies should work together to decide which strategies to implement and when, collect and share data, and disseminate emerging guidance.

[15]See http://www.cdc.gov/h1n1flu/schools/dismissal_form/.

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- Schools should examine and revise, as necessary, their current crisis or pandemic plans and procedures, including updating contact information, and communicate with vendors who supply critical products or services to plan for continuation of those services throughout the flu season. Critical services may include food service, hygiene supplies, and personal protective equipment for staff. This planning is especially important when suppliers may be small businesses in the local area that could also be affected by a flu outbreak.
- Schools should be a resource for families to help mitigate the secondary effects of school dismissals by referring them to assistance in the community or, where feasible, by providing direct assistance. Schools can communicate with families and the community about what they will do to decrease spreading influenza illness; and help families and communities understand the important roles they can play in reducing the spread of influenza and keeping schools open.
- Students, staff, and their families must take personal responsibility for staying home when ill, practicing hand hygiene and respiratory etiquette, and planning in advance for child care in the event of a school dismissal.
- Private sector support is essential for working parents and guardians who need to stay home to care for an ill child or find alternate child care in the event of a school dismissal. The economic impact of a school dismissal can have ripple-effects throughout the community and local economy. Flexible leave and workplace policies can keep parents from losing pay or even their jobs.
- Community-based and faith-based organizations can provide crucial support to families by educating community members about the importance of staying home when ill, hand hygiene, and respiratory etiquette. Often, they also can provide meals, alternative child care sites, transportation, and other services to ease the burden of staying home.

Deciding on a Course of Action

To decrease exposure of students and school staff to the influenza virus, CDC recommends a combination of targeted, layered strategies applied early and simultaneously based on trends in the severity of the disease, characteristics of the virus, expected impact, feasibility, and acceptability. These issues should be determined through collaborative decision-making involving education and public health agencies, parents, and the community.

CDC and its partners will continuously look for changes in the severity of influenza-like illness and will share what is learned with state and local agencies. However, states and local communities can expect to see a lot of differences in disease burden across the country.

Every state and community has to balance a variety of objectives to determine

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their best course of action to help decrease the spread of influenza. Decision-makers should explicitly identify and communicate their objectives which might be one or more of the following: (a) protecting overall public health by reducing community transmission; (b) reducing transmission in students and school staff; and (c) protecting people with high-risk conditions.

Some strategies can have negative consequences in addition to their potential benefits. In the particular case of school dismissals, decision-makers also must consider and balance additional factors: (a) how to ensure students continue to learn; (2) how to provide an emotionally and physically safe place for students; and (3) how to reduce demands on local health care services. The following questions can help begin discussions and lead to decisions at the state and local levels.

Decision-Makers and Stakeholders

Are all the Right Decision-Makers and Stakeholders Involved in the Decision-Making Process?

- Identify the decision-makers. In different jurisdictions, local and state health, education, and homeland security agencies may have relevant decision-making responsibilities. Direct involvement of governors, mayors, public health officials, or school superintendents may be needed.
- Identify the stakeholders. Stakeholders will vary from community to community but may include parent representatives, students, local business and faith community representatives, teachers, health care providers, hospitals, community organizations, school nurses, school food service directors, and vendors that supply schools.

What is the Process for Working Together?

- Do you have a process for regular input and collaboration on decisions?
- Are there strong, open communication channels between health and education officials? Does this include frequent information sharing?
- Do you regularly review your crisis and pandemic plans? Do you revise as needed?

Information Collection and Sharing

Can Local or State Health Officials Determine and Share Information About the Following?

- What is the severity and extent of spread of the disease in the state or locality? What is the rate of outpatient visits for influenza-like illness? What is the local hospitalization rate for influenza-like illness? Are the

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numbers of hospitalizations or deaths increasing? What percent of these hospitalized patients require admission to intensive care units? How many influenza deaths have occurred in the community? Are some groups being disproportionately affected?

- How busy are local health care providers and emergency departments? How many visits are they getting for influenza-like illness? Are they able to meet the increased demand for care from persons with influenza-like illness? Are local health care providers or emergency departments becoming overburdened?
- Are the hospital and intensive care unit (ICU) beds full with influenza patients? Is there available space in the ICUs? Are there enough ventilators?
- Do the hospitals have enough staff to provide care? Is there increasing absenteeism in health care workers due to influenza-like illness in themselves or their family members?
- Is there enough antiviral medication to treat sick patients at high risk for complications?

Can Local Education Agencies or Schools Determine and Share Information About the Following?

- What are school absenteeism rates? How many visits are being made to school health offices daily? How many students with influenza-like illness are being sent home during the school day?

Feasibility

Do You Have the Resources to Implement the Strategies Being Considered?

- What resources are available? Do you have access to the funds, personnel, equipment, and space needed?
- How long will the strategies take to implement? How long can the strategies be sustained?
- Are changes to legal authority or policy needed? How feasible are these changes?
- How can you most clearly communicate with the community about steps parents, students, individuals and families need to take and the reasons for recommendations?

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Acceptability

Have You Determined How to Address the Following Challenges to Implementing the Strategies?

- How are public concerns affecting the community? What can you do to empower personal responsibility for protective actions?
- Will the community support the strategies under consideration? What can you do to increase support?
- What secondary effects (for example, child nutrition, job security, financial support, health service access, and educational progress) might result from the strategies under consideration? Can you get the message out to businesses and employers that they need to have flexible leave policies that align with public health recommendations?
- Can these secondary effects be mitigated? Which community entities and organizations can help reduce the secondary effects?
- What can be done to increase community buy-in?

Preparing for the Flu: A Communication Toolkit for Schools (Grades K-12)[16]

A2

PREDICTING EMERGING DISEASES IN THE TWENTY-FIRST CENTURY: THE CASE OF ZOONOTIC INFLUENZA

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In this paper, we would like to pose a simple question: What have we learned from past experiences with emerging diseases that could help us understand the emergence and spread of 2009-H1N1 influenza A and the next pandemic pathogen? We hope to illustrate how, through intensive study and fusion of evolution, ecology, virology, and microbiology, we could be better prepared for, or even predict for, the next emergent pathogen.

Over the past four decades, we have seen the emergence of diseases such as AIDS, methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and

[16]See http://www.cdc.gov/h1n1flu/schools/toolkit/.
[17]New York, NY 10001.

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severe acute respiratory syndrome (SARS). The rate of disease emergence has increased significantly over this time, and there seem to be parallel problems in wildlife and even plants (Daszak et al., 2000; Anderson et al., 2004; Jones et al., 2008). In wildlife, a fungal disease has caused a series of extinctions of amphibian species globally, and a transmissible cancer threatens extinction of the Tasmanian devil (McCallum et al., 2007). In plants, diseases of crops and trees have been linked to anthropogenic spread through trade, climate change, and other factors (Anderson et al., 2004). What are the commonalities among these seemingly disparate groups? Are there patterns to emergence that might allow us to predict and prevent the next emerging disease? We should strike a note of caution at this point. In his 1998 address to the International Congress on Emerging Infectious Diseases, Professor Fred A. Murphy reminded us that predicting the next emerging disease's origin or impact is a significant challenge (Murphy, 1998). The biggest obstacle is probably the sheer size of the unknown pathogen diversity in wildlife, livestock, and other reservoir species with potential to infect humans, should we make the right type of contact. Later in this paper, we will present our approach to dealing with this unknown, but first we consider the commonalities in the process of emergence and how they lead us to a potential solution. We focus here on the emergence of new zoonotic diseases from other animal reservoirs.

There are undoubtedly factors that influence a pathogen's potential to spill over from wildlife to humans. As a simple case in point, rodent-borne zoonotic pathogens (e.g., hantaviruses) require the presence of rodent reservoirs and, although these creatures exist throughout the world, there are certain areas where rodent abundance is greater or the contact with humans is higher. Although this does not tell us exactly where a rodent-borne pathogen will emerge, it does provide an indication of where there is higher risk. In the same vein, substantial molecular phylogenetic evidence points to a Central-West African origin of HIV-1 from chimpanzees, a species widely hunted for bush meat there. The origins of SARS and some Ebola virus outbreaks have also been linked to the consumption of wildlife. It follows that patterns of human hunting, butchering, and consumption of bush meat will likely predict patterns of the emergence of some zoonotic infections. Finally, SARS coronavirus spread rapidly from China to the New World via infected people traveling on planes (Hufnagel et al., 2004). If we examine trends in global air travel, surely that will give us significant predictive power in analyzing where the next new pathogen in people is likely to spread to. In a very general sense, it becomes clear as we look at the source of each emerging pathogen that almost every emerging disease (perhaps every single one) was driven to emerge by some type of change in human behavior, demography, or anthropogenic environmental change. These emerging diseases are not, after all, "natural" events. If this is true, then it follows that we should be able to predict disease emergence by analyzing trends in demographic, socioeconomic, or environmental changes.

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To do this, our group has used a database approach pioneered by Mark Woolhouse's group in Edinborough and based on the database analyses commonly used in ecological studies of animal life history traits. In this approach, global spatial data on environmental changes (e.g., agricultural land-use change) and the outcomes of these changes (in this case of the occurrence of an emerging disease) are tested for correlation. To do this for disease emergence, we expanded a database of all pathogens known to emerge in people (Woolhouse, 2008). The distribution of the types of newly emerging pathogens offers a glimpse of what sort of pathogens are more likely to cause the next emerging disease. A disproportionate amount of these pathogens are drug-resistant bacteria (e.g., MRSA) and viruses (mainly RNA viruses, e.g., HIV-1, SARS CoV, and Chikungunya virus). This is not entirely surprising because of the recent rise in global use of a diverse array of antibiotics, and because of the mutation rates and lack of copy editing mechanisms in the RNA viruses, which make them better able to produce more diverse strains capable of establishing in new host species. The origins of emerging pathogens are also informative, with the majority being zoonotic (e.g., SARS CoV, the Lyme disease spirochete, and Ebola virus) and these zoonoses include many of the most significant infections to emerge recently. This likely reflects our increasingly close association with animals, a factor that may appear counterintuitive in developed countries where our meat is bought prepackaged in plastic, but is a virtue of the unprecedentedly large global human population and our globalized travel and trade networks. Even as we eat our lunch here at the Institute of Medicine workshop, we may be eating beef produced in Australia, anchovies from Peru, and blackberries grown in Guatemala. Thus, in our database of emerging diseases, we find zoonotic diseases emerging from this complex network of globalized agriculture and trade.

Taking the database of emerging diseases, we surveyed the literature for the most accurate information available on the geographic origin of the first known outbreaks for each pathogen. In plotting out the origin of each of the more than 400 emerging disease "events," we find a strong bias toward the developed countries of Europe, North America, and the Far East. This likely reflects the increased ability of these richer countries to identify emerging disease outbreaks and is perhaps due to their higher spending on healthcare. To correct for geographic and temporal biases in global reporting, we trawled through every paper published in *Journal of Infectious Diseases*[18] from 1980 to 2002, collated each author's geographic origin and the date of the work, and then incorporated these data into our analyses. Next, we developed a strategy to estimate the global spread of the vast diversity of unknown pathogens. To do this, we used a global database of the distribution of every mammalian species (Jones et al., 2008) and made the simple assumption that every species will carry a roughly equal number of pathogens,

[18]An international journal that publishes papers on all infectious diseases, not just emerging pathogens.

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known or unknown (Grenyer et al., 2006). We then used a general linear model (GLM), a multiple regression model, to test for correlation between the risk of an emerging disease and a series of presumed drivers of emergence: rainfall distribution, human population density and growth, and so on. Our results (Jones et al., 2008) show that all groups of emerging diseases (vector-borne, zoonotic diseases from wildlife, zoonotic diseases from other species, and drug-resistant infections) show strong correlation with human population density and growth. We found that zoonotic diseases from wildlife were strongly correlated with human density and mammalian biodiversity, suggesting that it is regions where human populations are coming into close contact with wildlife that are most at risk for the highest impact of future zoonotic emerging infectious diseases (EIDs). Finally, we were able to use the geographic distribution of risk, corrected for biases in reporting, to produce the first ever global maps of the risk of future emerging diseases (Jones et al., 2008). The maps for zoonotic diseases pointed to developing countries in the tropics (Central and West Africa, Mexico, parts of tropical Latin America, South Asia, Southeast Asia) as those places most likely to spawn the next emerging zoonotic pathogen. Importantly, these are also the regions least covered by our global effort to conduct surveillance for new diseases.

This predictive approach has great relevance for new strains of influenza. If we can develop predictive approaches to the emergence and spread of new pathogens, it may be possible to also do this for new strains of influenza. Influenza pandemics have occurred repeatedly in the twentieth century. In 1918, 1957, and 1968, these pandemic strains resulted in 50 million, 1 million, and 0.5 million deaths, respectively (Cox and Subbarao, 2000). The resulting strains circulating annually as seasonal flu cause millions of severe illnesses and approximately 500,000 deaths per year (Cox and Subbarao, 2000). In 1998, with the emergence of H5N1 virus direct from birds and again in 2009, with the emergence of a new strain of 2009-H1N1 influenza A virus, it became evident that there is significant potential for novel strains, to which humans have little or no immunity, to arise and spread as worldwide pandemics. Furthermore, it became clear that these strains could emerge from zoonotic reservoirs (poultry, wild birds, pigs) into the human population. What factors underlie this phenomenon? Influenza viruses are able to evolve into new strains capable of establishing in new host species, specifically their potential for genetic reassortment. This results in a diversity of influenza strains which was illustrated well in the 2009 pandemic, wherein the new strain included segments of avian, human, and swine origin (Smith et al., 2009). Swine-origin H1N1 viruses have circulated in North American pigs for over 80 years (Shope and Lewis, 1931). The precursor to this virus was first detected in commercial swine in the United States and was subsequently labeled as a notifiable disease in 2007. Further mixing and reassortment with other cocirculating viruses (e.g., H3N2 and H1N2) led the 2009-H1N1 influenza A virus to have gene segments from humans, swine, and birds and these segments were associated with three different continents (Smith et al., 2009). Phylogenetic

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analysis suggests the strain emerged between 10 and 15 years ago, but, due to a lack of surveillance, the direct ancestors are not known. However, the new gene segments that were not previously known to circulate in North American swine most closely resemble the Eurasian avian-like swine H1N1 (Smith et al., 2009). This suggests that live hog trade between Eurasia and North America could have facilitated the mixing that led the World Health Organization (WHO) to declare the first pandemic of the twenty-first century.

Phylogenetic analysis of 2009-H1N1 influenza A is useful, but it is limited in helping our understanding of the virus' origin and emergence. For example, it can point to the involvement of swine production, but, due to the incomplete surveillance and availability of global swine influenza sequences for the past two decades, it is currently not possible to trace back the virus spread through the swine trade. Likewise, it is currently impossible to deduce the relative roles of swine production, poultry production, wild bird migration, and human travel in the emergence of the strain. Our group analyzed swine and poultry imports to Mexico in the decade preceding the emergence of 2009-H1N1 influenza A using Food and Agriculture Organization (FAO) data from the UN Comtrade data portal (2009). We found that there was little trade between Mexico and countries other than Canada, the United States, and the United Kingdom, but that the volume of trade with these countries was extremely high (tens of thousands to hundreds of thousands during this period). Likewise, the volume of poultry traded among these countries was in the hundreds of thousands to tens of millions during this period, with multidirectional trade confounding the issue. This supports the phylogenetic findings of evidence for mixing of multiple strains. However, the lack of knowledge of recent evolution of each H1N1 viral gene segment precludes the use of this approach to determine viral origins.

There are very detailed data on human travel capacity, and it is possible to analyze the spread of the strain postemergence and to make some useful predictions. We used data on human air travel capacity from the International Air Transport Association (IATA, 2009) from around the time of the first emergence of 2009-H1N1 influenza A. We found that these data are a good predictor of the early spread of the virus from its origin near La Gloria, Mexico, especially when we included the likely secondary travel of passengers out of connection hubs (e.g., Los Angeles, Houston, and others). However, apparent anomalies in the case load were evident for some countries. For example, our air travel data predict that Brazil and Argentina (two countries traveled to extensively from Mexico) should have had higher caseloads than were reported in the weeks following the outbreak. We predicted that there was a "hidden" caseload due to the likely lower propensity of these countries to report than richer countries such as the United States—a product of less funding available for healthcare (testing and surveillance), less incentives for poorer people to report, and the lower number of testing facilities and doctors per capita. We tested this theory by incorporating measures of gross domestic product (GDP) and money spent on healthcare in

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these countries. We found that incorporating national healthcare resource data into our analyses allowed a much greater capacity to predict the international reporting of spread of this virus. In countries with lower healthcare resources, the reporting of 2009-H1N1 influenza A cases was significantly delayed, reflecting a likely lower capacity for testing and reporting, as well as other demographic issues. We concluded that strategies to prevent pandemic influenza virus emergence and spread in the future may include enhanced surveillance for reassortant strains in traded livestock and rapid deployment of control measures in the initial spreading phase to countries where travel data predict spread and where lower healthcare resources predict delays in reporting. Our results highlight the benefits, for all parties, when higher income countries provide additional healthcare resources for lower income countries, particularly those that have high air traffic volumes. The result is the potential for earlier detection of pathogens and reduced impact of pandemics.

What lessons can we learn from these approaches to disease emergence that we can apply to zoonotic influenza viruses? Broadly, we can conclude that predictive approaches to disease emergence require measurement of the capacity of anthropogenic changes to alter dynamics of viruses and their risk of spilling over to people. This has great relevance to highly pathogenic H5N1, which has repeatedly spilled over to people in Asia but so far has not been efficiently transmitted between people. Our group is involved in a new Fogarty International Center-funded initiative to collect the sort of data necessary for developing a predictive model for this pathogen that will be of use in predicting the risk for other zoonotic influenza strains. This project involves collaboration among groups working on the ground in South America, Africa, South Asia, and Southeast Asia. The ultimate goal is to build a mathematical model that describes the risk of influenza virus movement within wild bird populations, and between these and domestic poultry farms, pig farms, and then people. Mathematical models work best when they are underpinned (parameterized) with data on the factors involved in each important stage of emergence. In this case, each group will gather data on wild bird populations (e.g., diversity, abundance, contact with poultry), on poultry and pig populations (e.g., farm size, density, and agricultural practices), and on human populations (e.g., density and cultural practices relating to pigs and poultry). Once the data collection is complete, the spillover rates can be observed and the data used to parameterize a model that hopefully will help us to identify important risk factors *a priori*.

It seems logical to focus particular interest on farming practices. For example, poultry production has changed tremendously in the past 50 years following the widespread availability of cheap antibiotics to combat coccidiosis, the development of new rapid weight-gain bird varieties, and the growing demand for protein, particularly in Asia. The annual per capita consumption of poultry, pork, and beef in the United States shows a comparatively large increase in poultry compared to pork or beef (Figure A2-1). This increased demand has resulted

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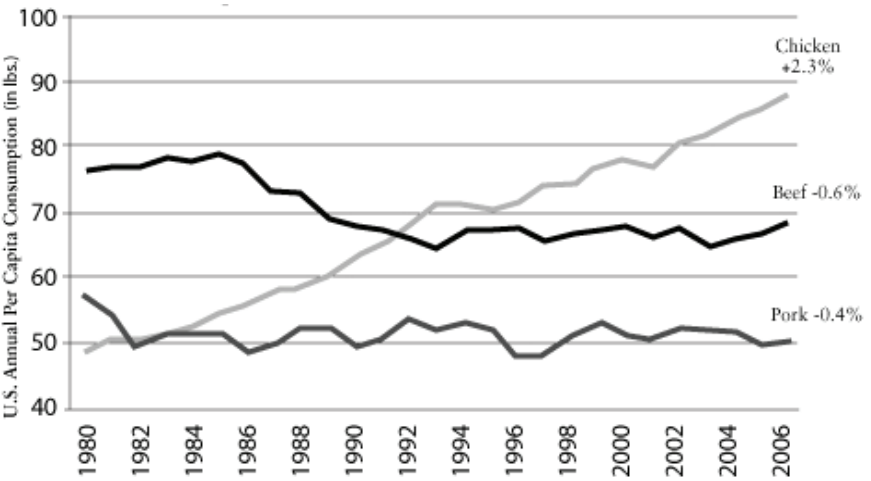

FIGURE A2-1 Chicken: a growth category. Compound annual growth rate 1980-2006. Per capita consumption has grown consistently for 26 years.
SOURCE: Reprinted with permission from Boric (2006).

in a shift from backyard production to vertically integrated commercial facilities that can now generate over 1 million kg of meat per year (MacDonald, 2008). The number of farms has decreased by 50 percent, yet production has gone up 500 percent (MacDonald, 2008). These commercial farms house birds in dense populations and, although there are varying degrees of biosecurity, there is a great deal of transmission potential within-farm and between farms. Live bird markets have also been associated with disease outbreaks (i.e., SARS) in the past and are another complicating factor in the influenza transmission cycle. One of the risk factors here is the mixing and clustering of many different species from vastly different areas. The markets typically house animals very tightly and have unsanitary conditions that may promote transmission. Waterfowl are thought to be the primary reservoir host for influenza viruses; however, nearly 100 species of birds have tested positive. Anseriformes (ducks, swans, and geese) includes the most commonly infected species and the prevalence for influenza viruses normally ranges between 1 and 15 percent (Olsen et al., 2006). H5N1 has also been isolated from a range of sick mammals, and the host diversity of this strain is probably underestimated. A further complexity here is that some species may act as "silent" carriers or reservoirs. For example, an H5N1 isolate that was very lethal in commercial poultry was found to only cause a mild passing illness in juvenile mallard ducks (Sturm-Ramirez et al., 2005) and similar findings have been seen with quail. More experimentation with different subtypes and species needs to be accomplished before we will be able to understand how these patho-

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gens impact the wide variety of hosts they can infect. This in turn will influence the potential for viral persistence and potentially spill over into humans.

Of the Anseriformes, the dabbling (or puddle) ducks have the greatest prevalence and mallards in particular have the highest prevalence (Olsen et al., 2006). The age structure of these populations is also important in that juvenile birds are more likely to have an infection than adults, and this likely is influenced by immunological status. Other migratory birds including the Charadriiformes (shorebirds, gulls, terns, and waders) can be infected but typically only at very low levels (Krauss et al., 2004; Olsen et al., 2006). However, this does not mean they are unimportant in the transmission cycle or maintenance of the virus. More intensive long-term data on how these viruses circulate and transmit between these birds are needed.

Finally, the potential for newly reassorted strains to emerge is probably heightened now because of the widespread circulation of 2009-H1N1 influenza A. We hope that our Fogarty International Center-funded program will both help identify the risk of co-infections (e.g., regions with high poultry and hog farm density) and actually find evidence in the testing that our groups will be doing. The recent report of hog farms in Indonesia with high prevalence of H5N1 (Cyranoski, 2005) and two very recent suspected cases of humans passing 2009-H1N1 influenza A onto hogs highlight this risk.

We conclude that there are a growing number of strategies being developed to predict the origin and spread of novel emerging pathogens. These strategies meld ecological, virological, and mathematical approaches to identify high-risk regions, activities, and behaviors, and they have some potential for prevention and control. At the same time, far more detailed and structured studies are needed to truly get to the underlying causes of zoonotic influenza emergence and help prevent the next human-to-human high-pathogenicity pandemic. To do these studies effectively will require some capital investment, likely within the range of a few tens of millions of dollars. However, we believe the potential reduction in pandemic risk would be a wise investment because the predicted pandemic mortality and associated economic costs are within the tens of billions of dollars (Meltzer et al., 1999).

References

Anderson, P. K., A. A. Cunningham, N. G. Patel, F. J. Morales, P. R. Epstein, and P. Daszak. 2004. Emerging infectious diseases of plants: pathogen pollution, climate change and agrotechnology drivers. *Trends in Ecology and Evolution* 19(10):535-544.

Boric, J. 2006. *Investing in chicken*, http://pennysleuth.com/investing-in-chicken-2/ (accessed March 24, 2010.

Cox, N. J., and K. Subbarao. 2000. Global epidemiology of influenza: past and present. *Annual Review of Medicine* 51:407-421.

Cyranoski, D. 2005. Bird flu spreads among Java's pigs. *Nature* 435(7041):390-391.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Daszak, P., A. A. Cunningham, and A. D. Hyatt. 2000. Emerging infectious diseases of wildlife—threats to biodiversity and human health. *Science* 287(5452):443-449.

Grenyer, R., C. D. L. Orme, S. F. Jackson, G. H. Thomas, R. G. Davies, T. J. Davies, K. E. Jones, V. A. Olson, R. S. Ridgely, P. C. Rasmussen, T. S. Ding, P. M. Bennett, T. M. Blackburn, K. J. Gaston, J. L. Gittleman, and I. P. F. Owens. 2006. Global distribution and conservation of rare and threatened vertebrates. *Nature* 444(7115):93-96.

Hufnagel, L., D. Brockmann, and T. Geisel. 2004. Forecast and control of epidemics in a globalized world. *Proceedings of the National Academy of Sciences* 101(42):15124-15129.

IATA (International Air Transport Association). 2009. *Aviation data for airline planners*, http://www.iata.org (accessed November 16, 2009).

Jones, K. E., N. G. Patel, M. A. Levy, A. Storeygard, D. Balk, J. L. Gittleman, and P. Daszak. 2008. Global trends in emerging infectious diseases. *Nature* 451(7181):990-993.

Krauss, S., D. Walker, S. P. Pryor, L. Niles, C. H. Li, V. S. Hinshaw, and R. G. Webster. 2004. Influenza A viruses of migrating wild aquatic birds in North America. *Vector-Borne and Zoonotic Diseases* 4(3):177-189.

MacDonald, J. M. 2008. *The economic organization of U.S. broiler production*, http://www.ers.usda.gov/publications/eib38/eib38.pdf (accessed November 16, 2009).

McCallum, H., D. M. Tompkins, M. Jones, S. Lachish, S. Marvanek, B. Lazenby, G. Hocking, J. Wiersma, and C. E. Hawkins. 2007. Distribution and impacts of Tasmanian devil facial tumor disease. *EcoHealth* 4(3):318-325.

Meltzer, M. I., N. J. Cox, and K. Fukuda. 1999. The economic impact of pandemic influenza in the United States: priorities for intervention. *Emerging Infectious Diseases* 5(5):659-671.

Murphy, F. A. 1998. Emerging zoonoses. *Emerging Infectious Diseases* 4(3):429-435.

Olsen, B., V. J. Munster, A. Wallensten, J. Waldenstrom, A. Osterhaus, and R. A. M. Fouchier. 2006. Global patterns of influenza A virus in wild birds. *Science* 312(5772):384-388.

Shope, R. E., and P. Lewis. 1931. Swine influenza: experimental transmission and pathology. *Journal of Experimental Medicine* 54(3):349-359.

Smith, G. J. D., D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghwani, S. Bhatt, J. S. M. Peiris, Y. Guan, and A. Rambaut. 2009. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* 459(7250):1122-1125.

Sturm-Ramirez, K. M., D. J. Hulse-Post, E. A. Govorkova, J. Humberd, P. Seiler, P. Puthavathana, C. Buranathai, T. D. Nguyen, A. Chaisingh, H. T. Long, T. S. P. Naipospos, H. Chen, T. M. Ellis, Y. Guan, J. S. M. Peiris, and R. G. Webster. 2005. Are ducks contributing to the endemicity of highly pathogenic H5N1 influenza virus in Asia? *Journal of Virology* 79(17):11269-11279.

UN Comtrade. 2009. *United Nations Commodity Trade Statistics Database*, http://comtrade.un.org/ (accessed November 16, 2009).

Woolhouse, M. E. J. 2008. Epidemiology: emerging diseases go global. *Nature* 451(7181):898-899.

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A3

THE SPRING 2009 INFLUENZA A H1N1 OUTBREAK: A LOCAL PUBLIC HEALTH PERSPECTIVE

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Between April 25, 2009, and July 31, 2009, 565 confirmed cases of 2009-H1N1 influenza A were reported to Public Health–Seattle and King County, WA, including 70 hospitalizations and three deaths (Figure A3-1). Racial and ethnic minorities were also disproportionately represented: 63 percent of cases were nonwhite compared to 24 percent of the county population, and 22 percent of cases were Hispanic compared to 6.8 percent of the county. Twenty-three languages were spoken by the 393 cases for which language data were available and 157 (40 percent) spoke a language other than English as the primary or secondary language at home. Among the foreign language speakers, Spanish was the most common language (48 percent), followed by Somali (13 percent) and Vietnamese (9 percent). Other languages were spoken by less than 5 percent of foreign language speakers (Kwan-Gett et al., 2009).

The Centers for Disease Control and Prevention's (CDC) initial criteria for reporting and testing of suspected cases of 2009-H1N1 influenza A included travel to an area where cases had been confirmed and resulted in a steady increase in the number of reports received locally, accelerating sharply after King County cases were confirmed during the week of April 26, 2009. The peak number of persons with influenza-like illness (ILI) presenting to local emergency departments (EDs) based on syndromic surveillance system data ranged from 200 to 375 percent greater than that during the 2008-2009 seasonal influenza outbreak and averaged 500 percent higher than pre-outbreak levels. Elevated levels of ED visits lasted for over one month, with highest volumes seen among patients in the 5-17 and 18-44 year-old age groups (Figure A3-2). Although the proportion of ED patients with ILI who were admitted to the hospital was comparable to that observed during the seasonal influenza period, an increased number of hospital admissions strained certain facilities, particularly those caring for children and tertiary care center intensive care units.

Syndromic surveillance at 18 of 19 county EDs allowed timely evaluation of the number and proportion of ED visits for ILI stratified by age and hospital,

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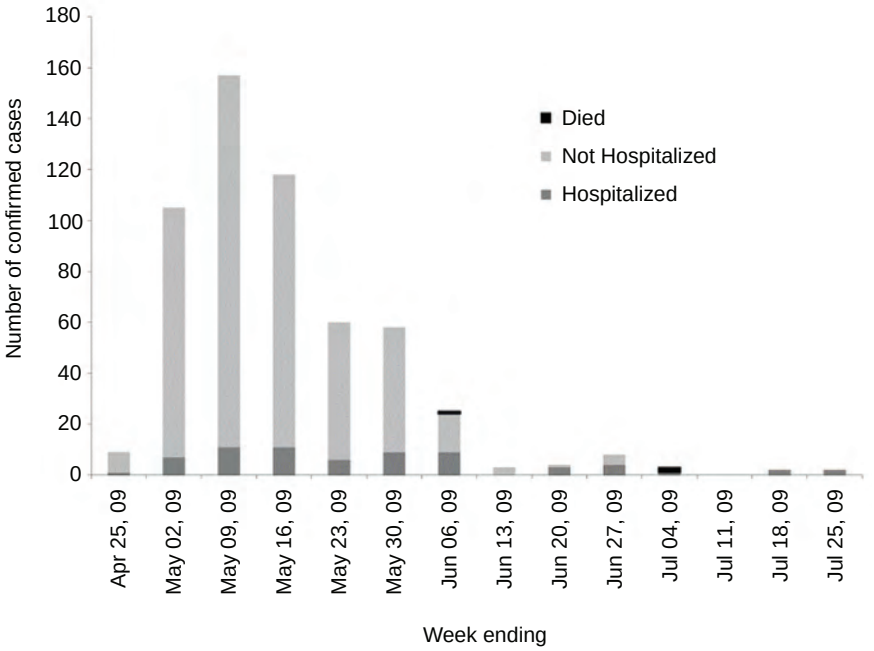

FIGURE A3-1 Laboratory-confirmed 2009-H1N1 influenza A infections by age, April-July 2009, King County, Washington.

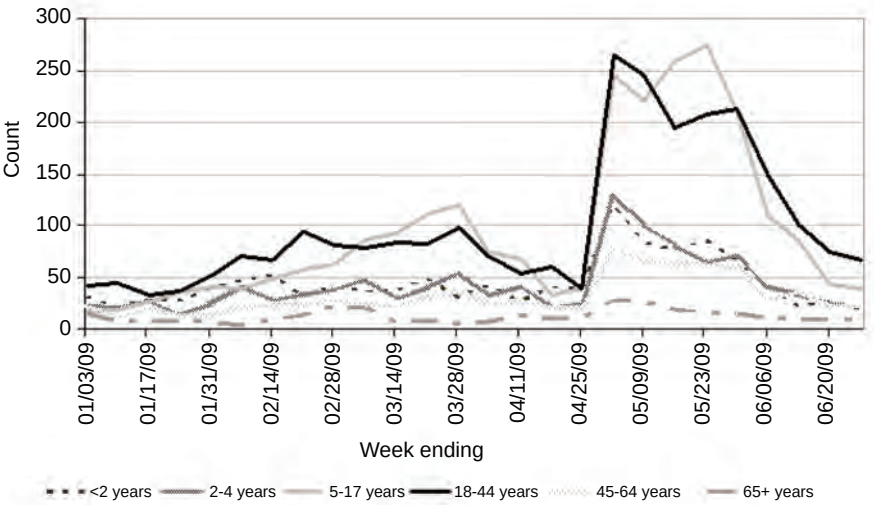

FIGURE A3-2 Emergency department visits for influenza-like illness, January 1, 2009, through June 20, 2009, King County, Washington.

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as well as number and proportion of ILI cases admitted to the hospital. We were also able to evaluate trends over time to compare current ILI activity and age distributions with previous influenza seasons. We observed a good correlation between syndromic ED ILI trends and laboratory-based surveillance data, and between hospitalized confirmed H1N1 cases and syndromic ED admissions among patients with ILI, suggesting that ED ILI data tracked the novel influenza A H1N1 outbreak well. Resources necessary to manage the syndromic surveillance system are provided through federal preparedness funding. Limitations of syndromic surveillance include the inability to do case follow-up easily (because data are deidentified), missing data (e.g., disposition), absence of standardized chief complaint categories or terms resulting in potential misclassification, and variable definitions of ILI used in syndromic systems around the country. Until syndromic ILI and pneumonia data can be validated, their sensitivity and specificity remain unknown.

School absenteeism reporting is a commonly employed indirect indicator of seasonal influenza activity and had special prominence during the spring 2009-H1N1 influenza A outbreak. The increased focus on absenteeism reporting highlighted the limitations of our current system and potential areas for improvement.

Until recently, school absenteeism reporting has been a passive, manual system, in which school personnel are requested to report weekly absenteeism. Participation in this system has been variable and inconsistent across King County's 19 public school districts (with 525 schools) and 225 private schools. Consequently, there are no reliable historical data to allow analysis of absenteeism trends over time. Absenteeism rates are reported at the school level. Data on grade-level rates are not provided, definitions of absence are not standardized, and the threshold for reporting (traditionally 10 percent) is arbitrary and not adjusted for baseline levels of absenteeism.

To promote increased participation in absenteeism reporting, in 2008 we developed a web-based reporting system that requested the following information: a weekly absenteeism report with peak absenteeism for the week, whether more than half of absenteeism was due to illness, and the predominant reasons for absenteeism. However, many schools did not report because of resource and staff constraints, and consistency of reporting was poor. To further simplify reporting and relieve schools of the associated administrative burden, after the spring 2009-H1N1 influenza A outbreak we implemented district-level automated electronic absenteeism reporting to collect aggregate counts of the daily absences by school and grade level. This system is made possible through collaboration among public health, school districts, and a cooperative of districts and educational service districts that were already collecting electronic data. Strengths of the system include complete data collection from participating school districts, the ability to analyze trends over time, establish baseline levels of absenteeism and define increases above baseline, and inclusion of grade level data. Limitations include

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lack of information about the reason for absence (which continues to require manual follow-up), and no long-term historical data. The extent to which local public health should be investing in school absenteeism surveillance systems and the public health value of such systems remain to be determined.

Over 200 staff and 40 volunteers were assigned to the Department's 2009-H1N1 influenza A response resulting in significant unbudgeted expenses. Our Health and Medical Area Command (HMAC) was fully activated for 19 days beginning on April 27 and many response activities continued after formal closure of the HMAC. HMAC functions included healthcare system situational awareness, regional medical resource management (including management of the strategic national stockpile), mass dispensing, risk communications, public information call center and regional call center coordination, epidemiology and surveillance, business continuity, and volunteer mobilization (including Medical Reserve Corps) for surge response.

The increase in outbreak-associated surveillance and epidemiological response activities overloaded the Department's Communicable Disease Epidemiology Section. Through the first seven weeks of the 2009-H1N1 influenza A outbreak response, the Section required an extra 10.6 full-time employees (FTE) daily, a total of 41 new surge staff working 2,468 hours. Over the first six weeks of the outbreak, the Section received 1,615 calls from heathcare providers alone—over 100 calls per day initially. Volunteers from the community and department staff reassigned from other programs were recruited to supplement core staff conducting case investigations, follow-up of school absenteeism reports and illness clusters, and surveillance data management. Training surge personnel during the outbreak response was burdensome for the regular staff occupied with response duties. Individual surge staff had different levels of experience and availability and had inconsistent schedules. Because surge staff did not have the experience or training necessary to assume lead roles for surveillance, epidemiological investigation, or outbreak response, the usual Section staff served as leads in our incident command response framework during the entire outbreak response and consequently experienced physical and mental fatigue. Because of the limited number of trained staff, shift work as is practiced in other emergency response activities was not possible.

Sustained media attention and reports of school closures raised public anxiety and likely contributed to a surge in outpatient medical visits for ILI and a large volume of phone calls to both the health department and healthcare facilities. Healthcare providers reported large numbers of patients presenting for care in EDs and primary care settings with mild illnesses. Complying with surveillance guidelines, clinicians requested 2009-H1N1 influenza A laboratory polymerase chain reaction (PCR) testing at the Public Health Laboratory (PHL) on large numbers of patients with nonspecific ILI symptoms. Consequently, public health staff were inundated with processing and investigating case reports, tracking laboratory test requests and results, analysis and reporting of surveillance data,

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and responding to questions from healthcare providers and facilities regarding clinical management, infection control considerations, surveillance, and reporting. At times, hospitals did not have adequate staffing to provide timely information on admitted cases and there were not enough public health staff to provide onsite support.

Currently, case reporting is limited to hospitalized cases, which reduces but does not eliminate the burden associated with case reporting and follow-up, and processing, analyzing, and reporting surveillance data. However, identifying and reporting cases continues to require additional resources at healthcare facilities and a proportion of reports are incomplete. More efficient and less labor-intensive surveillance and reporting mechanisms at the local level that take advantage of existing electronic databases would be useful both in routine practice and during health emergencies. Routine collection of information relevant to health disparities including socioeconomic factors such as health insurance coverage, homelessness, primary language spoken, and other social and demographic variables would allow a better understanding of disease risk factors including racial and ethnic data, but requires additional resources.

Healthcare System Response

Local EDs were rapidly overloaded with mildly ill and uncomplicated cases seeking testing and treatment. Outpatient healthcare providers were not prepared to manage cases requiring respiratory (airborne) infection control precautions and some clinics referred cases to EDs regardless of severity of illness. Healthcare providers reported an overwhelming number of phone calls, primarily from concerned patients who did not have serious illness. Standardized triage tools for the public and healthcare providers were not available during the spring 2009-H1N1 influenza A outbreak to help minimize unnecessary use of the healthcare system. Triage tools that are reviewed and endorsed by the appropriate medical professional organizations would be useful in managing future outbreaks. EDs also reported an increase in patients who were uninsured and/or did not have a primary health care provider; in 2008, 12.5 percent (approximately 153,000) of King County adults ages 18-64 years reported no health insurance coverage. The problem of medically underserved populations with no medical home placed additional unnecessary stress on healthcare systems.

Because of the surge in patients tested for 2009-H1N1 influenza A infection, healthcare facilities and laboratories reported shortages of nasopharyngeal swabs and viral transport medium. There was a failure of "just in time" purchasing as hospitals, outpatient facilities, and local vendors reported shortages of surgical masks, N95 respirators, and equipment for fit testing N95 respirators. Recommendations on N95 respirator use (personal protective equipment [PPE]) by healthcare workers by the CDC differed from those of the World Health Organization, the Society for Healthcare Epidemiology of America, the Association

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of Professionals in Infection Control, the Infectious Disease Society of America, and other expert professional groups (APIC, 2009; CDC, 2009a,b; IDSA, 2009; SHEA, 2009; WHO, 2009).

Variation in adoption of PPE recommendations by state and local public health agencies and healthcare systems resulted in confusion and hampered development of local infection control guidance. Healthcare providers perceived 2009-H1N1 influenza A to be similar to seasonal influenza with respect to apparent mode of transmission and severity of illness and logistical considerations made widespread adoption of N95 respirator use impractical. Therefore, most healthcare providers and systems reserved N95 masks for high-risk exposures. Differences in respirator policies among healthcare facilities led to inconsistent rates of equipment usage such that a small number of local healthcare facilities requested a large proportion of the regional stockpile of N95 respirators.

Clinicians and healthcare facilities also reported shortages of commercial rapid influenza diagnostic test kits. This was exacerbated by several factors, including the practice of testing cases of ILI for 2009-H1N1 influenza A regardless of severity of illness or need to guide clinical management, and a requirement for a positive rapid test result for subsequent H1N1 testing at the state PHL to reduce the volume of specimens submitted. Case investigations and conversations with local clinicians suggested that some clinicians inappropriately relied on results of 2009-H1N1 influenza A PCR testing at the PHL to guide case management, including infection control measures and antiviral treatment. The lack of widely available rapid, reliable, and affordable point-of-care diagnostic tests for 2009-H1N1 influenza A hampered both the medical and public health response to the evolving outbreak, and their development should be prioritized (IDSA, 2007).

As increasing numbers of persons meeting the 2009-H1N1 influenza A surveillance case definition were identified, the state PHL was inundated with specimens for PCR testing, resulting in delays in testing and reporting of results. For example, influenza subtyping results, needed to help guide empiric treatment during an outbreak in a long-term-care facility, were not available for more than a week. Although clinicians, healthcare facilities, and laboratories were requested to report suspected cases before submitting specimens to the PHL, many specimens were submitted directly to the PHL, bypassing the local health surveillance system and complicating tracking of cases and reporting of results. Pandemic response plans call for integration of clinical laboratories into the public health response (HHS, 2009). Some clinical laboratories, particularly those not affiliated with hospitals, were not well integrated into the public health outbreak response. Examples include not having systems to either receive or act on information from public health authorities and lack of familiarity with processing influenza specimens for submission to the PHL and procedures for reporting results.

Providing information and technical support for healthcare providers was a core component of the public health H1N1 outbreak response and was labor and

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time intensive. There was a high demand from clinicians for consultation with public health subject matter experts and for information on diagnosis, treatment, infection control, and community mitigation measures. Frequent written updates were disseminated by email listserv, broadcast fax, and web portals. Daily (and subsequent weekly) conference calls with a variety of healthcare system stakeholders were organized by public health and healthcare coalition staff.

The healthcare system response had several notable successes. HMAC, working through our King County Healthcare Coalition,[20] a collaboration between public health and regional healthcare system stakeholders to foster healthcare system emergency preparedness, promptly mobilized hospitals to prepare to implement pandemic response plans and successfully facilitated redistribution of scarce medical supplies among regional hospitals and when necessary through provision from the strategic national stockpile (SNS) and/or the county stockpile. HMAC coordinated communication with area hospitals to provide technical information (e.g., infection control and testing and treatment guidelines) and conducted conference calls with large pharmacy chains across the region to coordinate information regarding available antiviral inventories, protocols to protect pharmacy staff, screening criteria, and dispensing protocols for stockpiled antiviral drugs. HMAC mobilized county antiviral drug stockpiles and organized community dispensing clinics in response to shortages of antiviral drugs. A public call center was opened to provide general health information and medical triage and received 1,199 calls in just under a week of operation. Clinical and nonclinical health department staff and volunteers staffed the call center and a partnership with a regional private after-hours nurse consulting line was established for after-hours operation. Hospitals successfully employed the Hospital Incident Command System during the response.

During the spring outbreak, local intensive care unit (ICU) capacity and capability were stressed but not exceeded. However, hospitalized ICU cases required an unusually high level of medical resources and advanced treatment measures (rescue therapies), consistent with reports from other areas (ANZIC Influenza Investigators, 2009; White and Angus, 2009). The complexity of critical care management required by 2009-H1N1 influenza A cases raises the possibility of exceeding regional ability to care for highly complex cases (surge capability) independent of exceeding ICU bed surge capacity (Knebel and Trabert, 2007). Clinicians reported that caring for 2009-H1N1 influenza A cases was more demanding and stressful compared with cases of seasonal influenza requiring ICU admission. Because ICU occupancy rates are routinely at or near capacity, the potential also exists for exceeding available ICU beds and/or critical life-sustaining medical resources during a larger outbreak, including if ICU admissions for other illnesses are greater during the fall and winter compared to the spring. The spring outbreak also highlighted the pressing need to establish a system for triage and allocation

[20]See http://www.kingcounty.gov/healthservices/health/preparedness/hccoalition.aspx.

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of scarce medical resources during health emergencies. Although there are few available resources dedicated to this purpose, significant work remains to develop adequate regional critical care surge capacity.

Countermeasures: Antiviral Drugs

In response to large numbers of patients with ILI presenting to healthcare facilities, there was a spike in prescriptions for oseltamivir antiviral treatment. Healthcare providers reported an unusually high demand for treatment by persons with mild and uncomplicated illness and persons with potential exposures to H1N1 cases. There were also reports of healthcare workers filling prescriptions for personal antiviral drug stockpiles that resulted in the issuance of "Dear Doctor" letters urging judicious antiviral drug prescribing from the State Health Officer. Local pharmacies had few courses of oseltamivir available in stores because demand is typically low. In addition, pharmacies had difficulty replenishing their supplies rapidly. At least one healthcare facility did not provide oseltamivir from the hospital formulary to patients discharged from the ED or urgent care clinic, directing patients instead to community pharmacies. Pediatric oseltamivir formulation was in particularly short supply.

The extent to which clinicians from different healthcare systems (both within the private sector and between public and private sectors) complied with guidelines for administration of antiviral drugs varied, resulting in potential inequities in access to antiviral treatment. Another stressor on antiviral drug supplies was the CDC recommendation for postexposure chemoprophylaxis (PEP) for healthcare workers who had close contact with a suspected 2009-H1N1 influenza A case without using an N95 respirator. Because relatively few healthcare workers used N95 respirators, almost all ILI patient encounters met the criteria for PEP. (This recommendation was revised in October 2009.)

Access to antiviral drugs varied across geographic boundaries. Although national pandemic plans call for sufficient antiviral stockpiles to treat 25 percent of the U.S. population, the federal government has purchased a supply adequate to treat approximately 15 percent of the population, relying on subsidized purchases by states and local jurisdictions to provide the remainder (HHS, 2006). Not all local jurisdictions have purchased additional supplies to reach the target. King County previously purchased a local antiviral drug stockpile that together with the federal stockpile is sufficient to treat at least 25 percent of the local population; however, few other local health jurisdictions in Washington did so and no others have met the target for 25 percent population coverage. In order to ensure timely access to treatment before the national pharmaceutical stockpile was available locally, King County provided oseltamivir from the local stockpile to community locations. Neighboring counties were not able to do so, resulting in instances where patients were the referred across county lines for antiviral drug treatment.

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CDC activated delivery of the SNS with antiviral drugs and PPE to states on April 27, 2009. On May 4th, the first supplies of SNS antiviral drugs reached our local public health distribution center and it was not until May 14th that the remainder of the initial 25 percent SNS allocation reached the distribution center. In the intervening days, we used oseltamivir supplies from the county stockpile to supply six community-based antiviral drug distribution sites and supplied oseltamivir to local hospitals that could not access commercial supplies.

Current 2009-H1N1 influenza A antiviral treatment guidelines emphasize prompt treatment of all persons in high-risk groups to prevent severe complications and hospitalization. Yet, neither the healthcare system nor the public health system has the capacity to rapidly deliver treatment during a large-scale outbreak. Our experience suggests that the commercial drug distribution system (pharmacies) could play a potentially important role but may not be prepared at this time coordinate such a response with local public health agencies or to respond to unanticipated surge in demand for treatments.

School Closures and Community Mitigation Measures

On April 29th the first probable cases of 2009-H1N1 influenza A were announced in King County, including cases in school-aged children. CDC guidance at that time recommended precautionary school closure for cases of 2009-H1N1 influenza A (swine influenza) in students, and by May 1st, four elementary schools and one middle school in the county were closed by the local health officer. The benefits and potential unintended adverse consequences of school closures during influenza pandemics are not well defined (Cauchemez et al., 2009). National pandemic planning guidance focused on proactive school closures to decrease community transmission; reactive closures were not a focus of the plan (CDC, 2009c).

Notification of immediate reactive school closures were issued after public health officials were informed of laboratory-confirmed cases of 2009-H1N1 influenza A in students, typically late in the day after schools had been dismissed. This complicated communication with both school officials and the public. School officials used flyers, email, and phone messaging in attempts to contact parents. Communication was especially challenging with non-English-speaking families and single working parent households, where telephone contact numbers for some families were not available or current. In some cases, children from closed schools gathered at other locations and continued to participate in organized sports leagues. Following the closure of an elementary school serving diverse immigrant families who reside in a nearby low-income housing project, school children congregated in apartments and common areas of the housing project, frequently without the supervision of parents or other caregivers. Systems to allow education at home for students who were not ill were not in place at the time of the closures but may have been possible with sufficient advance warn-

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ing. A minority of public school districts have sufficient resources to include elementary schools on intranet websites used to communicate instructions to students and parents.

In Seattle public schools this school year, 44 percent of children qualify for nutritional support through the National School Lunch and School Breakfast Programs (State of Washington Office of the Superintendent of Public Instruction). During the spring outbreak there was no means to provide meals to children dependent on these programs when schools closed for a health emergency. Subsequently, the United States Department of Agriculture (USDA) authorized provision of reimbursable meals for schools closed for 2009-H1N1 influenza A and not for other health emergencies.[21] The provision is only applicable when schools are closed by health officials and not when school administration close schools because of a high level of illness in students or faculty. Significant local capacity and resource issues remain that must be addressed in order to provide meals to low-income children during school closures for 2009-H1N1 influenza A.

Because ILI was widespread in the community and the majority of cases were likely not diagnosed and reported, and because most cases appeared comparable to seasonal influenza, we discontinued the policy of reactive school closures locally on May 5th. After that date, we recommended keeping all students with symptoms of influenza out of school during their period of illness and recuperation, when they are potentially infectious to others. However, there was no practical way to ensure that ill children did not attend school. Schools and child daycare centers did not have the capacity to screen students for illness at entrance each day, and the responsibility fell primarily to parents. There was significant variability in the degree to which parents adhered to, and schools enforced, the recommended 7-day exclusion period for ill students. Some parents brought ill children to school, sometimes after administering fever-reducing medications, and were not available to retrieve the children. School officials speculated that working parents in lower socioeconomic status neighborhoods were concerned about losing wages and/or employment if they had to miss work to be with an ill child. Many parents and healthcare providers felt that the severity of illness did not justify extraordinary exclusion measures, and some healthcare providers provided "doctor's notes" to students with ILI authorizing return to school before the exclusion period had been completed. Based on this experience, we used resources from a National Association of County and City Health Officials (NACCHO) Advanced Practice Center Grant to develop educational materials for parents on how to recognize flu symptoms, and that encouraged them to develop strategies ahead of time so that children can stay home even if parents must continue to work. The materials created through the grant are made available to health jurisdictions nationally by NACCHO. Our health department designated a full-time liaison to schools to provide guidance and consultation

[21]See http://www.fns.usda.gov/cnd/governance/Policy-Memos/2009/SP_31-2009_os.pdf.

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during the 2009-H1N1 influenza A response, but resources are not available to allow this work to continue.

The school closure experience illustrated the value of incorporating local flexibility in national guidance and this was recognized in subsequent CDC school closure and illness exclusion guidance. Strategies for successful implementation of both proactive and reactive school closures should be incorporated into pandemic and other health emergency plans, including improved coordination and implementation of school closures by public health, school, and local emergency management agencies. Distinguishing between school closure and dismissal of classes should also be considered to allow administrative and other social services functions at schools to continue during health emergencies.

Communication

Intense national and local media coverage of severe cases and school closures contrasted with official statements and the public perception that the pandemic was "mild" and comparable in severity to seasonal influenza, complicating risk communication messaging. Media also showed high interest in the extent and progression of the outbreak, focusing on the latest confirmed case counts. In order to provide timely and accurate information to the local community, frequent press conferences were held that resulted in local media stories and coverage largely reflecting public health messages.

Public messaging regarding when to seek healthcare, however, failed to prevent a surge of mildly ill persons to healthcare facilities or to reduce the demand for testing and treatment of mild cases. Communication strategies and related methods that increase public compliance with recommendations on when to seek healthcare and treatment and community mitigation recommendations would improve local responses to future health emergencies. The use of standardized triage tools for the public should be explored and evaluated to minimize unnecessary use of limited healthcare system resources.

In order to manage the large number of telephone calls from healthcare providers and the public, we operated a public flu telephone hotline. Mobilization of the hotline was difficult because there were not enough expert clinicians available on short notice to rapidly develop phone protocols and train call center staff. In addition, H1N1 topics recorded in English and Spanish were available around the clock; about half of callers used these recordings only.

Coordinating information provided through the public health hotline and by multiple local healthcare systems was challenging and not specifically addressed in pandemic plans. Crafting appropriate messages for persons having ILI but with no regular healthcare provider or health insurance was problematic given the fact that these persons typically use EDs for primary care services.

In Washington State there is no requirement that healthcare providers obtaining or renewing a professional license provide contact information that can be

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used for communication during public health emergencies. Consequently, many healthcare providers are "not plugged in" to public health communication networks. Coverage is especially poor for nonprimary care and non-infectious disease practitioners and among clinicians practicing in certain ethnic communities.

An informal survey of clinicians who voluntarily subscribe to the Department's health alert listserv found approximately half of the respondents complained of "information overload" and of receiving similar (and sometimes conflicting, such as for PPE guidance) messages from national, state, and local public health agencies as well as professional societies and other sources, whereas the other half found the volume of information useful and appropriate. Healthcare providers that had planned for pandemic response reported that it had been useful; however, many practices, particularly smaller ones, had not planned. Communication from CDC to local public health was good, and it was improved over that during the SARS outbreak. Multiple venues were available for local health officials to engage CDC staff on a variety of response topics through regularly scheduled conference calls. On several occasions, it appeared that the release of updated national guidance was delayed for clearance by government agencies. A review of official clearance methods may be useful in order to ensure that the most efficient system is in place to expedite release and dissemination of new and revised guidance, an essential component of effective real-time outbreak management.

H1N1 Vaccination Program

The need to rapidly plan and implement a large-scale vaccine distribution and administration system severely taxed local public health capacity. In King County, 724 health care providers and/or vaccination clinic sites enrolled to provide H1N1 vaccine compared with 240 for our preexisting local Vaccines for Children (VFC) program managed by public health staff. Because there is no national program for adult immunization delivery analogous to the VFC program, healthcare providers that care for adult populations prioritized for 2009-H1N1 influenza A vaccination (including obstetricians, internal medicine specialists, and specialty clinics for high-risk adults such as HIV clinics and dialysis centers) are unfamiliar with procedures for ordering vaccine through the public health system and the associated administrative requirements. Many target groups for 2009-H1N1 influenza A vaccination have low seasonal influenza vaccination coverage rates, creating additional challenges. For example, in order to optimize access to vaccine for pregnant women, we assigned a special liaison to work with local birthing hospitals to ensure that the vaccine is available through either the hospital or the obstetrical practices admitting patients to the facility.

Ongoing uncertainty regarding the timing of availability and expected quantities of specific vaccine formulations, presumably due to the unpredictability of the manufacturing process, presented significant problems for local immunization

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planners. Although initial limited doses of live attenuated influenza virus vaccine (LAIV) were targeted to eligible populations of healthcare workers and healthy persons in early October by limiting the number of vaccination sites, expanding vaccine availability to high-risk target populations in the medical home and in the community requires significant supplies of injectable vaccines. Another difficulty hindering vaccine distribution and expanded access through the medical home is that the currently licensed injectable monovalent 2009-H1N1 influenza A vaccine for young children is especially scarce.

Misperceptions about vaccine safety among the public as well as among healthcare professionals have added to the complexity of the 2009-H1N1 influenza A vaccination program and engendered additional work for public health personnel who need to educate both healthcare system stakeholders and the public. Misinformation about the manufacturing process, use of adjuvants, risk of adverse events, and inadequate safety testing circulated for months prior to the release of the first doses of vaccine and before accurate and authoritative public information was made available on the CDC website (Steinhauer, 2009). Many healthcare professionals persist with concerns regarding the safety of LAIV (e.g., FluMist®) in eligible healthcare workers despite clear recommendations for this group from CDC and the vaccine's excellent safety record. A recent study showing decreased efficacy of LAIV against seasonal influenza in adults exacerbated concerns about the acceptability of LAIV among healthcare workers (Monto, 2009). Anxiety about the mercury (thimerosal) content of vaccines also threatens to decrease public acceptance of 2009-H1N1 influenza A vaccination, particularly among populations that have become accustomed to or favor receiving thimerosal-free injectable formulations that are in short supply. This problem is exacerbated in Washington, where the state legislature passed a law in 2007 prohibiting administration of vaccines containing more than a trace of mercury to pregnant women and children less than three years of age. Paradoxically, when the law was suspended through an emergency order by the state secretary of health because of a shortage of thimerosal-free formulations of 2009-H1N1 influenza A vaccine, it activated a provision in the law requiring healthcare providers to notify the parent or guardian of all children less than 18 years of age and pregnant or lactating women that they are receiving a vaccine with "more mercury than is usually allowed." Few local obstetrical practices are willing to offer thimerosal-containing injectable vaccine to pregnant patients despite having no other available option, and virtually all healthcare providers have expressed a preference for thimerosal-free vaccine. Sustained efforts to educate and increase the public's trust in immunizations and vaccine safety would be useful during health emergencies due to vaccine-preventable diseases.

Vaccine supply shortfalls further complicated local vaccine delivery and public messaging. Optimistic national forecasts for vaccine availability raised expectations among the public and influenced public health vaccination program strategy. Early media reports heralded the onset of the national 2009-H1N1

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influenza A vaccination program and the arrival locally of the first doses of 2009-H1N1 influenza A (LAIV) vaccine. This further raised interest among healthcare providers and the public, including target populations with underlying medical or age-related risks for severe illness and pregnant women who are not eligible for LAIV (which was the predominant formulation initially available). Local vaccination program implementation plans did not emphasize strategies for supply shortages because initial national supply projections were robust. For example, national forcasts predicted that by the end of October, vaccine supply would be adequate to cover 75 percent of the local target population recommended for vaccination by the CDC's Advisory Committee on Immunization Practices (ACIP; CDC, 2009d). However, by the time the second wave of 2009-H1N1 influenza A peaked locally in late October, King County had only received enough vaccine to immunize approximately 17 percent of the ACIP target population. Variable practices across jurisdictions occurred related to restriction of eligibility for vaccination to one or more subsets of the target population as described in the ACIP guidance and in the use of sequential versus simultaneous vaccination of risk groups within the target population and/or target population subsets. Most health care systems offered vaccine to all their healthcare workers, not just those in direct patient contact, before making it available to patients.

The ability to implement the 2009-H1N1 influenza A vaccination program vastly exceeded our routine public health immunization program capacity. Our Department's immunization program includes a total of 10.5 FTEs, including both public health nurses and administrative staff engaged in the administration of the VFC program and associated activities. In order to manage enrollment of new vaccination providers; provide technical support to participating healthcare providers; conduct necessary oversight and management of vaccine ordering, delivery, and utilization; and continue routine VFC program operations for all other recommended vaccines that healthcare providers must continue to administer during this time, more than 16 new full-time staff were required. As with other public health surge staffing, finding appropriately trained and experienced staff to supplement the small core of public health program experts is difficult if not impossible on short notice.

The primary strategy for administering 2009-H1N1 influenza A vaccine locally is to use the existing healthcare system or "medical home," including safety-net clinics, supplemented by regional pharmacies and a relatively small number of special community vaccination clinics. Due to repeated funding reductions in recent years, the department has minimal capacity to provide clinical immunization services. Immunization clinic nurse capacity was reduced by 70 percent from 2004 to 2009, from 10.3 to 3.0 FTEs. As a consequence, the department does not have the ability to staff community school-based or other vaccination clinics. A recent survey in Washington State found that, on a typical day, 31 of the state's 36 local health jurisdictions had one vaccinator available to provide routine immunizations and only two jurisdictions had four vaccinators available.

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In addition to diminishing immunization nurse capacity, a number of other positions relevant to pandemic and other health emergency response activities were reduced or eliminated due to budget cuts in 2009: the Department's Child Care Health program including six public health nurses, a nutritionist, an educator, and administrative support; our Children with Special Health Care Needs program with 3.5 public health nurse positions; and the loss of three death investigator positions in the Medical Examiner's Office. This predicament is not unique among local health jurisdictions. NACCHO reports that, in 2008, 27 percent of local health departments nationally had budget cuts and 53 percent had layoffs resulting in 7,000 jobs lost; in 2009, 44 percent of local health departments had budget cuts and 32 percent had layoffs with approximately 8,000 jobs lost and an additional 12,000 local health department (LHD) employees subjected to reduced hours or mandatory furloughs (NACCHO, 2009). Federal "flu allocation" stimulus funding helps mitigate additional unbudgeted expenses but does not provide real-time capacity or sustainable resources.

Summary

Local public health capacity to respond to the 2009-H1N1 influenza A outbreak and other large-scale health emergencies is tenuous and unstable, waxing and waning with availability of year-to-year grants and other short-term funding supplements. We have used CDC preparedness funds, one-time pandemic flu allocations, and NACCHO grants to develop, enhance, and test a wide range of response capabilities for influenza pandemics and other public health emergencies. With these resources, we were able to develop capacity in a number of areas critical to effective outbreak and health emergency response that were essential to our 2009-H1N1 influenza A outbreak response. Examples include creation and staffing of a regional Healthcare Coalition to coordinate public health and healthcare system preparedness planning and develop community-wide medical surge capabilities; the capability to activate and manage alternate care facilities; establishing a toll-free public hotline incorporating nurses on-site as well as an external nurse consultation line; and integration of public health preparedness activities with those of organizations serving vulnerable populations (including development of a communication tool to rapidly connect with these critical partners during disasters). In addition, key disease surveillance, investigation, and response positions (including for the development and operation of syndromic and school absenteeism surveillance and epidemiologic response), our communications team's emergency preparedness and response activities, and emergency preparedness planning for vulnerable populations are all dependent on federal grants funds and other limited, competitive awards.

In addition to local budget cuts that reduced the core public health workforce, our response to the 2009-H1N1 influenza A outbreak has been hampered by significant reductions over the past three years in federal public health preparedness

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funding. CDC preparedness grants for building and sustaining core capabilities have been reduced by 37 percent since 2006. Training funds to prepare staff for their emergency roles has dropped by 30 percent. One-time federal pandemic flu preparedness funds, which accounted for nearly 20 percent of our preparedness resources in 2006, have not been restored. Consequently, key staff positions responsible for disease surveillance, vulnerable populations planning, risk communications, medical surge planning, and other core preparedness capabilities were recently eliminated. As a result of these cuts, surge capacity planning with key community organizations such as long-term-care facilities, nursing homes, and ambulatory care facilities has been suspended. Similar reductions in funding for hospital emergency preparedness activities threaten the future viability of our regional healthcare coalition and the medical response capacity for future large-scale public health emergencies. Unlike certain material resources, public health personnel trained in emergency response are not a just-in-time commodity.

Conclusion

The spring 2009-H1N1 influenza A outbreak highlighted accomplishments, gaps, and challenges in the local public health and medical response to large-scale health emergencies. It also provided opportunities for improvement across the health emergency response spectrum that should be addressed before the next inevitable outbreak or natural disaster. Inadequate long-term sustainable funding for both core public health and health emergency preparedness undermines the ability of local communities to adequately prepare for and respond to large-scale health emergencies of any type.

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References

ANZIC Influenza Investigators, S. A. Webb, V. Pettilä, I. Seppelt, R. Bellomo, M. Bailey, D. J. Cooper, M. Cretikos, A. R. Davies, S. Finfer, P. W. Harrigan, G. K. Hart, B. Howe, J. R. Iredell, C. McArthur, I. Mitchell, S. Morrison, A. D. Nichol, D. L. Paterson, S. Peake, B. Richards, D. Stephens, A. Turner, and M. Yung. 2009. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *New England Journal of Medicine* 361(20):1925-1934.

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

APIC (Association of Professionals in Infection Control). 2009. *SHEA, APIC, ACOEM, and IDSA joint position statement: healthcare personnel at high-risk for severe influenza illness: care of patients with suspected or confirmed novel H1N1 influenza A, August 11, 2009*, http://www.apic.org/Content/NavigationMenu/GovernmentAdvocacy/IssuesInitiatives/PersonalProtectiveEquipmenttoProtectHealthcareWorkersfromNovelH1N1Influenza/Personal_Protective_.htm (accessed October 29, 2009).

Cauchemez, S., N. M. Ferguson, C. Wachtel, A. Tegnell, G. Saour, B. Duncan, and A. Nicoll. 2009. Closure of schools during an influenza pandemic. *Lancet Infectious Diseases* 9(8):473-481.

CDC (Centers for Disease Control and Prevention). 2009a. *Interim guidance on infection control measures for 2009 H1N1 influenza in healthcare settings, including protection of healthcare personnel*, http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm (accessed October 29, 2009).

———. 2009b. *Summary of HICPAC recommendations for care of patients with confirmed or suspected 2009 H1N1 influenza infection in healthcare settings, July 23, 2009*, http://www.cdc.gov/ncidod/dhqp/hicpac_h1n1.html (accessed October 29, 2009).

———. 2009c. *Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States*, http://www.flu.gov/professional/community/index.html (accessed October 30, 2009).

———. 2009d. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *Morbidity and Mortality Weekly Report* 58(RR-10):1-8.

HHS (Department of Health and Human Services). 2006. *Pandemic influenza implementation plan, part I of II*. Washington, DC: HHS.

———. 2009. *HHS pandemic influenza plan supplement 2 laboratory diagnostics*, http://www.hhs.gov/pandemicflu/plan/sup2.html#s2-II (accessed October 29, 2009).

IDSA (Infectious Disease Society of America). 2007. *Pandemic and seasonal influenza: principles for U.S. action*. Alexandria, VA: IDSA, http://www.idsociety.org/influenza.htm (accessed October 29, 2009).

———. 2009. *IDSA endorses SHEA position statement on infection control, June 11, 2009*, http://www.idsociety.org/pandemicinfluenzapolicy.htm (accessed October 29, 2009).

Knebel, A., and E. Trabert, eds. 2007. *Medical surge capacity and capability handbook*, second edition. Washington, DC: HHS, http://www.hhs.gov/disasters/discussion/planners/mscc/ (accessed October 29, 2009).

Kwan-Gett, T., A. Baer, and J. Duchin. 2009. Spring 2009 H1N1 influenza outbreak in King County, Washington. *Disaster Medicine and Public Health Preparedness* 3:S109-S116.

Monto, A. S. 2009. Comparative efficacy of inactivated and live attenuated influenza vaccines. *New England Journal of Medicine* 361(13):1260-1267.

NACCHO (National Association of County and City Health Officials). 2009. *Survey of local health department job losses and program cuts*. Washington, DC: NACCHO, http://www.naccho.org/advocacy/upload/LHD-job-and-service-cuts-2009.pdf (accessed December 17, 2009).

SHEA (Society for Healthcare Epidemiology of America). 2009. *SHEA position statement: interim guidance on infection control precautions for novel swine-origin influenza A H1N1 in healthcare facilities*, http://www.shea-online.org/Assets/files/policy/061209_H1N1_Statement.pdf (accessed October 29, 2009).

Steinhauer, J. 2009 (October 16). Swine flu shots revive debate about vaccines. *New York Times*, http://www.nytimes.com/2009/10/16/health/16vaccine.html (accessed November 30, 2009).

White, D. B., and D. C. Angus. 2009. Preparing for the sikest patients with 2009 influenza A H1N1. *Journal of the American Medical Association* 302(17):1905-1906.

WHO (World Health Organization). 2009. *Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses, June 25, 2009*, http://www.who.int/csr/resources/publications/swineflu/swineinfinfcont/en/index.html (accessed October 29, 2009).

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INTERNATIONAL LAW AND EQUITABLE ACCESS TO VACCINES AND ANTIVIRALS IN THE CONTEXT OF 2009-H1N1 INFLUENZA

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Introduction

The emergence and spread of a novel strain of influenza A (H1N1) in 2009 (hereinafter 2009-H1N1 influenza A) has confronted states and intergovernmental organizations with yet another set of global health challenges. Key among these challenges has been the perceived need to increase access for low-income countries to vaccine and antivirals effective against 2009-H1N1 influenza A. Meeting this need has been framed as a challenge that implicates global equity, justice, and solidarity. Experts, including the Director-General of the World Health Organization (WHO), have called for developed countries to share 2009-H1N1 influenza A vaccines they have ordered with low-income countries in the name of equity, justice, morality, and solidarity. Margaret Chan, the WHO Director-General, argued in July 2009 that "The lion's share of these limited [2009-H1N1 influenza A vaccine] supplies will go to wealthy countries. Again we see the advantage of affluence. Again we see access denied by an inability to pay" (Chan, 2009a). Similarly, Lawrence O. Gostin argued in connection with access to vaccine for 2009-H1N1 influenza A that "[s]erious questions of social justice arise when wealth, rather than need, becomes the primary allocation criterion" (Gostin, 2009). Laurie Garrett of the Council on Foreign Relations and Tadashi Yamada of the Bill & Melinda Gates Foundation have likewise argued that the United States and other developed countries have a moral obligation to make vaccine for 2009-H1N1 influenza A available to low-income countries (Garrett, 2009a; Yamada, 2009).

In addition, in light of both the ongoing virus and benefit sharing controversies connected with highly pathogenic avian influenza A (H5N1) (HPAI-H5N1) and the access problems sparked by the 2009-H1N1 influenza A virus, the challenge of access to knowledge products related to influenza has become a major issue of global health governance. For Garrett, the access issue concerning 2009-H1N1 influenza A vaccines constitutes a core challenge facing global governance and international cooperation (Garrett, 2009b). The Bill & Melinda Gates Foundation has argued that "[d]eveloped countries and vaccine manufacturers should urgently agree upon a mechanism to ensure access to vaccine by developing

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countries" (Bill & Melinda Gates Foundation, 2009). WHO's influenza specialist Keiji Fukuda told a meeting of the Institute of Medicine's Forum on Microbial Threats in September 2009 that the access question "is the flash point right now, for global solidarity. . . . It is the fundamental issue of our times. . . . Benefit-sharing is the central global issue of our time" (Garrett, 2009b, p. 12). Fukuda also argued that countries must develop a better global framework to address access challenges *before* the next influenza or other highly transmissible disease crisis breaks over the world (Fukuda, 2009).

This paper explores the call for a global framework on access to influenza vaccines and antivirals from legal and political perspectives. The analysis reveals that the path to creation of such a global framework is strewn with significant obstacles that are not overcome by incantations of the need for "equity, justice, and solidarity." Legally, international law specific to global health and generally on the allocation and creation of resources provides few, if any, precedents for establishing a global access framework. Politically, the self-interested calculations of developed states with respect to supplies of influenza vaccines and antivirals do not create a firm basis for an international agreement on sharing. The decision by a number of developed countries on September 17, 2009, to share a percentage of their 2009-H1N1 influenza A vaccine supplies (White House, 2009), the U.S. postponement of its donation pledge because of domestic vaccine shortages, and the problems the donation program faced by the end of 2009 illustrate the harsh international politics of vaccine sharing, rather than revealing increasing commitment to greater equity, justice, and solidarity with people in low-income countries.

Access to Vaccines and Antivirals in Connection with 2009-H1N1 Influenza A

As responses to the 2009-H1N1 influenza A pandemic have unfolded, WHO officials and other experts have identified the problem that low-income countries will not have significant access to vaccine developed for the 2009-H1N1 influenza A virus (Chan, 2009a; Fidler, 2009; Fukuda, 2009; Garrett, 2009c; Gostin, 2009; Yamada, 2009) and may also face shortages of antiviral treatments (President's Council of Advisors on Science and Technology, 2009; Whalen, 2009). The problem of equitable access to vaccine for influenza strains is not a new issue, having cropped up controversially in connection with access to vaccine for HPAI-H5N1 from 2007 to the present (Fidler, 2008). The reappearance of yet another controversy involving equitable access to influenza vaccine has stimulated arguments that the international community needs to avoid suffering through this problem with each new potentially dangerous influenza strain. Rather than ad hoc, reactive responses that favor access for countries with more wealth and power, the proposed solution involves crafting a global framework that will guide access to vaccines, antivirals, and potentially other kinds of response technologies and supplies (e.g., masks).

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At the meeting of the Institute of Medicine's Forum on Microbial Threats on 2009-H1N1 influenza A held in September 2009, WHO's Fukuda repeatedly mentioned the need for a global framework to prevent access crises from occurring in the future (Fukuda, 2009). Fukuda noted the ineffectiveness and inefficiency of the reactionary, ad hoc attempts to increase vaccine access for 2009-H1N1 influenza A. Fukuda's reasons why a global framework is necessary echo those given in other analyses of this issue: (1) developing this global access framework would achieve global equity, solidarity, and justice; and (2) creating and operating the global framework is in the enlightened self-interest of all countries, including developed countries, with respect to handling the challenges pandemics pose. These calls for a global access framework represent arguments in favor of the negotiation and implementation of a new kind of global health governance mechanism.

Foreign Policy Skepticism About the Need for a Global Access Framework in the Wake of 2009-H1N1 Influenza A

Although the calls for a global access framework to produce more equity, solidarity, justice, and enlightened self-interest generally resonate well in the global health community, foreign policy makers present a more skeptical audience, and understanding this skepticism is important to grasping the difficulty of creating a global access framework. Proponents for such a framework often assert that it is needed because access to vaccine for pandemic influenza (or other dangerous viral pathogens) should not be allocated according to the ability to pay (Chan, 2009a; Gostin, 2009; Yamada, 2009). However, as the foreign policy skeptic might point out, virtually all health-related resources—vaccines, antibiotics, potable water, sanitation, health care, prenatal services, and education—reflect access disparities between rich and poor within and among countries. What makes the access concerns with respect to 2009-H1N1 influenza A so special that the international community must create a global access response to this global health problem?

Public health experts have raised concerns on these grounds, which would reinforce the foreign policy skeptic's view of the matter. In response to the appeal by the United Nations (UN) and WHO at the end of September 2009 for $1.5 billion to buy vaccines and antivirals for low-income countries, Christopher Murray, Director of the Institute for Health Metrics and Evaluation at the University of Washington, argued that "[g]iven that the world spends about $22 billion on all global health problems, is it really wise to spend $1.5 billion only on swine flu? I would prioritize other areas like maternal and child health, where the need is urgent and huge" (Cheng, 2009). Similarly, Philip Stevens of the London-based International Policy Network asserted that "WHO is peddling an alarmist, unscientific agenda to raise funds. The U.N. is operating on pure conjecture that we will face anarchy and chaos in the developing world should the virus mutate" (Cheng, 2009).

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One response to this foreign policy and public health skepticism is that WHO declared the 2009-H1N1 influenza A outbreak a pandemic on June 11, 2009 (Chan, 2009b), the first time in over 40 years that the world has experienced an influenza pandemic. However, one of the biggest controversies surrounding 2009-H1N1 influenza A has been the pandemic declaration by WHO. Critics have attacked the criteria used by WHO in its pandemic alert system to declare the existence of a pandemic, mainly because the criteria do not include virus severity as a factor. As Garrett argued, "The problem is that there is *no relationship* between the geographically characterized WHO Pandemic Influenza Phases system and the *severity of disease threat to human beings*" (Garrett, 2009b, p. 5 [emphasis in original]).

The failure of the alert system to include any severity criterion brought the system into disrepute, and WHO agreed that it would revise the system to reflect virus severity (Hitt, 2009). WHO's Fukuda even expressed regret about the manner in which WHO applied its pandemic alert system to 2009-H1N1 influenza A (Fukuda, 2009). WHO's willingness to change the system it was trying to apply convinced many people that the world was experiencing a pandemic that was not *really* a pandemic. The mild nature of the epidemiological impact of the 2009-H1N1 influenza A virus, to date, has reinforced the sense that the pandemic declaration lacks credibility, particularly when many other infectious diseases cause more morbidity and mortality than 2009-H1N1 influenza A has caused or, at present, promises to cause. Wealth disparities also adversely affect responses to these infectious disease threats and cause life-saving resources to be allocated on the basis of ability to pay. Thus, the argument that 2009-H1N1 influenza A deserves heightened treatment diplomatically because it was declared a pandemic is not persuasive.

Skepticism about the call for a global access framework in light of 2009-H1N1 influenza A involves other doubts. One such doubt arises from confusing messages communicated by global health experts, who argue, on the one hand, that low-income countries must get vaccine access for equity, solidarity, and justice reasons, but, on the other hand, who often argue for more international health aid because such countries suffer from inadequate domestic capacities to execute health programs because of shortages of healthcare workers, weak or nonexistent response capacities, and fragile or broken health systems. For example, Sangeeta Shashikant, a legal advisor to the Third World Network, argued in connection with access to vaccine for 2009-H1N1 influenza A that "[t]here is no mechanism to make sure we will get the medicines to those who need them" (Whalen, 2009). Dr. Christophe Fournier, President of the *Medecins Sans Frontieres* (MSF) International Council, identified "[t]he lack of health care workers, medicine and supplies in many countries . . . [as] a legitimate cause for grave concern" in connection with addressing the 2009-H1N1 influenza A threat (MSF, 2009a). The Gates Foundation's Principles to Guide Global Allocation of Pandemic Vaccine also drew attention to this problem, although more obliquely,

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by stating that: "[a]ll countries obtaining pandemic vaccine should ensure that mechanisms are in place to provide the vaccine to their populations, to ensure that this scarce resource is not wasted, and donors should be prepared to provide resources and technical assistance to help countries bolster these mechanisms" (Bill & Melinda Gates Foundation, 2009).

The tension between the messages insisting on access but warning of incapacities to deliver vaccines and antivirals effectively raises the problem that increasing global access to vaccines and antivirals in such a context might produce equity without epidemiological benefit. In the context of antivirals, improper use related to inadequate capacities can lead to resistant strains, which could spread and erode the utility of antiviral medications for larger populations in connection with 2009-H1N1 influenza A and potentially other strains of influenza as well. As the President's Council of Advisors on Science and Technology put it, "[r]esistance to these [antiviral] agents, especially oseltamivir, as a result of viral mutation or genetic recombination, can be a major factor limiting antiviral effectiveness" (President's Council of Advisors on Science and Technology, 2009, p. 35). In the case of resistant strains, the global health damage of ineffective use or misuse of antivirals might overshadow public health benefits procured through greater access in low-income countries.

Another skeptical question concerns why low-income countries have not raised the issue of the vaccine and antiviral access crisis previously during annual seasonal influenza outbreaks when the access problems (e.g., limited supply combined with great wealth disparities) are essentially the same. As Yamada pointed out, "the sobering truth is that even if production were switched over completely from seasonal influenza vaccine to pandemic influenza vaccine, there would not be nearly enough for everyone in the world" (Yamada, 2009, p. 1129). The lack of adequate production capacities in the event of an influenza pandemic has been raised many times before, as has the need to increase aggregate global production for influenza vaccines during interpandemic years (e.g., Fedson, 2004). But, before the emergence of HPAI-H5N1 and 2009-H1N1 influenza A, no access crisis over global inequity, lack of solidarity, and injustice materialized. This reality raises the possibility that politics, as much or more than equity, solidarity, and justice, might be playing a role in the current controversy triggered by access to vaccines and antivirals concerning 2009-H1N1 influenza A.

A more specific foreign policy reason submitted for why access to vaccine for 2009-H1N1 influenza A is politically important (and, thus, by extension, a proactive global framework) concerns the possibility, raised by Garrett at the September 2009 meeting of the Forum on Microbial Threats, that low-income countries would link access to vaccine to progress on negotiations important to developed countries, including the Doha Development Round negotiations in the World Trade Organization (WTO) and the climate change negotiations taking place in Copenhagen in December 2009. However, threatening to scupper the Doha Round and the Copenhagen negotiations over access to 2009-H1N1 influenza A vaccine is not

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credible if the motivation behind the linkage threat is to improve global health equity, solidarity, and justice. The potential global health benefits that successful conclusion of the Doha Round (e.g., poverty reduction) and the Copenhagen talks (e.g., cutting greenhouse gas emissions and addressing mitigation and adaptation strategies) could create, especially for low-income countries, far outweigh the problems associated with vaccine access to 2009-H1N1 influenza A, especially because the impact of the virus has, to date, been relatively mild. In the event, health concerns, whether about vaccine access for 2009-H1N1 influenza A or climate change generally, did not feature in the Copenhagen negotiations (Garrett, 2009c).

Global Framework Challenges: Legal Considerations

Foreign policy skepticism about the need for a global access framework in the wake of 2009-H1N1 influenza A does not mean that calls for such a framework have no impact or policy importance. Overcoming skepticism requires, however, navigating the complexity of negotiating an effective global access framework. This challenge raises the need to understand legal and political considerations that would arise in a diplomatic push for a global access framework either specific to 2009-H1N1 influenza A or more generally. In terms of legal considerations, negotiating a global access framework will involve using or referencing international law. Part of the point of creating such a framework is to move the international community away from ad hoc, reactive approaches to vaccine and drug access to a more formal, rational, and harmonized strategy. Thus, this section looks at three important issues concerning international law's potential role in the creation of a global access framework: (1) what existing international health agreements contribute to the goal of a global access framework; (2) how other efforts to increase access to vaccines and drugs for other diseases inform the idea for a global access framework; and (3) how, more generally, international law is used in creating and allocating resources.

Existing Global Health Legal Regimes

A number of international legal regimes that support global health exist, but none include any express obligations related to increasing access to health-related resources. Four examples suffice to demonstrate this point. First, the WHO Constitution is one of the most important international health treaties, but it does not contain any legally binding provisions that require WHO member states to increase access to health-related resources for low-income countries. The importance of increasing such access is identified in the preamble's principle that "[t]he extension to all peoples of the benefits of medical, psychological and related knowledge is essential to the fullest attainment of health" (WHO, 1946), and WHO has exercised its powers to help low-income countries get better access to vaccines, drugs, and other health technologies. But, as the controversies over

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access, among others, to HIV/AIDS drugs, medicines for neglected communicable diseases, and vaccines and antivirals in connection with HPAI-H5N1 and 2009-H1N1 influenza A demonstrate, the WHO Constitution does not provide a firm foundation on which to build a global access framework.

Second, some international human rights treaties contain what is called a "right to health," which might provide some legal traction for moving forward a global access framework (e.g., Office of the United Nations High Commissioner for Human Rights, 1966, Article 12). However, the obligations related to the right to health in human rights treaties focus mainly on a State Party's responsibilities for its own population. Hence, the right to health has more significance for equitable access within a country's jurisdiction. Although the right to health includes an undertaking "to take steps . . . through international assistance and cooperation" (Article 2.1), this "duty to assist" other nations remains general in nature and generates controversies about its scope and substance. Efforts to clarify these international obligations in the right to health, such as that attempted in General Comment No. 14 on the Right to Health (Committee on Economic, Social, and Cultural Rights, 2000, paras. 34-37), have not resolved the disagreements. Thus, the right to health does not provide a strong legal foundation on which to build a global access framework. In addition, the United States is not a party to any human rights treaty that contains the right to health, so framing the legal basis for a global access framework through this right does not attract the interest or participation of the United States.

Third, other existing international legal regimes for global health also provide no rules or norms that could provide deep anchor points for creation of a global access framework. For example, although the International Vaccine Institute (IVI) is an intergovernmental organization among 40 States Parties established by treaty to conduct research, training, and technical assistance for vaccines needed in developing countries (IVI, 2009), the IVI is not mentioned in the debates about equitable access to pandemic vaccines. It has not been identified as relevant to either the HPAI-H5N1 or the 2009-H1N1 influenza A access controversies because it does not work on influenza vaccines.

Similarly, the groundbreaking International Health Regulations 2005 (IHR 2005) do not include any provisions that directly advance more equitable access to vaccines and drugs. The most relevant part of the IHR 2005 is the weak obligation for States Parties "to undertake to collaborate with each other, to the extent possible . . . in the provision or facilitation of technical cooperation and logistical support, particularly in the development, strengthening and maintenance of the public health capacities required under these Regulations" (IHR 2005, Article 44.1(b)). Even though the WHO Director-General declared 2009-H1N1 influenza A a public health emergency of international concern under the IHR 2005 (WHO, 2009a), the access crisis illustrates that the IHR 2005's obligation to undertake to collaborate to the extent possible has not provided a solid basis on which to improve access to vaccine and antivirals.

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Other Efforts to Increase Access to Vaccines and Drugs

The lack of solid grounding for equitable access in existing international legal regimes supporting global health does not mean that efforts to increase such access have been few and far between. Many activities to increase access to vaccines and drugs have been undertaken through a number of different strategies:

- Efforts by intergovernmental organizations, such as WHO (WHO, 2009b), the Pan American Health Organization (PAHO, 2009), the United Nations Children's Fund (UNICEF, 2009), and the United Nations Development Programme, to purchase and distribute vaccines and drugs in low-income countries, including the WHO effort to develop a stockpile of vaccine for HPAI-H5N1 (World Health Assembly, 2007);
- Bilateral activities by donor countries to make vaccines or drugs more available to low-income countries (e.g., the President's Emergency Plan for AIDS Relief [PEPFAR], 2009);
- Advocacy by nongovernmental organizations (NGOs) for improved access to vaccines and drugs for populations in poor countries (e.g., the Campaign for Access to Essential Medicines operated by *Medecins sans Frontieres* [MSF, 2009b]);
- Donations by private-sector pharmaceutical companies of vaccines or drugs for diseases that mainly affect low-income countries (e.g., the donation by Sanofi-Aventis of 100 million doses of 2009-H1N1 vaccine to WHO [WHO, 2009c]);
- Innovative research, delivery, and financing mechanisms designed to increase access to vaccines and drugs in poor countries (e.g., GAVI Alliance, 2009; Global Fund to Fight AIDS, Tuberculosis, and Malaria, 2009; the International Finance Facility for Immunization, 2009; Advance Market Commitments for Vaccines, 2009; and various public-private partnerships, such as the Multilateral Initiative on Malaria, 2009); and
- The assertion of sovereignty over viruses to create leverage to try to ensure that virus sharing for global surveillance leads to benefit sharing in terms of access to vaccines (e.g., Indonesia's assertion of "viral sovereignty" over HPAI-H5N1 samples [Fidler, 2008]).

Although they represent diverse strategies, these examples share common features that raise questions about the feasibility of a global access framework. First, each example reflects the dominance of ad hoc approaches to access problems, often connected with specific diseases, which is the kind of approach that the idea for a global framework seeks to avoid. Thus, these examples do not provide a template for the global framework objective.

Second, the examples reveal fragmentation in the efforts made to increase access. Examples are numerous, but there is little evidence that coordination takes

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place among all these efforts or that any over-arching strategy guides these access initiatives. In fact, the proliferation of efforts, especially in the area of innovative governance and financing mechanisms, is part of what has produced concerns about the cacophony that exists in global health governance today (Fidler, 2007). This reality means that these various efforts do not provide precedents for a framework that seeks to guide access policies globally in advance of the next pandemic.

Finally, none of these access initiatives, except the assertion of "viral sovereignty," has any specific basis in international law. Intergovernmental organizations that purchase and distribute vaccines and drugs to poor countries undertake these activities under their general international legal authorities provided by their constitutions or charters. But, as described earlier with respect to the WHO Constitution, these general provisions are not specific to the challenge of increasing access to vaccines or drugs. The GAVI Alliance, the Global Fund, the International Finance Facility for Immunization, the Advance Market Commitment for Vaccines, and the Multilateral Initiative on Malaria are all not based in international legal instruments and, thus, create no binding legal obligations on states that participate. As described more later, claims of sovereignty, although well grounded in international law, cause problems for efforts to increase equitable access and, in the process, improve global solidarity and promote a more just world.

Increasing Access to Antiretrovirals: A Good Model?

One of the more successful efforts to increase access to health treatments has been the global activities aimed at making antiretrovirals (ARVs) more accessible to persons in low-income countries infected with HIV/AIDS. These activities have involved passionate and politically savvy activism by human rights groups and other NGOs and have triggered controversies over protecting intellectual property rights for pharmaceuticals in international trade agreements. The prominence of, and progress made by, this global campaign deserves a closer look in connection with the desire to have a global access framework. In short, does the movement to increase access to ARVs provide a model for advancing the objective of a global access framework?

Analysis of the global ARV access campaign reveals that this campaign is not a good model for a global access framework, especially with respect to the close association of the framework idea and the threat posed by pandemic influenza. First, the global ARV campaign was heavily shaped by human rights thinking and activism, largely because HIV/AIDS produced consequences that connected with human rights issues, including discrimination, stigma, gender issues, sexual orientation concerns, and the presence of a massive epicenter in one of the poorest regions of the world, sub-Saharan Africa. Pandemic influenza does not generate the same kind of human rights profile as HIV/AIDS, which means that human

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rights-centric HIV/AIDS strategies do not translate well into the influenza context. In addition, the success of the campaign for greater ARV access has also produced serious global health concerns, such as a perceived response imbalance that privileges treatment over prevention (e.g., Garrett, 2008). With influenza, the major objective is to increase prevention through the use of vaccines, so, again, the ARV access campaign does not fit the pandemic influenza problem that has sparked interest in the creation of a global access framework.

International Law and the Allocation of Resources

Given the lack of traction that health-specific international agreements and access-specific efforts in global health provide for the global access framework idea, perhaps general international law related to the allocation of valuable resources might provide some insights to inform the desire to craft such a framework. Unfortunately, this approach does not provide a pathway to progress. In terms of tangible, physical resources, such as oil, timber, or commodities, the leading principle of resource allocation in international law is sovereignty, which privileges territorial control and extensions of sovereignty or exclusive control over offshore and ocean resources (e.g., the extension of coastal state sovereignty or exclusive control seaward through international legal rules on the territorial sea, contiguous zone, continental shelf, and exclusive economic zone) (Churchill and Lowe, 1999).

The principle of sovereignty also acts as the principle of resource allocation in contexts more directly relevant to the idea of a global access framework. As revealed in the controversy over virus and benefits sharing concerning HPAI-H5N1, states have sovereignty, and thus exclusive control, over viruses and other biological materials found within their territories or locations under their jurisdiction. The negotiations on virus and benefits sharing with respect to HPAI-H5N1 have accepted, as an allocation principle, the sovereignty-based approach found in the Convention on Biological Diversity, as illustrated by the World Health Assembly's recognition of "the sovereign right of States over their biological resources" (World Health Assembly, 2007).

In addition, sovereignty determines the allocation of ownership and control of vaccines and drugs—the country in which vaccines and drugs are manufactured has sovereignty over such resources until they leave its territory, and the country into which vaccines and drugs are imported or sold then has sovereignty over them under international law. Thus, any strategy to increase access to vaccines and drugs through a global framework faces a "triple sovereignty problem" because the strategy has to address claims of sovereignty where the virus strains are isolated, where vaccines or drugs are manufactured, and then where vaccines and drugs are sold or exported.

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International Law and the Creation of Resources

International law can also play a role in the creation of resources. States frequently use international law to generate certain types of resources, access to which is in their mutual self-interests. For example, states use international law to increase flows of information among themselves because better information awareness lowers the transaction costs of collective action. Examples of this strategy can be found in many areas of international law, including infectious disease control (e.g., IHR 2005), law enforcement cooperation (e.g., mutual legal assistance treaties), and counterterrorism policies (e.g., information sharing provisions of counterterrorism treaties). Similarly, states use international law to create more intangible resources, such as access to economic markets (e.g., agreements under the WTO) and security alliances (e.g., North Atlantic Treaty Organization). Market access is valuable to countries because it allows them to tap into the trade benefits grounded in the theory of comparative advantage. Security alliances permit states to deter and defend against potential military threats more efficiently than they could accomplish without international cooperation.

However, the record of international law is weaker with respect to creating resources, access to which generates competition and diverging interests among states. The international system has long experienced controversies between rich and poor countries over "technology transfer" scenarios in which the poor countries seek access to technologies and capabilities in the possession of rich countries or their multinational enterprises. These controversies were prominent during the 1970s when low-income countries sought access to advanced technologies under the rubric of the New International Economic Order in order to improve equity and justice for poor countries (UN General Assembly, 1974). The recent intergovernmental negotiations on HPAI-H5N1 virus and benefit sharing have stalled over failure by the negotiating countries to agree to technology transfers from developed countries in exchange for sharing virus specimens by low-income countries (Fukuda, 2009).

This inability to reach an accord with respect to HPAI-H5N1 replicates the older pattern of states failing to cut effective deals concerning technology transfers. The common thread across the history of "technology transfer" efforts to create and distribute resources is that equity, solidarity, and justice only provide weak incentives for states to create cooperative governance mechanisms. This longstanding pattern in international politics poses problems for the desire to create a global access framework because this framework will have to address the problem of unequal access to valuable technological resources for health, as has been seen in the "difficult and divisive" (Chan, 2009a) negotiations on public health, innovation, and intellectual property rights generally and virus and benefit sharing specifically.

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Enlightened Self-Interest, Smart Public Health?

Perhaps sensing that calling for a global access framework by appealing to equity, solidarity, and justice is not sufficient, proponents of greater access often argue that increasing such access to vaccines and drugs represents enlightened self-interest and smart public health. In terms of 2009-H1N1 influenza A, the argument is that the sharing of vaccine by developed countries with low-income countries will produce more benefits for developed countries than not sharing. One of those benefits is that sharing actually will increase public health protection for rich and poor countries alike. For example, Gostin argued that "[e]quitable access to a vaccine against swine influenza is not merely a moral imperative. It is also critically necessary to safeguard global health" (Gostin, 2009). Whether these arguments from self-interest and public health are persuasive is, however, subject to doubt.

For purposes of analysis, assume that developed and developing countries are facing a mild pandemic, such as the current one associated with 2009-H1N1 influenza A. A decision to share vaccine for a mild influenza strain might yield some positive public health benefits in poor countries (assuming such countries can effectively use the donated vaccine), but the public health payoff in developed countries of such benefits will not likely be significant because the strain in question only causes mild impact. In addition, the political benefits to developed countries of donating vaccine are limited because the global public health impact of the donated vaccine during a mild pandemic will probably not be dramatic, if it could even be measured convincingly. This reasoning helps explain why some public health experts, as noted earlier, question the expenditure of large sums of money on vaccine for the mild 2009-H1N1 influenza A pandemic when other, more pressing global health problems remain neglected.

In the context of a severe pandemic, developed countries will know that the virulent influenza virus will infect their populations, probably in multiple waves, even if low-income countries use donated vaccine supplies properly. In facing this probable threat, developed countries will have political and public health self-interests to keep as much vaccine as possible to protect their populations from the successive cycles of the severe strain. This analysis reveals that political self-interests of developed countries to share 2009-H1N1 influenza A vaccine with low-income countries are strongest in a context—a mild pandemic—in which the public health impact of the vaccine's use may not be impressive.

Important to keep in mind with respect to this analysis is that WHO has agreed to revise its pandemic influenza alert system to include a criterion reflecting the severity of influenza strains. What this promised change means is that the next time WHO declares the existence of a pandemic, the influenza strain will be causing more severe public health damage on a widespread scale than 2009-H1N1 influenza A has caused. As noted earlier, this scenario is the one in which

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developed countries with access to vaccine will be least likely to be willing to share generously with poor countries. This scenario is also why developed countries are unlikely to agree to a global access framework that limits their ability to obtain and use vaccine to protect their populations from a severe pandemic influenza strain.

Epidemiological Uncertainties, Political Dilemmas

The call for a global access framework faces other obstacles as well, such as the political dilemmas created by epidemiological uncertainties associated with pandemic influenza viruses. These epidemiological uncertainties create incentives for developed countries not to want to develop a global access framework. The unstable, constantly changing nature of influenza viruses creates short-term epidemiological uncertainty because a virus strain may undergo genetic shift and produce a more severe public health impact. If such a mutation occurred, countries would need more vaccine and antivirals for their populations, giving those with access an incentive to keep as much as possible and minimize sharing. Thus, this short-term epidemiological uncertainty creates incentives for states that likely will have access to vaccines and antivirals not to agree, in advance, to a global access framework that might leave them with fewer resources to fight a damaging influenza outbreak.

A longer-term epidemiological uncertainty leads to a similar disincentive. The 2009-H1N1 influenza A pandemic is the first influenza pandemic to occur in 40 years. The next pandemic may occur tomorrow or decades from now. Given that the next pandemic might be many years away, countries may not have strong incentives to incur the transaction costs of negotiating and implementing a global access framework for a threat that may, or may not, appear in the distant future.

Donations of Vaccine for 2009-H1N1 Influenza A

On September 17, 2009, nine developed countries announced that they would make 10 percent of their 2009-H1N1 influenza A vaccine supplies available to low-income countries through WHO (White House, 2009). Later in September, the UN System Coordinator for Avian and Human Influenza announced that other countries would also be donating 10 percent of their 2009-H1N1 influenza A vaccine supplies for use in low-income countries (Evans, 2009). The nature and timing of these donations confirms the analysis presented in this paper. These donations were not made until two developments occurred. First, clinical tests of the 2009-H1N1 influenza A vaccine revealed that adults could be immunized with a one-dose injection rather than the anticipated two-dose regimen. This unexpected result from the clinical trials essentially doubled the available supply of vaccine, making it possible for developed countries to continue to have

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enough vaccine to cover their entire populations and still donate a percentage for use in low-income countries. None of the donating developed countries has left itself short of vaccine for its own population in making donations for low-income countries. The donation decision was, therefore, relatively cost-free politically and from a self-interested public health perspective.

Second, the donations were announced after the epidemiological data confirmed that the 2009-H1N1 influenza A pandemic was a mild pandemic globally. The data from regions affected by 2009-H1N1 influenza A were telling a similar story of a mild strain rather than the feared killer strain reminiscent of the 1918-1919 influenza catastrophe. Although influenza viruses are wickedly unstable, the consistent data were not revealing warning signs of dangerous mutations in the circulating strain. With more and better data in hand confirming the pandemic as rather mild, the decision to donate vaccine for low-income countries became, politically and from a self-interested public health perspective, easier, especially when developed countries retained more than enough vaccine after donations to cover their entire populations. In short, developed countries that decided to donate vaccine to low-income countries have done so in a context in which the political and public health risk of donation was minimal.

The nature and timing of these donation decisions suggests that the incentives for developed countries to agree in advance to a global access framework are not significant, especially if developed countries can continue to use their superior power and resources to get priority access to vaccines and drugs, protect their entire populations, minimize political costs, and—if the epidemiological circumstances are favorable—appear generous. The next declared influenza pandemic will be more severe because WHO has indicated that it will change its pandemic alert system to reflect virus severity, so the political and public health risks will be higher the next time. As analyzed earlier, the foreseeability of such escalated risks will make developed countries less inclined to tie their hands through a global access framework.

The decision the United States made at the end of October 2009 to postpone its vaccine donation because of shortages of 2009-H1N1 influenza A vaccine for its domestic population (Agence-France-Presse, 2009) also illustrates the weakness of incentives for developed countries to share vaccine when they perceive they face a serious domestic threat from influenza. This decision came just over a month after the announcement of the 10 percent donation pledge, providing an indication of how uncertainty with influenza and with vaccines can change a country's perceived national interests on sharing vaccine.

In mid-December 2009, WHO provided an update on the donation effort, which revealed that donation pledges of vaccine, supplies, and funds had yet to meet any of the identified needs (see Table A4-1) and that WHO had only placed vaccine orders for three developing countries (Afghanistan, Azerbaijan, and Mongolia).

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TABLE A4-1 Overview of Resource Mobilization (millions)

Resource	Need	Pledges	Gap[a]
Vaccines (doses)	200.0	178.4	21.6
Syringes	200.0	74.5	125.5
Safety boxes	2.0	0.5	1.5
US$ for global operations	62.6	35.7	26.9
US$ for in-country operations	170.0	31.3	138.7

[a]Is equal to the difference between needs and pledges.
SOURCE: WHO (2009d).

Getting Beyond Global Clichés: Global Access Framework Components

A key political and diplomatic factor that will affect whether countries might answer the call for creating a global access framework will be the content of the framework. Proponents of creating this framework have to articulate what would be required in order to achieve the goals of equity, solidarity, and justice. Many arguments that have been made in favor of greater vaccine and antiviral access in the context of 2009-H1N1 influenza A provide no details about what the global framework should contain and how countries should negotiate such a framework. The task of filling out those details has to take into account the thus-far-unsuccessful negotiations on virus and benefit sharing concerning HPAI-H5N1—negotiations which are grappling with the central issues facing the access challenge for 2009-H1N1 influenza A. In others words, building a global access framework would take place under the dark cloud that the HPAI-H5N1 controversy and failed negotiations have produced in global health.

In addition, a simple list of possible components of a global access framework reveals the potential enormity, complexity, and difficulty of any negotiations on creating such a framework (see Box A4-1). The negotiations for a global access framework would likely be long and complicated. New international health governance mechanisms can take long periods of time to negotiate. For example, the IHR 2005 took a decade to reach an agreement, 12 years from the start of the revision process to the IHR 2005's entry into force, and 17 years before state parties have to be in full compliance with the IHR 2005. In addition, most experts acknowledge that WHO member states would not have adopted the IHR 2005 without the painful shock administered by the 2003 outbreak of severe acute respiratory syndrome (SARS). The experience with the IHR 2005 does not, of course, mean that every other global health negotiation will take as long to be completed, but it stands as a warning that expectations of a quickly negotiated, agreed upon, and implemented global access framework are unrealistic.

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BOX A4-1
Possible Components of a Global Access Framework

- Mechanisms to increase global vaccine and antiviral production capacities, both in aggregate terms and in geographical diversity;
- Provisions to increase interpandemic demand for seasonal influenza vaccines and antivirals;
- Means to improve preparedness and response capabilities (potentially through strategies that link up with implementation of the IHR 2005);
- Approaches to stimulate research and development of new vaccine and antiviral manufacturing technologies and techniques and to improve other scientific knowledge (e.g., concerning use of adjuvants); and
- Demarcation of clear "triggers" for preparedness and response actions in the pandemic alert system.

Conclusion

This paper has highlighted that calls for creating a global framework to increase equity, solidarity, and justice through improved access to vaccines and antivirals for poor countries face serious obstacles. In the context of the current "mild" H1N1 pandemic, the rhetoric of "equity, solidarity, and justice" is not necessarily very convincing with respect to this public health problem, especially when compared to other, more serious global health problems also plagued by health resources being allocated on the basis of ability to pay. Unfortunately, no good models, templates, or precedents for a global access framework exist in international law specific to health or in general international law on allocation and creation of resources. Political incentives not to create a global access framework are significant whether a pandemic threat is mild or severe. These sobering conclusions suggest that proponents of a global access framework, who draw on the harsh lessons of the 2009-H1N1 influenza A pandemic, need to devise a sophisticated political strategy, as well as an epidemiological one, to achieve this goal.

References

Advance Market Commitments for Vaccines. 2009. http://www.vaccineamc.org/ (accessed October 12, 2009).

Agence France-Presse. 2009 (October 29). *Americans first before U.S. gives H1N1 flu vaccine*, http://newsinfo.inquirer.net/breakingnews/world/view/20091029-232857/Americans-first-before-US-gives-H1N1-flu-vaccineexec (accessed January 5, 2010).

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Bill & Melinda Gates Foundation. 2009. *Proposed principles to guide global allocation of pandemic vaccines*, http://www.gatesfoundation.org/topics/Documents/Pandemic-Flu-Principles-2009.pdf (accessed October 12, 2009).

Chan, M. 2009a. *Strengthening multilateral cooperation on intellectual property and public health*. Address to the World Intellectual Property Organization Conference on Intellectual Property and Public Policy Issues, Geneva, Switzerland, July 14, http://www.who.int/dg/speeches/2009/intellectual_property_20090714/en/index.html (accessed October 12, 2009).

———. 2009b. *World now at start of 2009 influenza pandemic, June 11*, http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html (accessed October 12, 2009).

Cheng, M. 2009. UN seeks $1.5 billion for swine flu. *Associated Press*, http://www.google.com/hostednews/ap/article/ALeqM5h8A6JZsRfa0BonhLtd-vSiQerP4QD9ATOITG1 (accessed October 12, 2009).

Churchill, R. R., and A. V. Lowe. 1999. *The law of the sea*, third edition. Manchester, UK: Manchester University Press.

Committee on Economic, Social, and Cultural Rights. 2000 (August 11). *General Comment No. 14—The right to the highest attainable standard of health (article 12 of the International Covenant on Economic, Social, and Cultural Rights), U.N. Doc. E/C.12/2000/4*, http://www.unhchr.ch/tbs/doc.nsf/(symbol)/E.C.12.2000.4.En (accessed October 12, 2009).

Evans, R. 2009 (September 25). More H1N1 vaccines likely for poor countries: U.N. *Reuters*, http://www.reuters.com/article/healthNews/idUSTRE58O4LG20090925?feedType=RSS&feedName=healthNews&pageNumber=2&virtualBrandChannel=0&sp=true (accessed October 12, 2009).

Fedson, D. S. 2004. Vaccination for pandemic influenza: a six point agenda for interpandemic years. *Pediatric Infectious Diseases Journal* 23(1 Suppl.):S74-S77.

Fidler, D. P. 2007. Architecture amidst anarchy: global health's quest for governance. *Global Health Governance* 1(1).

———. 2008. Influenza virus samples, international law, and global health diplomacy. *Emerging Infectious Diseases* 14(1):88-94.

———. 2009. H1N1 after action review: learning from the unexpected, the success, and the fear. *Future Microbiology* 4(7):767-769.

Fukuda, K. 2009 (September 15). *2009 influenza (H1N1) pandemic: lessons for going forward*. Presentation at the Forum of Microbial Threats Workshop on the Domestic and International Aspects of the 2009 Influenza A (H1N1) Pandemic: Global Challenges, Global Solutions, http://www.iom.edu/Activities/PublicHealth/MicrobialThreats/2009-SEP-15.aspx (accessed November 10, 2009).

Garrett, L. 2008 (July 30). The wrong way to fight AIDS. *New York Times*, http://www.nytimes.com/2008/07/30/opinion/30iht-edgarrett.1.14888763.html (accessed October 12, 2009).

———. 2009a (July 28). Laurie Garrett interview: U.S. global health leader MIA on swine flu, *ScienceInsider*, http://blogs.sciencemag.org/scienceinsider/2009/07/laurie-garrett.html (accessed October 12, 2009).

———. 2009b. Global health update, October 7.

———. 2009c. Global health update, December 23.

GAVI Alliance. 2009. http://www.gavialliance.org/ (accessed October 12, 2009).

Global Fund to Fight AIDS, Tuberculosis, and Malaria. 2009. http://www.theglobalfund.org/en/ (accessed October 12, 2009).

Gostin, L. O. 2009 (August 8-9). Global goal for vaccine quest. *Australian*, http://www.theaustralian.news.com.au/story/0,25197,25896462-23289,00.html (accessed October 12, 2009).

Hitt, E. 2009 (May 22). WHO to revise definition of global pandemic. *Medscape Today*, http://www.medscape.com/viewarticle/703209 (accessed October 12, 2009).

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

International Finance Facility for Immunization. 2009. http://www.iff-immunisation.org/ (accessed October 12, 2009).

IVI (International Vaccine Institute). 2009. http://www.ivi.org/ (accessed October 12, 2009).

MSF (Médécins Sans Frontières). 2009a. *Medical need, not purchase power, should determine the global response to the influenza A (H1N1) pandemic: an interview with Dr. Christophe Fournier, President of MSF International Council*, http://www.msfaccess.org/main/access-patents/medical-need-not-purchase-power-should-determine-the-global-response-to-the-influenza-a-h1n1-pandemic/ (accessed October 12, 2009).

———. 2009b. *Campaign for access to essential medicines*, http://www.msfaccess.org/ (accessed October 12, 2009).

Multilateral Initiative on Malaria. 2009. http://www.mimalaria.org/ (accessed October 12, 2009).

Office of the United Nations High Commissioner for Human Rights. 1966. *International Covenant on Economic, Social, and Cultural Rights*, http://www2.ohchr.org/english/law/cescr.htm (accessed October 12, 2009).

PAHO (Pan American Health Organization). 2009. *PAHO revolving fund for vaccine procurement*, http://www.paho.org/english/hvp/hvi/revol_fund.htm (accessed October 12, 2009).

PEPFAR (U.S. President's Emergency Plan for AIDS Relief). 2009. *The United States President's Emergency Plan for AIDS Relief*, http://www.pepfar.gov/ (accessed October 12, 2009).

President's Council of Advisors on Science and Technology. 2009. *Report to the President on U.S. preparedness for 2009-H1N1 influenza*, http://www.whitehouse.gov/assets/documents/PCAST_H1N1_report.pdf (accessed October 12, 2009).

UN (United Nations) General Assembly. 1974. *Declaration on the Establishment of a New International Economic Order*, http://www.un-documents.net/s6r3201.htm (accessed October 12, 2009).

UNICEF (United Nations Children's Fund). 2009. *Immunization: procuring supplies for children*, http://www.unicef.org/supply/index_immunization.html (accessed October 12, 2009).

Whalen, J. 2009 (May 16). Rich nations lock in flu vaccine as poor ones fret. *Wall Street Journal*, http://online.wsj.com/article/SB124243015022925551.html (accessed October 12, 2009).

White House. 2009. *President announces plan to expand fight against global H1N1 pandemic*, http://www.whitehouse.gov/the_press_office/President-Announces-Plan-to-Expand-Fight-Against-Global-H1N1-Pandemic/ (accessed October 12, 2009).

WHO (World Health Organization). 1946. *Constitution of the World Health Organization*, http://www.who.int/governance/eb/who_constitution_en.pdf (accessed October 12, 2009).

———. 2009a. *Swine influenza*, http://www.who.int/mediacentre/news/statements/2009/h1n1_20090425/en/index.html (accessed October 12, 2009).

———. 2009b. *Immunization supply and procurement*, http://www.who.int/immunization_supply/en/ (accessed October 12, 2009).

———. 2009c. *WHO welcomes Sanofi-Aventis' donation of vaccine*, http://www.who.int/mediacentre/news/statements/2009/vaccine_donation_20090617/en/index.html (accessed October 12, 2009).

——— 2009d. *Pandemic (H1N1) 2009 vaccine deployment update, December 17*, http://www.who.int/csr/disease/swineflu/vaccines/h1n1_vaccination_deployment_update_20091217.pdf (accessed January 5, 2010).

World Health Assembly. 2007. *Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits*, http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R28-en.pdf (accessed October 12, 2009).

Yamada, T. 2009. Poverty, wealth, and access to pandemic influenza vaccines. *New England Journal of Medicine* 361(12):1129-1131.

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A5

IN VITRO AND *IN VIVO* CHARACTERIZATION OF NEW SWINE-ORIGIN H1N1 INFLUENZA VIRUSES[23]

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Influenza A viruses cause recurrent outbreaks at local or global scale with potentially severe consequences for human health and the global economy. Recently, a new strain of influenza A virus was detected that causes disease in and transmits among humans, probably owing to little or no pre-existing immunity to the new strain. On 11 June 2009 the World Health Organization declared that the infections caused by the new strain had reached pandemic proportion. Characterized as an influenza A virus of the H1N1 subtype, the genomic segments of the new strain were most closely related to swine viruses (Novel Swine-Origin Influenza A [H1N1] Virus Investigation Team, 2009). Most human infections with swine origin H1N1 influenza viruses (S-OIVs) seem to be mild; however, a substantial number of hospitalized individuals do not have underlying health issues, attesting to the pathogenic potential of S-OIVs. To achieve a better assessment of the risk posed by the new virus, we characterized one of the first US S-OIV isolates, A/California/04/09 (H1N1; hereafter referred to as CA04), as well as several other S-OIV isolates, in vitro and in vivo. In mice and ferrets, CA04 and other S-OIV isolates tested replicate more efficiently than a currently circulating human H1N1 virus. In addition, CA04 replicates efficiently in non-human primates, causes more severe pathological lesions in the lungs of infected mice, ferrets and non-human primates than a currently circulating human H1N1 virus, and transmits among ferrets. In specific-pathogen-free miniature pigs, CA04 replicates without clinical symptoms. The assessment of human sera from different age groups suggests that infection with human H1N1 viruses antigenically closely related to viruses circulating in 1918 confers neutralizing antibody activity to CA04. Finally, we show that CA04 is sensitive to approved and experimental antiviral drugs, suggesting that these compounds could function as a first line of defence against the recently declared S-OIV pandemic.

Sequence analyses of recently emerged swine-origin H1N1 viruses (S-OIVs) revealed the absence of markers associated with high pathogenicity in avian and/or mammalian species, such as a multibasic haemagglutinin (HA) cleavage site (Kawaoka and Webster, 1988) or lysine at position 627 of the PB2 protein (Hatta et al., 2001). To characterize the new viruses *in vitro* and *in vivo*, we amplified the following S-OIVs in Madin–Darby canine kidney (MDCK) cells: A/California/04/09 (CA04), A/Wisconsin/WSLH049/09 (WSLH049), A/Wisconsin/WSLH34939/09 (WSLH34939), A/Netherlands/603/09 (Net603) and A/Osaka/164/09 (Osaka164). WSLH34939 was isolated from a patient who required hospitalization, whereas the remaining viruses were isolated from mild cases. These viruses represent the currently recognized neuraminidase (NA) variants among S-OIVs: CA04, NA-106V, NA-248N; Osaka164, NA-106I, NA-248N; WSLH049, NA-106I, NA-248D; WSLH34939, NA-106I, NA-248D; and Net603, NA-106V, NA-248N.

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In MDCK cells and primary human airway epithelial cells, CA04 grew to titres comparable to those typically obtained for contemporary human H1N1 influenza viruses (Supplementary Figure A5-4). Confocal, transmission electron and scanning electron microscopy revealed virions of remarkably filamentous shape (Supplementary Figure A5-5), in marked contrast to the spherical shape observed with negatively stained virions (http://www.cdc.gov/h1n1flu/images.htm). The biological significance of the morphology of CA04 remains unknown.

To evaluate the pathogenicity of S-OIV in mammalian models, we conducted studies in mice, ferrets, non-human primates and pigs. BALB/c mice intranasally infected with a high dose ($>10^4$ plaque forming units (p.f.u.)) of CA04 (Supplementary Figure A5-6) experienced weight loss and those infected with the highest dose of this virus were humanely killed, in contrast to animals infected with a recent human H1N1 virus (A/Kawasaki/UTK-4/09, KUTK-4). The 50% mouse lethal dose (MLD_{50}) was $10^{5.8}$ p.f.u. for CA04 and $.10^{6.6}$ p.f.u. for KUTK-4. For the additional S-OIV isolates tested, the MLD_{50} values were $>10^{6.4}$ p.f.u. for Osaka164, $>10^{6.6}$ p.f.u. for WSLH049, $10^{4.5}$ p.f.u. for WSLH34939 and $>10^{5.8}$ p.f.u. for Net603.

On day 3 after infection of mice, similar titres were detected in nasal turbinates of mice infected with 10^5 p.f.u. of S-OIVs or KUTK-4 (Supplementary Table A5-2); however, S-OIVs replicated more efficiently in the lungs of infected animals, which may account for the prominent bronchitis and alveolitis with viral antigen on day 3 after infection with CA04 (Supplementary Figure A5-7a, b). On day 6 after infection, virus titres followed a similar trend and the lungs of CA04-infected mice showed bronchitis and alveolitis with viral antigen, although signs of regeneration were apparent (Supplementary Figure A5-7c). We detected viral-antigen-positive bronchial epithelial cells, but not alveolar cells, on day 3 after infection of mice infected with KUTK-4 (Supplementary Figure A5-7e). By day 6, infection in KUTK-4-inoculated mice had progressed to bronchitis and peribronchitis; however, viral antigen was rarely detected in these lesions (Supplementary Figure A5-7f).

There were marked differences in the induction of pro-inflammatory cytokines in the lungs of mice infected with CA04 compared with KUTK-4 (Supplementary Figure A5-8a–c). Infection with KUTK-4 resultedin limited induction of pro-inflammatory cytokines/chemokines in the lungs, inmarked contrast to infection withCA04. Increased production of interleukin-10 (IL-10; Supplementary Figure A5-7a) in lungs of CA04-infected mice at day 6 after infection probably reflects a host response to dampen over-exuberant pulmonary inflammation and promote tissue repair. Infection with CA04 led to strong induction of both interferon-γ (IFN-γ) and IL-4 in the lungs. The selective induction of the T_H2 cytokine IL-5 in CA04-infected, but not in KUTK-4-infected, mice on day 6 after infection is noteworthy (Supplementary Figure A5-7b), but further studies are needed to understand the relevance of this finding to viral control. IL-17 has been reported to have a role in protection against lethal influenza and also in eliciting

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inflammatory responses (Iwakura et al., 2008; Hamada et al., 2009); however, the enhanced viral replication and lung pathology observed in CA04-infected mice was not linked to dysregulated IL-17 production.

Cynomolgus macaques (*Macaca fascicularis*) have been used to study highly pathogenic avian H5N1 viruses (Baskin et al., 2009; Rimmelzwaan et al., 2001) and the 1918 pandemic virus (Kobasa et al., 2007). Infection of cynomolgus macaques with CA04 (see Methods for detailed procedures) resulted in a more prominent increase in body temperature than infection with KUTK-4 (Supplementary Fig. A5-9). This difference might originate from the observed differences in virus titres (Table A5-1 and Supplementary Table A5-3). No remarkable difference in body weight loss was found between the two groups (data not shown). CA04 replicated efficiently in the lungs and other respiratory organs of infected animals, similar to highly pathogenic influenza viruses (Baskin et al., 2009; Kobasa et al., 2007) (Table A5-1). By contrast, conventional human influenza viruses are typically limited in their replicative ability in the lungs of infected primates (Baskin et al., 2009; Kobasa et al., 2007) (Table A5-1), although a seasonal H1N1 virus was isolated from one animal on day 7 after infection. Pathological examination revealed that CA04 caused more severe lung lesions than did KUTK-4 (Fig. A5-1 and Supplementary Fig. A5-10). On day 3 after infection with CA04, alveolar spaces were occupied by oedematous exudate and inflammatory infiltrates (Fig. A5-1a, b); severe thickening of alveolar walls was also observed (Fig. A5-1b). Viral-antigen-positive cells were distributed in the inflammatory lesions, and many of these cells were elongated with thin cytoplasm and hemming around the alveolar wall, indicating type I pneumocytes (Fig. A5-1c). In addition to type I pneumocytes, CA04 viral antigens were also detected in considerable numbers of cuboidal, cytokeratin-positive cells, hence identified as type II pneumocytes (Fig. A5-1d and Supplementary Fig. A5-11), as has been reported for highly pathogenic avian H5N1 influenza viruses6. Upon infection with KUTK-4, large sections of infected lungs showed thickening of the alveolar wall on day 3 after infection (Fig. A5-1e). Although the infiltration of inflammatory cells was prominent at the alveolar wall (Fig. A5-1f), viral antigens were sparse and detected in type I (but not type II) pneumocytes (Fig. A5-1g). By contrast, the lungs of non-infected animals show clear alveolar spaces (Fig. A5-1h).

On day 7 after infection, lung pathology remained more severe for CA04- than for KUTK-4-infected lungs (Supplementary Fig. A5-10), although regenerative changes were seen for CA04. Nonetheless, considerable numbers of antigen-positive cells were still detectable (Supplementary Fig. A5-10c). Collectively, these findings demonstrate that CA04 causes more severe lung lesions in non-human primates than does a contemporary human influenza virus.

Induction of pro-inflammatory cytokines/chemokines in the lungs of CA04-infected macaques was variable at day 3 after infection (Supplementary Fig. A5-12). However, consistent with persisting lung pathology and inflammation on day 7 after infection, the levels of MCP-1, MIP-1α, IL-6 and IL-18 were markedly higher in the lungs of two of three CA04-infected macaques.

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TABLE A5-1 Virus Titres in Organs of Infected Cynomolgus Macaques

Organ	A/California/04/09 (H1N1)						A/Kawasaki/UTK-4/09 (H1N1)					
	Day 3 after infection			Day 7 after infection			Day 3 after infection			Day 7 after infection		
	1	2	3	4	5	6	7	8	9	10	11	12
Nasal mucosa	4.7	3.3	—	—	—	—	—	—	—	—	—	—
Oro/nasopharynx	6.3	4.4	4.7	—	7.9	—	—	—	4.3	—	—	4.8
Tonsil	6.4	—	—	—	7.1	—	—	—	2.8	—	—	3.0
Trachea	5.9	2.0	5.6	—	—	—	2.0	4.1	—	3.7	—	5.4
Bronchus (right)	5.7	2.9	4.3	—	5.1	—	—	2.5	—	3.5	—	3.8
Bronchus (left)	5.9	—	6.1	—	5.1	—	—	—	—	3.3	—	5.1
Lung (upper right)	5.7	5.6	4.5	—	—	—	2.7	—	—	—	—	—
Lung (middle right)	5.6	6.4	6.9	—	—	—	2.3	2.6	2.5	—	—	—
Lung (lower right)	6.1	4.5	6.0	—	—	—	2.6	2.6	—	—	—	3.4
Lung (Upper left)	4.7	4.3	6.4	—	—	—	—	—	—	—	—	—
Lung (middle left)	5.8	4.3	6.3	—	—	—	—	—	—	—	—	—
Lung (lower left)	6.7	4.5	6.6	—	—	—	—	—	—	—	—	2.3
Conjunctiva	3.6	—	—	—	—	—	—	—	—	—	—	—

Cynomolgus macaques were inoculated with $10^{7.4}$ p.f.u. of virus (6.7 ml) through multiple routes (see Methods). Three macaques per group were killed on days 3 and 7 after infection for virus titration. No virus was recovered from lymph nodes (chest), heart, spleen, kidneys or liver of any of the animals. A dash indicates that virus was not detected (detection limit: 2 $\log_{10}$ p.f.u.g^{-1}). Numbers 1-12 indicate animal identification number. Values indicate virus titre (mean $\log_{10}$ p.f.u.g^{-1}).

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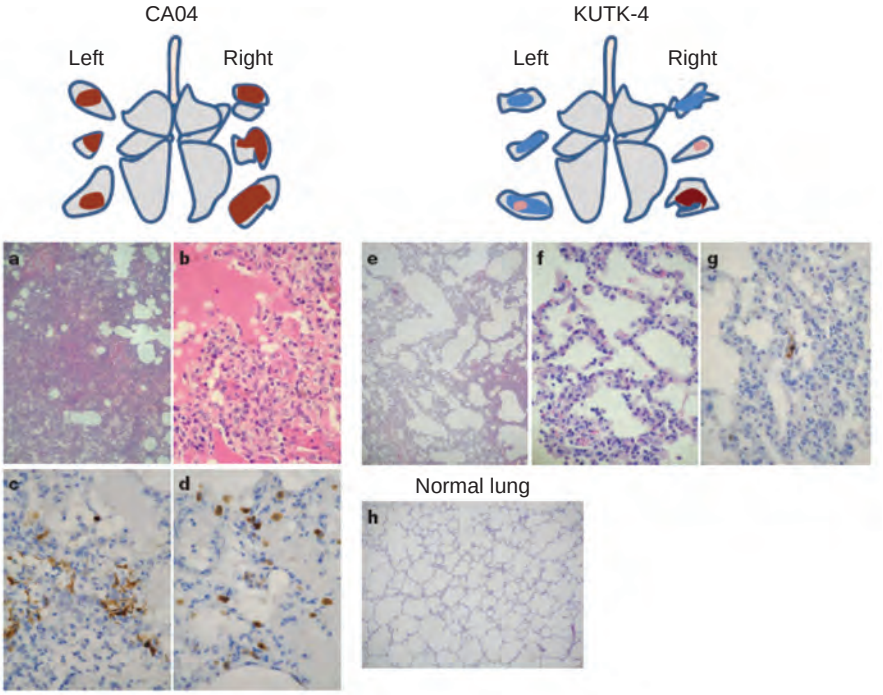

FIGURE A5-1 Pathological examination of the lungs of infected cynomolgus macaques. A-h Representative pathological images of CA04-infected (macaque no. 1, a-d), KUTK-4 infected (macaque no. 7, e-g) and mock-infected (h) lungs on day 3 after infection. One or two sections per lung lobe were examined. Representative findings are shown to depict the distribution of lesions in the sections (shown as cross-sections placed next to illustrations of ach lung lobe), with or without viral antigen, as follows: brown, severe lung lesion containing moderate to many viral-antigen-positive cells; pink, mild lung lesions containing a few viral-antigen-positive cells; blue, lung lesions with alveolar wall thickening, with remaining air spaces unaffected. Original magnification: a, e, h, ×40; b-d-f, g, ×400.

Ferrets are widely accepted as a suitable small-animal model for influenza virus pathogenicity and transmissibility studies. Infection of ferrets with S-OIVs or KUTK-4 did not cause marked changes in body temperature or weight in any group (data not shown). Although all test viruses were detected in nasal turbinates at similar titres on day 3 after infection (Supplementary Table A5-4), S-OIVs replicated to higher titres in trachea and lungs.

Pathological examination detected similar levels of viral antigen in the nasal mucosa of both CA04- and KUTK-4-infected ferrets (Supplementary Fig. A5-13a and e). However, the lungs of CA04-infected ferrets showed more severe broncho-

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pneumonia with prominent viral antigen expression in the peribronchial glands and a few alveolar cells (Supplementary Fig. A5-13b–d) on day 3 after infection. By contrast, most of the lung appeared normal after infection with KUTK-4 (Supplementary Fig. A5-13f and g). Thus, in all three mammalian models tested, CA04 seemed to be more pathogenic than a contemporary human H1N1 virus, KUTK-4.

Efficient human-to-human transmission is a critical feature of pandemic influenza viruses. To assess the transmissibility of CA04, naive ferrets in perforated cages were placed next to ferrets inoculated with 10^6 p.f.u. of CA04 (see Methods for detailed procedures). This experimental setting allows for aerosol transmission (that is, the exchange of respiratory droplets between the inoculated and noninoculated ferrets) but prevents transmission by direct and indirect contact. All three contact ferrets were positive for CA04 virus on days 3 and 5 after infection (Supplementary Table A5-5). This transmission pattern is comparable to those of two human control influenza viruses that are known to transmit among ferrets: KUTK-4 and A/Victoria/3/75 (H3N2) (Maines et al., 2006). By contrast, an avian influenza virus (A/duck/Alberta/35/76; H1N1) did not transmit (Supplementary Table A5-5).

Genetic analysis suggests that S-OIV originated in pigs (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009). However, there were no confirmed influenza virus outbreaks in Central American pigs before the reported S-OIV infections in humans. To assess S-OIV replication in pigs, we inoculated specific-pathogen-free miniature pigs, which are easier to manage, with CA04 or a classical swine influenza virus (A/swine/Hokkaido/2/81, H1N1). No signs of disease were observed (data not shown), although both viruses replicated efficiently in the respiratory organs of these animals (Supplementary Tables A5-6 and A5-7). Slightly higher titres of CA04 were detected in lungs on day 3 after infection, which is supported by pathological findings that show more apparent bronchitis and bronchiolitis in pigs infected with CA04 (Supplementary Fig. A5-14). The asymptomatic infection of CA04, despite efficient virus replication, might explain the lack of reports of S-OIV outbreaks in pigs before virus transmission to humans.

Antiviral compounds are the first line of defence against pandemic influenza viruses. Sequence analysis suggests that S-OIVs are resistant to ion channel inhibitors such as amantadine and rimantadine (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009). We therefore tested the licensed neuraminidase inhibitors oseltamivir and zanamivir, the experimental neuraminidase inhibitor R-125489 (the active form of CS-8958 [Yamashita et al., 2009]) and the experimental compound T-705 (a broad-spectrum viral RNA polymerase inhibitor [Furuta et al., 2002]) for their efficacy against CA04. In cell culture, CA04 was highly susceptible to all compounds tested (Supplementary Table A5-8), as were the human H1N1 control viruses A/Kawasaki/UTK-23/08 and KUTK-4, with the exception of the known oseltamivir resistance of KUTK-4. Comparable sensitivities were also found in an enzymatic neuraminidase inhibition assay (Hayden et

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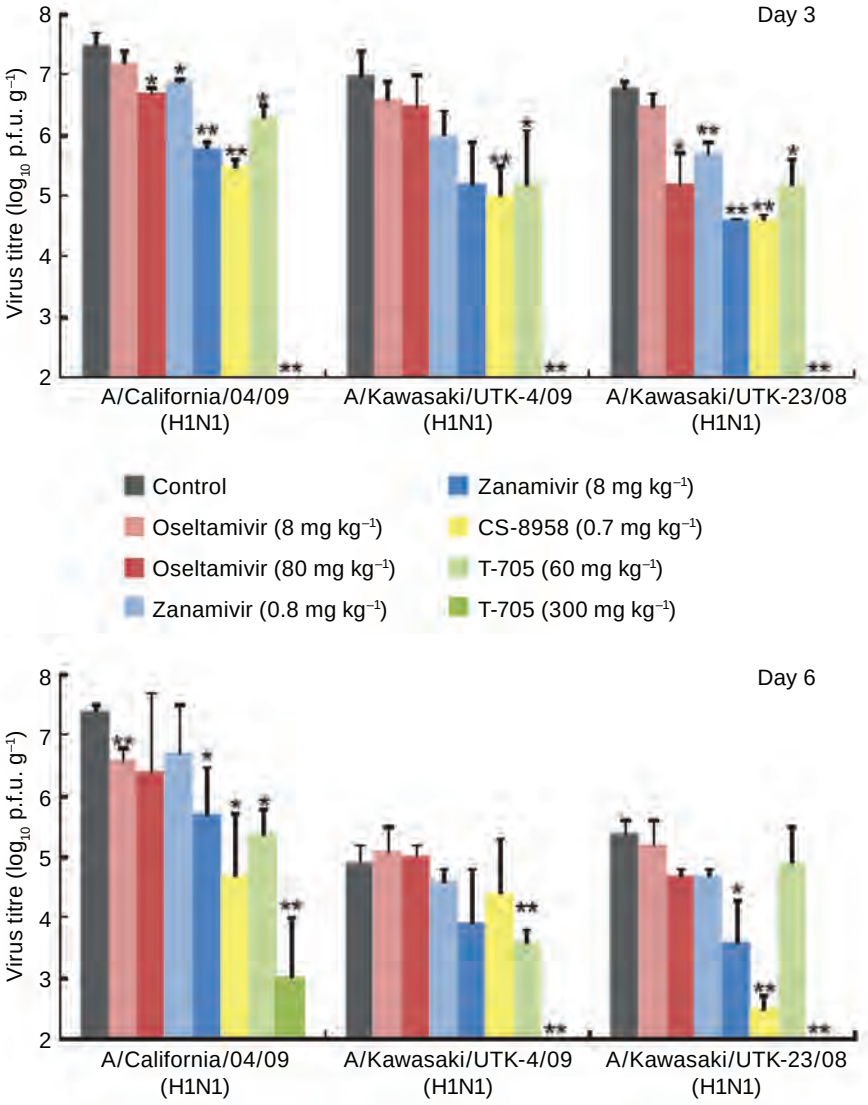

FIGURE A5-2 CA04 sensitivity to antiviral compounds in mice. Mice were intranasally inoculated with 10^4 p.f.u. (50 µl) of CA04, KUTK-4 or A/Kawasaki/UTK-23/08 (H1N1). At 1 h after infection, mice were administered oseltamivir phosphate, zanamivir, CS-8958, T-705, or distilled water and PBS (control). Three mice per group were killed on days 3 and 6 after infection and the virus titres in lungs were determined by plaque assays in MDCK cells; results are reported as means ± s.d. The statistical significance of differences in lung virus titres of control mice and those treated with antivirals were assessed by use of the Student's *t*-test (asterisk, $P < 0.05$; double asterisk, $P < 0.01$).

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al., 2000) (Supplementary Table A5-9) and in mice (Fig. A5-2), consistent with observations in clinical settings.

A recent report suggested that 33% of individuals over 60 years of age had neutralizing antibodies to CA04 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5819a1.htm; Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention), probably due to previous exposure to antigenically similar H1N1 viruses. In fact, both the human H1N1 viruses that circulated until 1957 and the classical swine virus HA gene of S-OIVs are descendants of the 1918 pandemic virus, possibly explaining their antigenic relatedness. In 1977, H1N1 viruses re-emerged that were genetically and antigenically very closely related to viruses circulating in the 1950s (Nakajima et al., 1978) and should thus have elicited neutralizing antibodies to CA04 among younger age groups; however, this does not seem to be the case, according to the above described report. To resolve this puzzling finding, we assessed the neutralizing activities of sera collected from a broad range of age groups against CA04 and KUTK-4. We used two sets of donor sera, collected in 1999 from residents and workers in a nursing home (donor set 1), and in April 2009 from workers and patients in a hospital (donor set 2). High neutralizing activity against KUTK-4 was detected for many sera in donor set 2 (Fig. A5-3), but not for sera in donor set 1, probably because these sera were collected before the emergence of the current human H1N1 viruses. Interestingly, with few exceptions, no appreciable neutralizing antibodies against CA04 were found for individuals born after 1920; however, many of those born before 1918 had high neutralizing antibody titres (individual neutralizing antibody titres are shown in Supplementary Table A5-9). These data indicate that infection with the 1918 pandemic virus or closely related human H1N1 viruses, but not infection with antigenically divergent human H1N1 viruses circulating in the 1920s to 1950s, and again since 1977, elicited neutralizing antibodies to S-OIVs.

Our findings indicate that S-OIVs are more pathogenic in mammalian models than seasonal H1N1 influenza viruses. In fact, the ability of CA04 to replicate in the lungs of mice, ferrets and non-human primates, and to cause appreciable pathology in this organ, is reminiscent of infections with highly pathogenic H5N1 influenza viruses (Peiris et al., 2004), as acknowledged in a recent report by the World Health Organization (http://www.who.int/wer/2009/wer8421/en/index.html). We therefore speculate that the high replicative ability of S-OIVs might contribute to a viral pneumonia characterized by diffuse alveolar damage that contributes to hospitalizations and fatal cases where no other underlying health issues exist (http://www.who.int/wer/2009/wer8421/en/index.html). In addition, sustained person-to-person transmission might result in the emergence of more pathogenic variants, as observed with the 1918 pandemic virus (reviewed in Wright et al., 2007). Furthermore, S-OIVs may acquire resistance to oseltamivir through mutations in their NA gene (as recently witnessed with human H1N1 viruses [Moscona, 2009]), or through reassortment with co-circulating,

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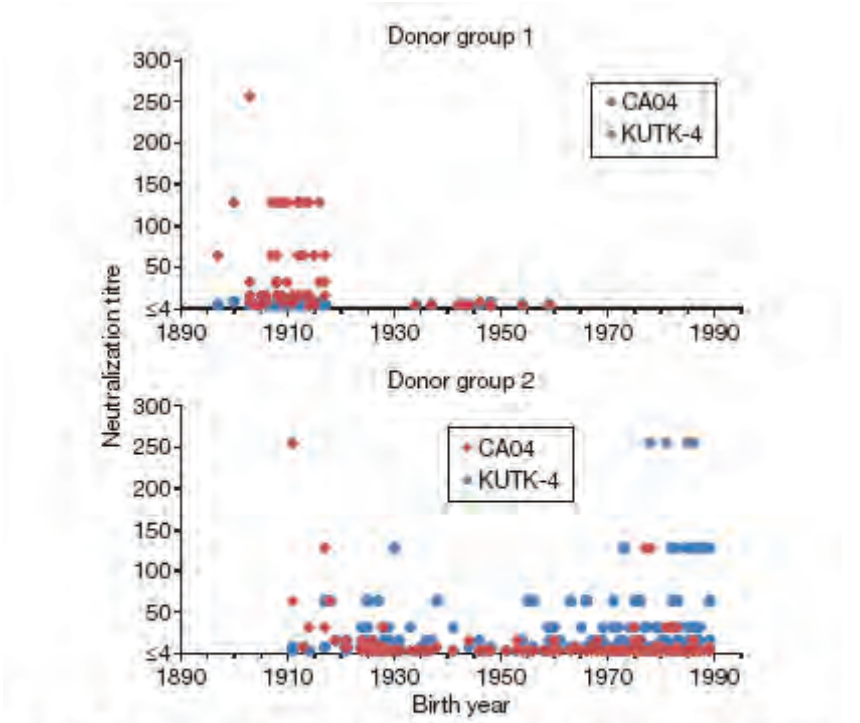

FIGURE A5-3 Neutralization activities in human sera against viruses. Human sera of donor groups 1 (collected in 1999) and 2 (collected in April and May of 2009) were subjected to neutralization assays with CA04 and KUTK-4. Because the sera of donor group 1 were collected in 1999, little neutralization activity was expected against KUTK-4, which was isolated in 2009.

oseltamivir-resistant seasonal human H1N1 viruses. Collectively, our findings are a reminder that S-OIVs have not yet garnered a place in history, but may still do so, as the pandemic caused by these viruses has the potential to produce a significant impact on human health and the global economy.

Methods Summary

Viruses and Cells

All swine-origin H1N1 viruses were isolated and passaged in MDCK cells to produce viral stocks. The viruses and their passage histories are described in Methods. All experiments with S-OIVs were performed in approved enhanced biosafety level 3 (BSL3) containment laboratories.

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MDCK cells and MDCK cells overexpressing the β-galactoside α2,6-sialyltransferase I gene (Hatakeyama et al., 2005) were maintained in Eagle's minimal essential medium (MEM) containing 5% newborn calf serum. Human airway epithelial (HAE) cells were obtained from residual surgical tissue trimmed from lungs during the process of transplantation. The bronchial specimens were dissected and enzymatically digested, and monolayers of HAE cells were isolated, cultured and differentiated as previously described (Jakiela et al., 2008).

Animals

Five- and six-week-old female BALB/c mice (Jackson Laboratory and Japan SLC Inc.), approximately three-to-four-year-old cynomolgus macaques (Ina Research Inc.), five-to-eight-month-old male ferrets (Marshall Farms and Triple F Farms) and two-month-old female specific-pathogen-free miniature pigs (Nippon Institute for Biological Science) were used according to approved protocols for the care and use of animals. Detailed procedures are provided in Methods.

Antiviral Sensitivity of Viruses in Mice

Five-week-old female BALB/c mice (Japan SLC Inc.; groups of six) were anaesthetized with sevoflurane and intranasally inoculated with 10^4 p.f.u. (volume, 50 µl) of CA04, KUTK-4, or A/Kawasaki/UTK-23/08 (H1N1). At 1 h after infection, mice were administered antiviral compounds as described in detail in Methods. Three mice per group were killed on days 3 or 6 after infection and the virus titres in lungs were determined by plaque assays in MDCK cells.

Methods

Viruses

A/California/04/09 (H1N1; CA04) was provided by the Centers for Disease Control (CDC). A/Wisconsin/WSLH049/09 (H1N1) was isolated from a patient with mild symptoms, whereas A/Wisconsin/WSLH34939/09 (H1N1) was isolated from a hospitalized patient. A/Netherlands/603/09 (H1N1) was isolated from a patient with mild symptoms and was provided by R. Fouchier. A/Osaka/164/09 (H1N1) was also isolated from a patient with mild symptoms.

The following influenza viruses served as controls: A/Kawasaki/UTK-4/09 (H1N1; KUTK-4; passaged twice in MDCK cells), an oseltamivir-resistant seasonal human virus; A/WSN/33 (H1N1; generated by reverse genetics and passaged twice in MDCK cells), a typical spherical influenza virus (Noda et al., 2006); A/Kawasaki/UTK-23/08 (H1N1; passaged twice in MDCK cells), an oseltamivir-sensitive seasonal human virus; A/Victoria/3/75 (H3N2; passaged several times in eggs after it was obtained from the CDC), a human virus; A/swine/Hokkaido/2/81

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(H1N1; passaged several times in eggs), a classical swine virus; and A/duck/Alberta/35/76 (H1N1; passaged several times in eggs), an avian virus. All experiments with S-OIV viruses were performed in enhanced biosafety level 3 (BSL3) containment laboratories at the University of Wisconsin-Madison, which are approved for such use by the CDC and the US Department of Agriculture, or in BSL3 containment laboratories at the University of Tokyo, the Shiga University of Medical Science, or the Hokkaido University, all of which are approved for such use by the Ministry of Agriculture, Forestry and Fisheries, Japan.

Viral Pathogenesis in Mice

Six-week-old female BALB/c mice (Jackson Laboratory) were used in this study. Baseline body weights were measured before infection. Three mice per group were anaesthetized with isoflurane and intranasally inoculated with 10^2, 10^3, 10^4, or 10^5 p.f.u. (50 µl) of CA04 and KUTK-4, or undiluted virus from virus stocks (CA04, $10^{6.5}$ p.f.u.; KUTK-4, $10^{6.6}$ p.f.u.). Body weight and survival were monitored daily for 14 days and mice with body weight loss of more than 25% of pre-infection values were killed. For virological and pathological examinations, 6 mice per group were intranasally infected with 10^5 p.f.u. of S-OIVs and KUTK-4 and 3 mice per group were killed on days 3 and 6 after infection. The virus titres in various organs were determined by plaque assays in MDCK cells.

Growth Kinetics of Virus in Human Airway Epithelial (HAE) Cells

Cultures of differentiated HAE cells were washed extensively with PBS to remove accumulated mucus and infected with virus at a multiplicity of infection (MOI) of 0.001 from the apical surface. The inoculum was removed after 1 h of incubation at 35°C, and cells were further incubated at 35°C. Samples were collected at 12, 24, 48, 72 and 96 h after infection from the apical surface. Apical harvesting was performed by adding 500 µl of medium to the apical surface, followed by incubation for 30 min at 35˚C, and removal of the medium from the apical surface. The titres of viruses released into the cell culture supernatant were determined by plaque assay in MDCK cells.

Experimental Infection of Cynomolgus Macaques

Approximately three-to-four-year-old cynomolgus macaques (*Macaca fascicularis*) from the Philippines (obtained from Ina Research Inc.), weighing 2.1–3.0 kg and serologically negative by AniGen AIV antibody ELISA, which detects all influenza A virus subtypes (Animal Genetics Inc.), were used in this study. Baseline body weights were established by two or three measurements before infection. Under anaesthesia, telemetry probes (TA10CTA-D70, Data Sciences International) were implanted in the peritoneal cavities of animals to monitor body temperature. Six macaques per group were intramuscularly

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anaesthetized with ketamine (5 mg per kg) and xylazine (1 mg per kg) and inoculated with a suspension containing $10^{6.5}$ p.f.u. ml^{-1} of CA04 or KUTK-4 virus through a combination of intratracheal (4.5 ml), intranasal (0.5 ml per nostril), ocular (0.1 ml per eye) and oral (1 ml) routes (resulting in a total infectious dose of $10^{7.4}$ p.f.u.). Macaques were monitored every 15 min for changes in body temperature. On days, 1, 3, 5 and 7 after infection, nasal and tracheal swabs and bronchial brush samples were collected. On days 3 and 7 after infection, 3 macaques per group were killed for virological and pathological examinations. The virus titres in various organs and swabs were determined by plaque assays in MDCK cells. Experiments were carried out in accordance with the Guidelines for the Husbandry and Management of Laboratory Animals of the Research Center for Animal Life Science at Shiga University of Medical Science, Shiga, Japan, and approved by the Shiga University of Medical Science Animal Experiment Committee and Biosafety Committee.

Experimental Infection of Ferrets

We used five-to-eight-month-old male ferrets (Marshall Farms and Triple F Farms), which were serologically negative by haemagglutination inhibition (HI) assay for currently circulating human influenza viruses. Baseline body temperatures and body weights were established by one or two measurements before infection. Six ferrets per group were intramuscularly anaesthetized with ketamine and xylazine (5 mg and 0.5 mg per kg of body weight, respectively) and intranasally inoculated with 10^6 p.f.u. (500 µl) of S-OIVs or KUTK-4. On days 3 and 6 after infection, 3 ferrets per group were killed for virological and pathological examinations. The virus titres in nasal washes and various organs were determined by plaque assays in MDCK cells.

Experimental Infection of Miniature Pigs

Two-month-old female specific-pathogen-free miniature pigs (Nippon Institute for Biological Science), which were serologically negative by AniGen AIV antibody ELISA for currently circulating influenza viruses, were used in this study. Baseline body temperatures were measured once before infection. Four pigs per group were intranasally inoculated with $10^{6.2}$ p.f.u. (1 ml) of viruses. Nasal swabs were collected daily. On day 3 after infection, two pigs per group were killed and their tissues collected for examination. On day 14 after infection, the remaining two pigs per group were killed for virological and pathological examinations. Virus titres in various organs and swabs were determined by plaque assays in MDCK cells. The miniature pigs used in this study were housed in self-contained isolator units (Tokiwa Kagaku) at a BSL3 facility and experiments were conducted in accordance with guidelines established by the Animal Experiment Committee of the Graduate School of Veterinary Medicine, Hokkaido University, Japan.

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Pathological Examination

Excised tissues of the nasal turbinates, trachea and/ or lungs of killed mice, macaques, ferrets and pigs were preserved in 10% phosphate-buffered formalin. Tissues were then processed for paraffin embedding and cut into 5-μm-thick sections. One section from each tissue sample was stained using a standard haematoxylin-and-eosin procedure, whereas another one was processed for immunohistological staining with an anti-influenza virus rabbit antibody (R309; prepared in our laboratory) that reacts comparably with CA04 and KUTK-4. Specific antigen–antibody reactions were visualized by 3,3′-diaminobenzidine tetrahydrochloride staining using a Dako EnVision system (Dako Co. Ltd).

Ferret Transmission Study

For transmission studies in ferrets, animals were housed in adjacent transmission cages that prevent direct and indirect contact between animals but allow spread of influenza virus through the air. Three or two 5-to-8-month-old ferrets were intranasally inoculated with 10^6 p.f.u. (500 μl) of CA04, KUTK-4, A/Victoria/3/75 (H3N2) or A/duck/Alberta/35/76 (H1N1) (inoculated ferrets). One day after infection, three or two naive ferrets were each placed in a cage adjacent to an inoculated ferret (contact ferrets). All ferrets were monitored daily for changes in body temperature and weight, and the presence of clinical signs. To assess viral replication in the upper respiratory tract, viral titres were determined in nasal washes collected from virus-inoculated and contact ferrets on day 1 after inoculation or co-housing, respectively, and then every other day (up to 9 days).

Cytokine and Chemokine Measurement

For cytokine and chemokine measurement, homogenates of mouse lungs were processed with the Bio-Plex Mouse Cytokine 23-Plex and 9-Plex panels (Bio-Rad Laboratories), whereas macaque lung homogenates were measured with the MILLIPLEX MAP Non-human Primate Cytokine/Chemokine Panel–Premixed 23-Plex (Millipore). Array analysis was performed by Bio-Plex Protein Array system (Bio-Rad Laboratories).

Antiviral Sensitivity of Viruses in Mice

To test the antiviral sensitivity of viruses in mice, animals were infected as described in the Methods Summary section and 1 h later administered the following antiviral compounds: (1) oseltamivir phosphate: 8 or 80 mg per kg per 400 μl (divided into two oral administrations per day) for 5 days; (2) zanamivir: 0.8 or 8 mg per kg per 50 μl in one daily intranasal administration for 5 days; (3) CS-8958: 0.7 mg per kg per 50 μl in one intranasal administration; (4) T-705:

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60 or 300 mg per kg per 400 µl (divided into two oral administrations per day) for 5 days; (5) or distilled water orally (200 µl) and PBS intranasally (50 µl). Three mice per group were killed on days 3 or 6 after infection and the virus titres in lungs were determined by plaque assays in MDCK cells.

Sensitivity to Antiviral Compounds in Tissue Culture

MDCK cells overexpressing the β-galactoside α2,6-sialyltransferase I gene (or, for studies with T-705, regular MDCK cells) were infected with CA04, KUTK-4, or A/Kawasaki/UTK-23/08 (H1N1) at a multiplicity of infection of 0.001. After incubation for 1 h at 37°C, growth medium containing various concentrations of oseltamivir carboxylate (the active form of oseltamivir), zanamivir, R-125489 (the active form of CS-8958), or T-705 was added to the cells. Twenty-four hours later, the culture supernatants were harvested and the 50% tissue-culture infectious dose ($TCID_{50}$) in MDCK cells determined. On the basis of the $TCID_{50}$ value, the 90% inhibitory concentration (IC_{90}) was calculated.

Neuraminidase Inhibition Assay

To assess the sensitivity of viruses to neuraminidase inhibitors (that is, oseltamivir, zanamivir and CS-8958), neuraminidase inhibition assays were performed as described previously (Kiso et al., 2004). Briefly, diluted viruses were mixed with various concentrations of oseltamivir carboxylate, zanamivir, or R-125489 in 2-(*N*-morpholino) ethanesulphonic acid containing calcium chloride, and incubated for 30 min at 37°C. Then, we added methylumbelliferyl-*N*-acetyl-neuraminic acid (Sigma) as a fluorescent substrate to this mixture. After incubation for 1 h at 37°C, sodium hydroxide in 80% ethanol was added to the mixture to stop the reaction. The fluorescence of the solution was measured at an excitation wavelength of 360 nm and an emission wavelength of 465 nm and the 50% inhibitory concentration (IC_{50}) was calculated.

Neutralization Assay with Human Sera

Human sera were collected in 1999 or 2009 from donor group 1 (age range: 50–112 years as of 2009, mean = 92.7 ± 15.0 years) or 2 (age range: 20–68 years as of 2009, mean = 48.2 ± 23.7 years), respectively. These sera were treated with receptor destroying enzyme (DENKA SEIKEN CO.) to remove inhibitors of influenza virus replication. One hundred $TCID_{50}$ (50% tissue culture infectious dose) of CA04 and KUTK-4 were pre-incubated with twofold serial dilutions of treated sera, incubated for 60 min on MDCK cells, which were then observed for cytopathic effects to determine the neutralizing activity of the test sera. Our research protocol was approved by the Research Ethics Review Committee of the Institute of Medical Science, the University of

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Tokyo (approval numbers: 21-6-0428 for donor group 1; 21-7-0529 for donor group 2).

Immunofluorescence Microscopy

MDCK cells were infected with CA04, KUTK-4, or WSN and fixed with 4% paraformaldehyde 16–24 h later. Infected cells were incubated with the following primary antibodies: mouse anti-HA (7B1b), anti-HA (IVC102), or mouse anti-HA (WS3-54) antibody against CA04, KUTK-4 or WSN, respectively. Cells were then incubated with Alexa Fluor 488 goat anti-mouse immunoglobulin G (Invitrogen), and examined with a confocal laser-scanning microscope (LSM510META; Carl Zeiss).

Electron Microscopy

MDCKcells were infected with CA04, KUTK-4 orWSNat a multiplicity of infection of 10. At 16–24 h after infection, cells were processed for ultrathin section electron microscopy and scanning electron microscopy as described previously (Noda et al., 2006; Neumann et al., 2005).

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Author Contributions

Y. I., K. S., M. K., T. W., Y. S., M. H., Y. M., D. T., Y. S.-T., T. N., M. Imai, S. W., K. I.-H., T. H., N. S., H. K., K. O. and Y. K. designed the experiments;

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Y. I., K. S., M. K., T. W., Y. S., M. H., D. T., Y. S.-T., T. N., S. S., M. Imai, Y. H., S. W., C. L., S. Y., K. F., S. M., H. Imai, S. K., M. Ito, R. T., K. I.-H., M. S., T. H., Kei Takahashi, A. M., H. Ishigaki, M. Nakayama, M. Okamatsu, Kazuo Takahashi, D. W., P. A. S., R. S., H. S., Y. F., M. Yamashita, K. M., K. N., M. Nakamura, R. B.-S., J. G., H. M. and M. Yamazaki performed the experiments; Y. I., K. S., M. K., T. W., Y. S., M. H., Y. M., Y. S.-T., T. N., M. Imai, S. W., C. L., S. Y., K. I.-H., T. H., H. G., M. S., M. Ozawa, G. N., H. K., K. O. and Y. K. analysed data; Y. I., K. S., M. K., T. W., Y. S., M. H., Y. M., Y. S.-T., T. N., M. Imai, K. I.-H., M. S., M. Ozawa, G. N., K. O. and Y. K. wrote the manuscript. Y. I., K. S., M. K., T. W., Y. S., M. H. and Y. M. contributed equally to this work.

Author Information

Reprints and permissions information is available at www.nature.com/reprints. The authors declare competing financial interests: details accompany the full-text HTML version of the paper at www.nature.com/nature. Correspondence and requests for materials should be addressed to Y. K. (kawaokay@svm.vetmed.wisc.edu).

Supplementary Information is linked to the online version of the paper at www.nature.com/nature and also following this paper.

References

Baskin, C. R. *et al.* Early and sustained innate immune response defines pathology and death in nonhuman primates infected by highly pathogenic influenza virus. *Proc. Natl Acad. Sci. USA* 106, 3455–3460 (2009).

Furuta, Y. *et al. In vitro* and *in vivo* activities of anti-influenza virus compound T-705. *Antimicrob. Agents Chemother.* 46, 977–981 (2002).

Hamada, H. *et al.* Tc17, a unique subset of CD8 T cells that can protect against lethal influenza challenge. *J. Immunol.* 182, 3469–3481 (2009).

Hatakeyama, S. *et al.* Enhanced expression of an α2,6-linked sialic acid on MDCK cells improves isolation of human influenza viruses and evaluation of their sensitivity to a neuraminidase inhibitor. *J. Clin. Microbiol.* 43, 4139–4146 (2005).

Hatta, M., Gao, P., Halfmann, P. & Kawaoka, Y. Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. *Science* 293, 1840–1842 (2001).

Hayden, F. G. *et al.* Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. *N. Engl. J. Med.* 343, 1282–1289 (2000).

Iwakura, Y., Nakae, S., Saijo, S. & Ishigame, H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. *Immunol. Rev.* 226, 57–79 (2008).

Jakiela, B., Brockman-Schneider, R., Amineva, S., Lee, W. M. & Gern, J. E. Basal cells of differentiated bronchial epithelium are more susceptible to rhinovirus infection. *Am. J. Respir. Cell Mol. Biol.* 38, 517–523 (2008).

Kawaoka, Y. & Webster, R. G. Sequence requirements for cleavage activation of influenza virus hemagglutinin expressed in mammalian cells. *Proc. Natl Acad. Sci. USA* 85, 324–328 (1988).

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Kiso, M. *et al.* Resistant influenza A viruses in children treated with oseltamivir: Descriptive study. *Lancet* 364, 759–765 (2004).

Kobasa, D. *et al.* Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature* 445, 319–323 (2007).

Maines, T. R. *et al.* Lack of transmission of H5N1avian-human reassortant influenza viruses in a ferret model. *Proc. Natl Acad. Sci. USA* 103, 12121–12126 (2006).

Moscona, A. Global transmission of oseltamivir-resistant influenza. *N. Engl. J. Med.* 360, 953–956 (2009).

Nakajima, K., Desselberger, U. & Palese, P. Recent human influenza A (H1N1) viruses are closely related genetically to strains isolated in 1950. *Nature* 274, 334–339 (1978).

Neumann, G. *et al.* Ebola virus VP40 late domains are not essential for viral replication in cell culture. *J. Virol.* 79, 10300–10307 (2005).

Noda, T. *et al.* Architecture of ribonucleoprotein complexes in influenza A virus particles. *Nature* 439, 490–492 (2006).

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N. Engl. J. Med.* 360, 2605–2615 (2009).

Peiris, J. S. *et al.* Re-emergence of fatal human influenza A subtype H5N1 disease. *Lancet* 363, 617–619 (2004).

Rimmelzwaan, G. F. *et al.* Pathogenesis of influenza A (H5N1) virus infection in a Primate model. *J. Virol.* 75, 6687–6691 (2001).

Wright, P. F., Neumann, G. & Kawaoka, Y. *Fields Virology* (eds Knipe, D. M. et al.) 1691–1740 (Wolters Kluwer/Lippincott Williams & Wilkins, 2007).

Yamashita, M. *et al.* CS-8958, a prodrug of the new neuraminidase inhibitor R-125489, shows long-acting anti-influenza virus activity. *Antimicrob. Agents Chemother.* 53, 186–192 (2009).

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Supplementary Information

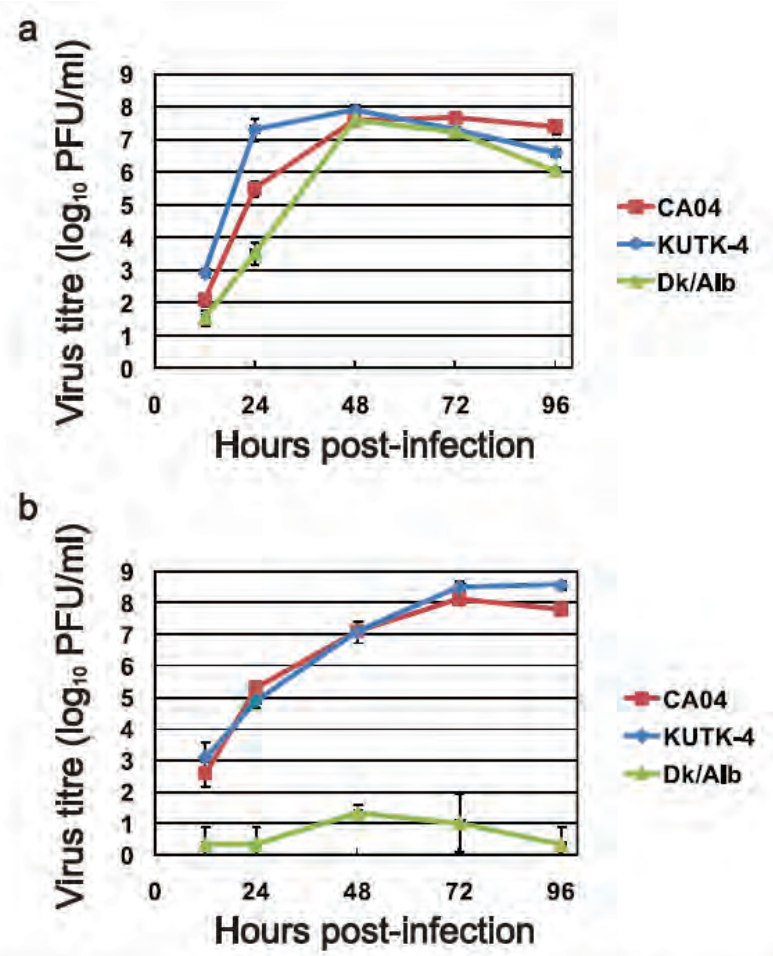

FIGURE A5-4 Growth properties of viruses in cells. MDCK cells were infected with CA04 (red), KUTK-4 (blue), or A/duck/Alberta/35/76 (H1N1; Dk/Alb, green) at an MOI of 0.001 (a). Differentiated human airway epithelial cells were infected with CA04 (red), KUTK-4 (blue), or A/duck/Alberta/35/76 (H1N1; Dk/Alb, green) at an MOI of 0.001 (b). The supernatants of infected cells were harvested at the indicated times and virus titres were determined by plaque assays in MDCK cells. Error bars indicate standard deviations from three independent experiments.

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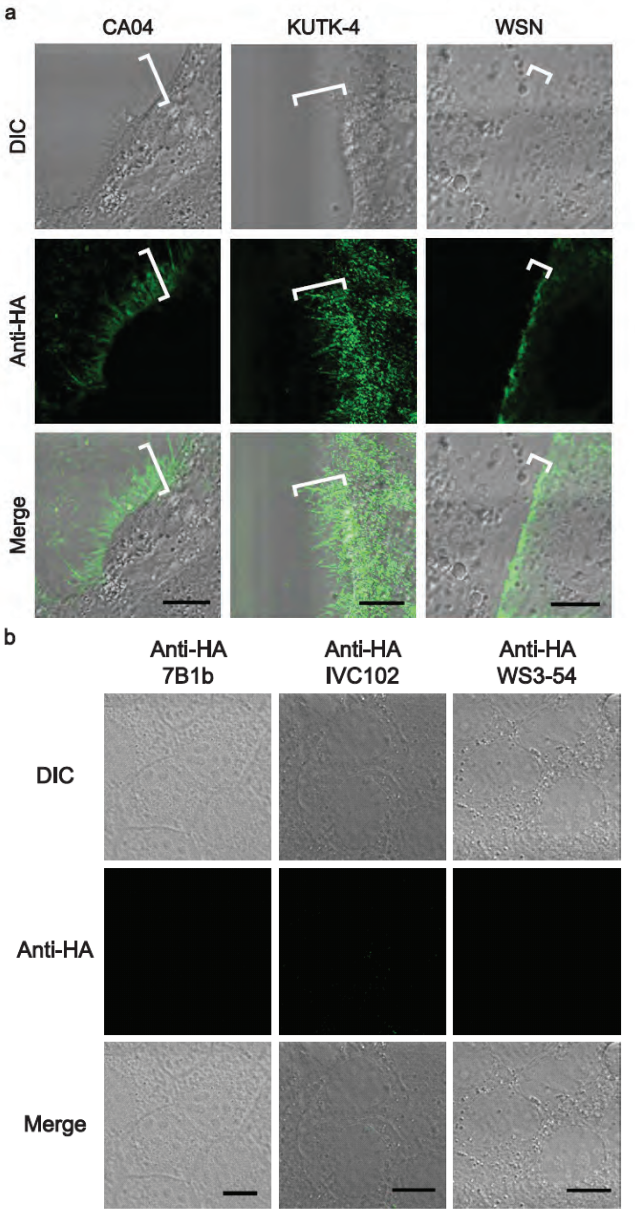

FIGURE A5-5 a-d Morphology of budding CA04 virions. MDCK cells infected with A/California/04/09 (H1N1) (CA04, left), A/Kawasaki/UTK-4/09 (H1N1) (KUTK-4, middle), or A/WSN/33 (H1N1) (WSN, right) were examined with confocal microscopy

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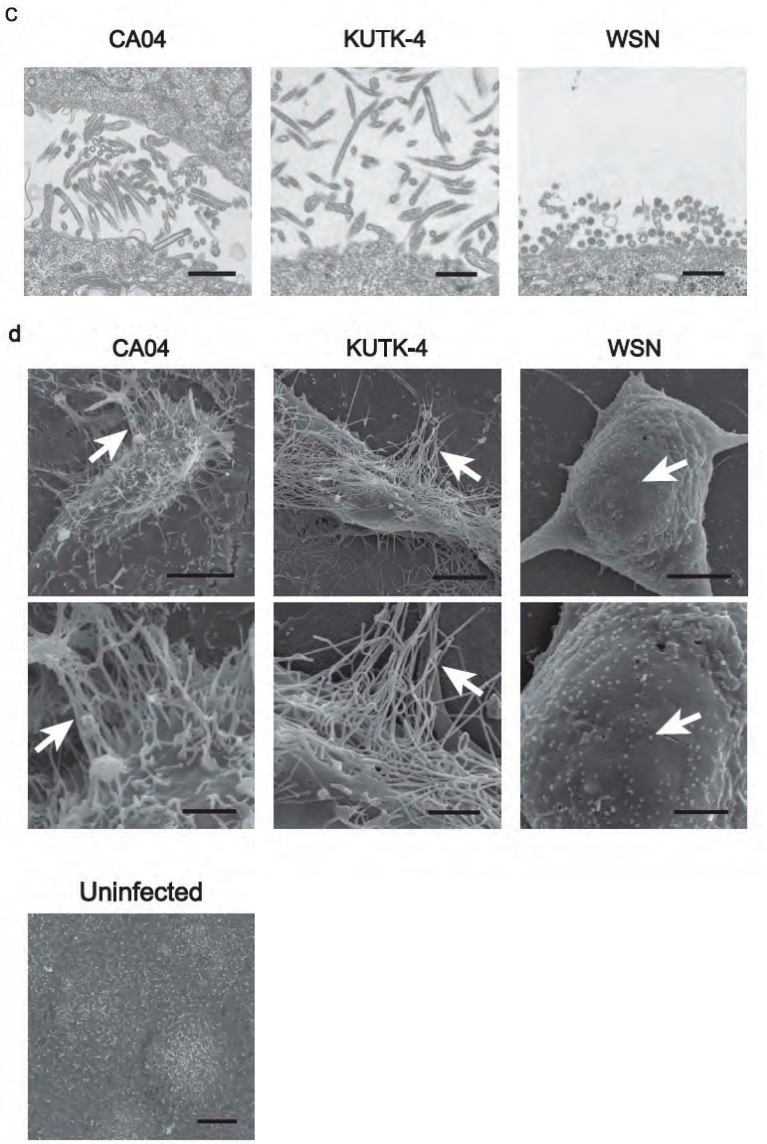

FIGURE A5-5 continued

(**a**); mock-infected cells were processed similarly (**b**). Virus-infected cells were observed by transmission electron (TEM, **c**) and scanning electron microscope (SEM, **d**) (Kawaoka and Webster, 1988). Brackets in **a** and arrows in **d** indicate budding viruses. Scale bar: **a and b**, 10 µm; **c**, 500 nm; **d**, 5 (upper panels) and 2 µm (lower panels). DIC, differential interference contrast.

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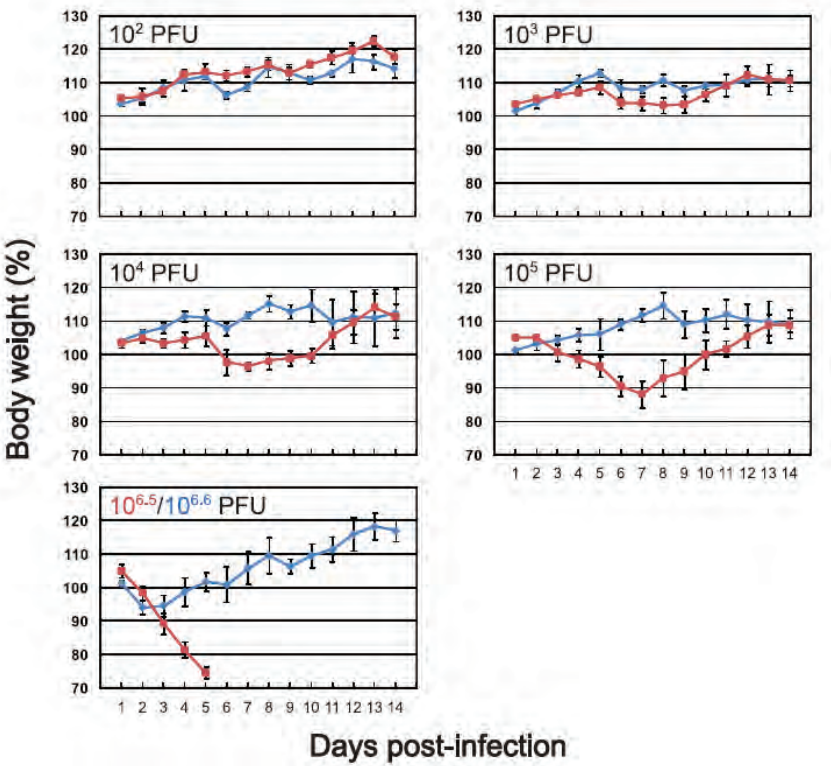

FIGURE A5-6 Body weight changes in infected mice. Three mice per group were intranaasally inoculated with 10^2, 10^3, 10^4, or 10^5 PFU (each in 50 µl) of CA04 (red) or KUTK-4 (blue), or undiluted virus ($10^{6.5}$ PFU for CA04 and $10^{6.6}$ PFU for KUTK-4). Body weights were monitored daily. Mice with body weight loss of more than 25% of pre-infection values were euthanized. The values are means ± SD from three mice.

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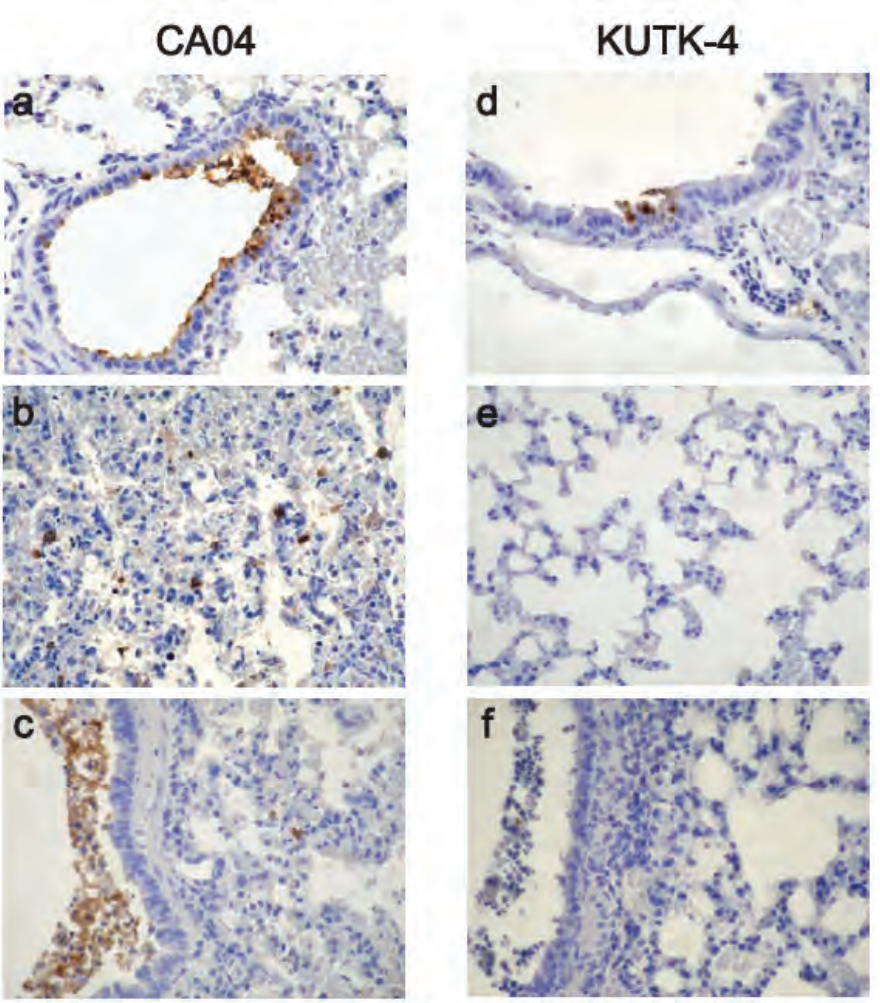

FIGURE A5-7 Pathological findings in infected mice. Representative pathological findings for the lungs of mice infected with CA04 (**a-c)**, or KUTK-4 **(d-f)**. infection with CA04 resulted in detectable viral antigen in bronchiolar epithelia and desquamated cells in the bronchial lumen on day 3 pi (**a**). Also, prominent alveolar thickening with scattered antigen-positive cells in the alveolus was observed (**b**). By day 6, epithelia were regenerative but accumulation of antigen-positive cell debris in the lumen was prominent (**c**). Upon infection with KUTK-4, a small number of viral antigen-positive cells was detected in the bronchial and bronchial epithelia on day 3 pi (**d**), but no viral antigen was detected in the alveolar area (**e**). On day 6 pi, accumulation of cell debris in the bronchiolar lumen with peribronchiolitis was observed, but viral antigens were rarely detected in these lesions (**f**).

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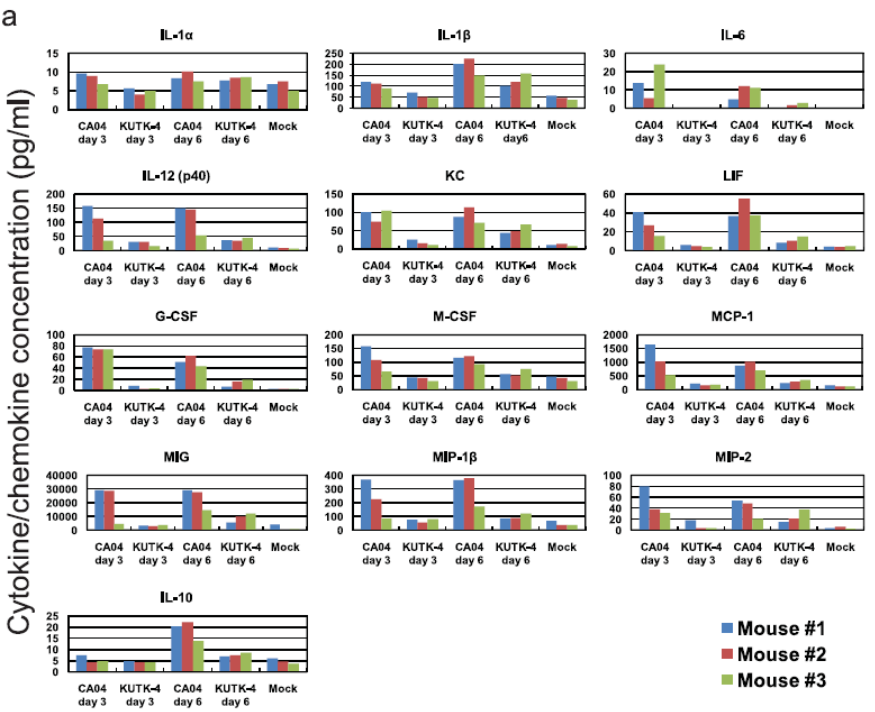

FIGURE A5-8 Pro-inflammatory cytokine/chemokine responses in the lungs of infected mice. The concentrations of various cytokines/chemokines were measured in the lungs of mice by use of a protein array analysis with the Bio-Plex Mouse Cytokine 23-Plex and 9-Plex panels (Bio-Rad laboratories). IL-12 (p70) was not detected. IL-18 data are not available due to technical problem of the manufacturer.

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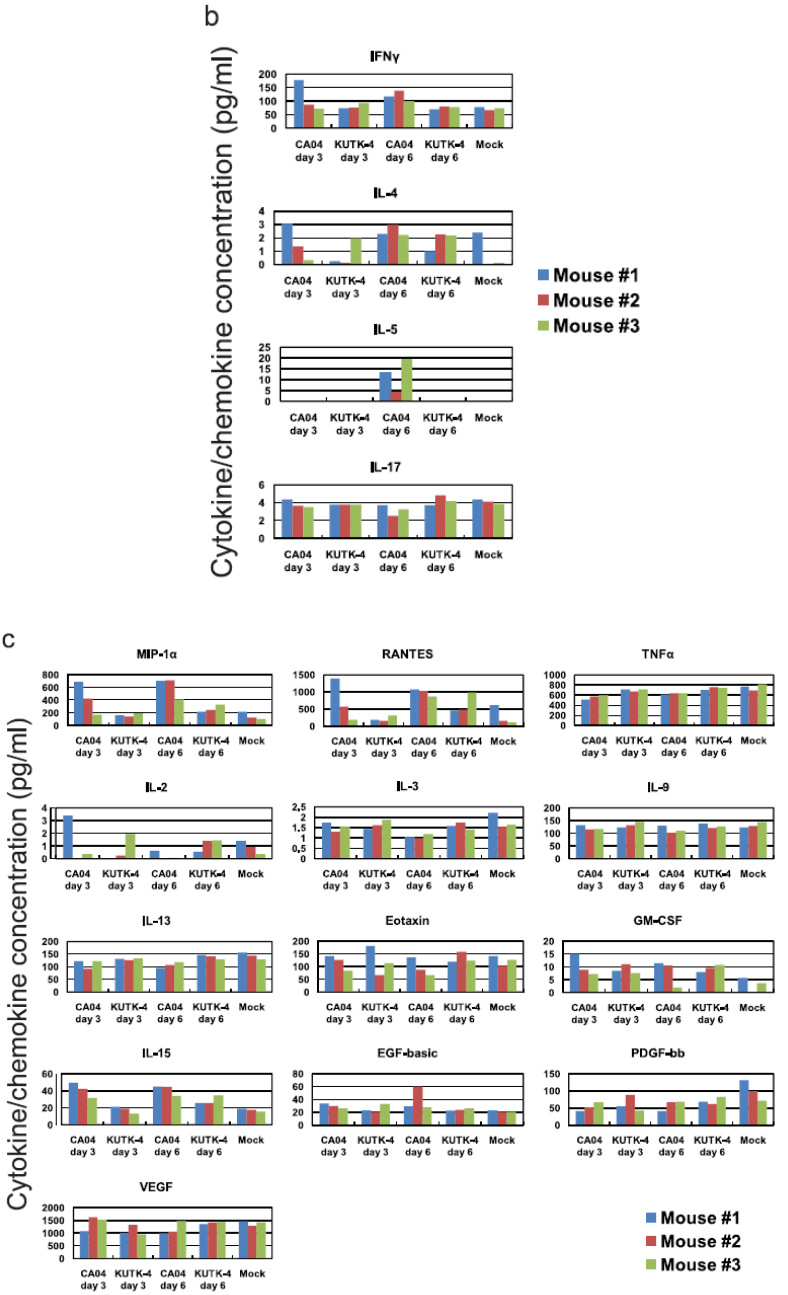

FIGURE A5-8 continued

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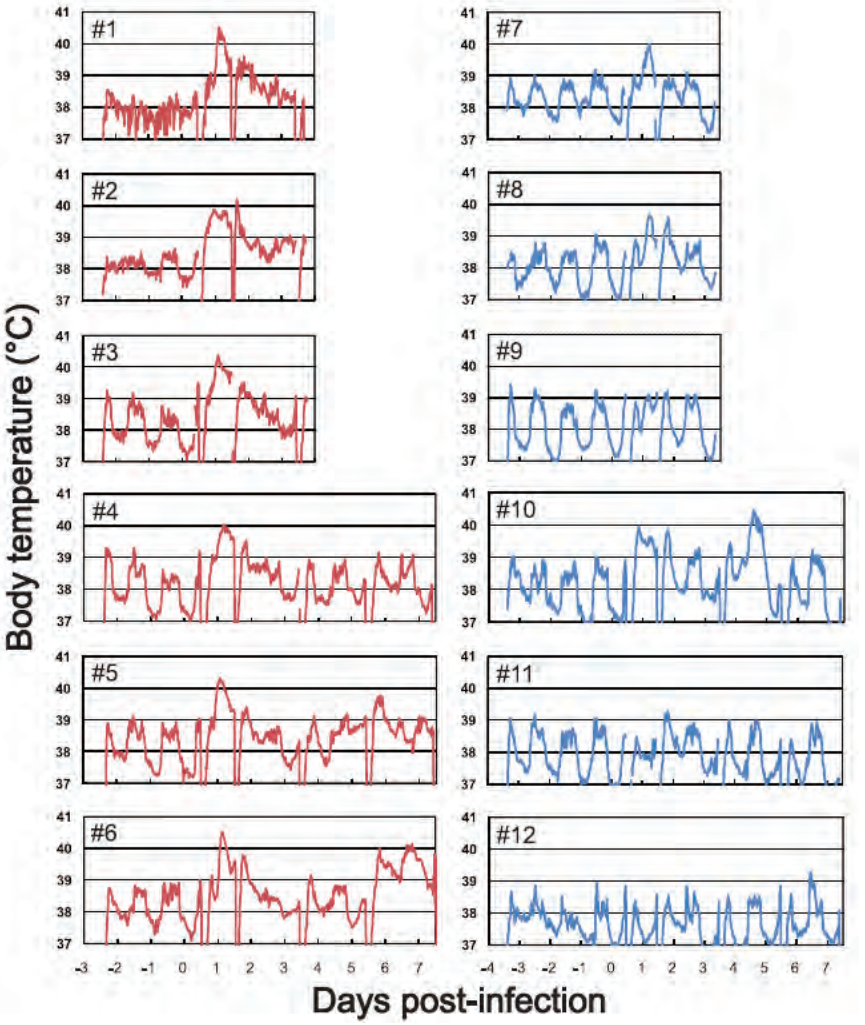

FIGURE A5-9 Body temperatures of infected cynomolgus macaques. Six macaques per group were inoculated with $10^{7.4}$ PFU (total volume: 6.7 ml) of CA04 (red #1-6) or KUTK-4 (blue, #7-12) through multiple routes (see Supplementary materials and methods). Temperatures were monitored every 15 minutes by telemetry probes implanted in the peritoneal cavities. The periodic sharp reduction in body temperatures on days 0, 1, 3, and 7 was caused by anesthesia required for sampling. Monkeys #1-3 and #7-9 were euthanized on day 3.

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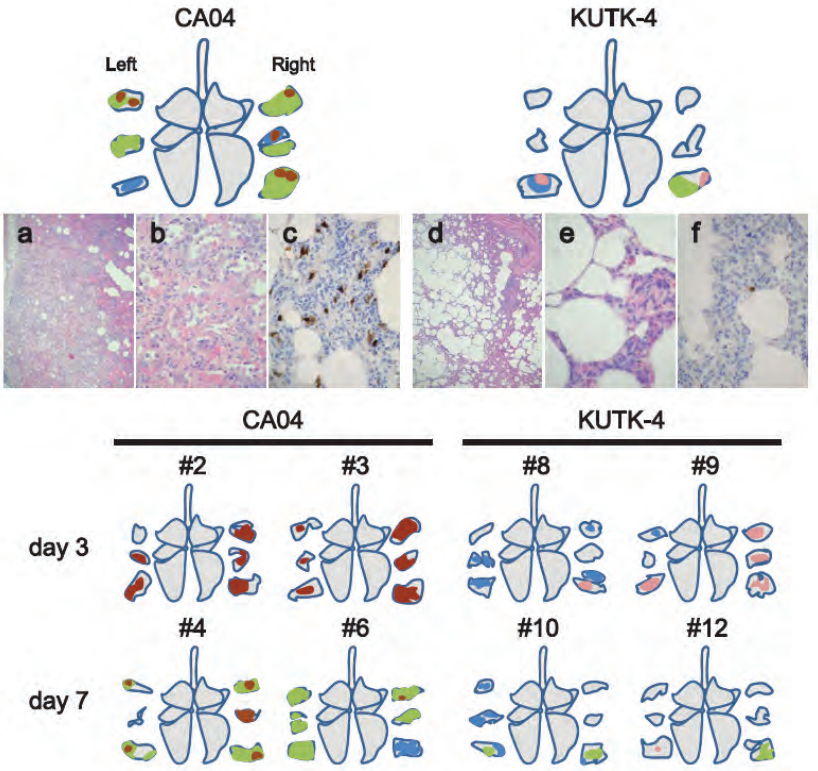

FIGURE A5-10 Pathological findings in infected cynomolgus macaques. Shown are representative pathological findings in the lungs of cynomolgus macaques on day 7 post infection with CA04 (macaque #5, **a-c**) or KUTK-4 (macaque #11, **d-f**) (upper portion). Schematic figures summarize the distribution of lesions, with or without viral antigen, in the lungs of the remaining virus-inoculated macaques. Colors: green, severe lung lesions where alveolar spaces were filled with edema fluid, inflammatory cells, or cell debris; brown, severe lung lesions containing moderate to many viral antigen-positive cells; pink, mild lung lesions containing a few viral antigen-positive cells; blue, lung lesions where severe alveolar wall thickening was prominent, but air spaces were preserved. (**a**) Alveolar spaces were not clear because of inflammatory exudate. (**b**) Large areas of affected lung contained accumulated cell debris, inflammatory infiltrates, fibrin, and edema fluid; alveolar walls were thickened by infiltration of inflammatory cells. (**c**) Viral antigen-positive cells were detected extensively in lung lesions in some areas. (**d**) In most areas, alveolar spaces were still clear, although thickening of the alveolar walls was apparent. (**e**) Most lung lesions consisted of thickening of alveolar walls by mononuclear cells. (**f**) A few antigen-positive cells were detected in lung lesions.

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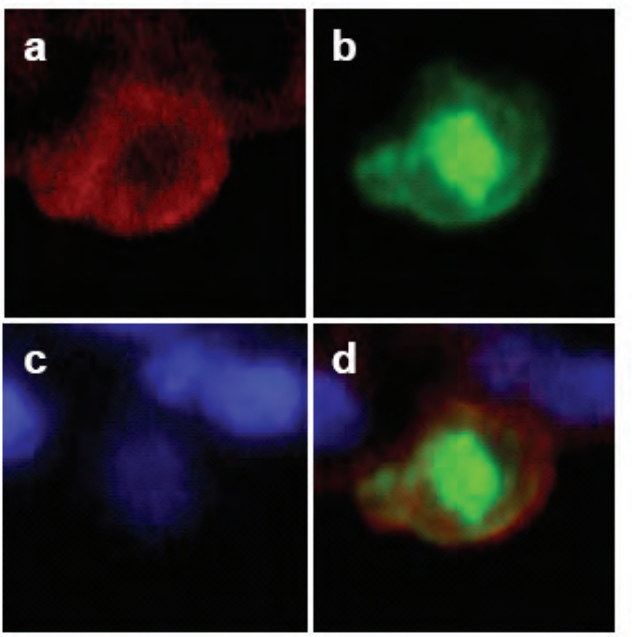

FIGURE A5-11 Detection of viral antigens in type II pneumocytes in the lungs of CA04-infected cynomolgus macaques. On day 3 post-infection, cells were stained with anti-cytokeratin (N1590, DAKO) antibody (**a**; red) and anti-influenza (H1N1) antibody (**b**; green). The nucleus was stained with DAPI (**c**). Considerable amounts of viral antigen were detected in type II pneumocytes (**d**).

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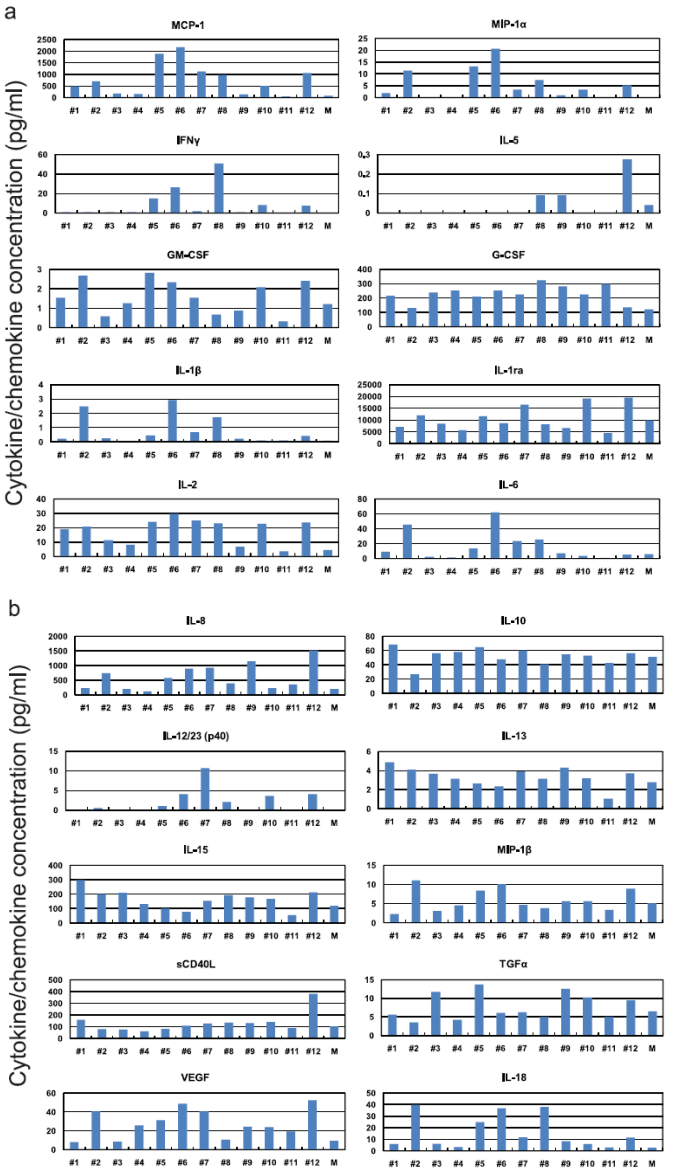

FIGURE A5-12 Pro-inflammatory cytokine/chemokine responses in the lungs of infected cynomolgus macaques. The concentrations of various cytokines/chemokines in the lungs of infected cynomolgus macaques on day 3 post-infection were measured by protein array analysis with the MILLIPLEX MAP Non-human Primate Cytokine/Chemokine Panel – Premixed 23-Plex (Millipore, Bedford, MA). We did not detect IL-4, IL-17, or TNFα in the lungs or G-CSF and IL-4 in the sera.

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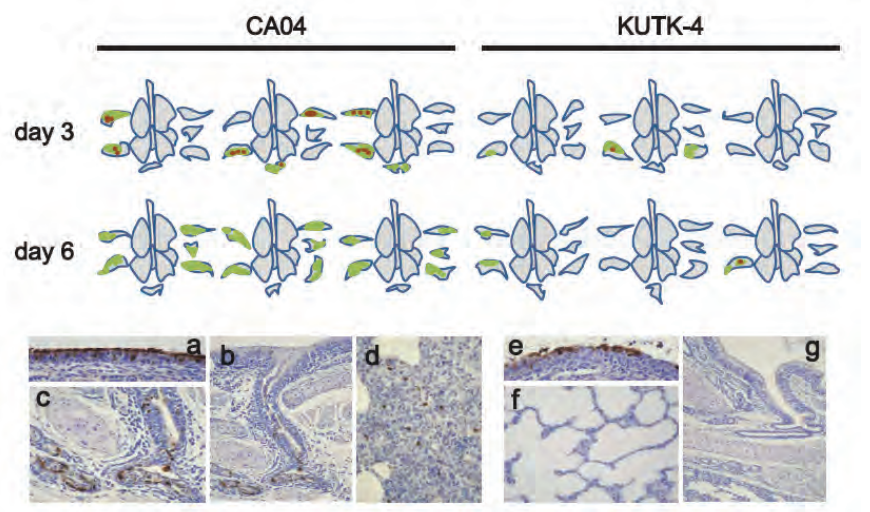

FIGURE A5-13 Pathological findings in infected ferrets. CA04-omfected ferret lungs showed severe and wide lung lesions with viral antigen on day 3 pi and without viral antigen on day 6 pi. KUTK-4-infected ferret lungs showed limited lung lesopns with viral antigen on days 3 and 6 pi. Representative pathological findings of nasal mucosa and lungs of CA04-(**a-d**), and KUTK-4-(**e-g**) infected ferrets on days 3 and 6 pi. (**a**) Extensive viral antigen present at the nasal epithelium on day 3 pi in CA04-infected ferret. (**b**) and (**c**) In the lungs, viral antigen was mainly detected in the peribroncial glands with severe peribronchitis and bronchopneumonia (**d**) Sparse viral antigen was detected within alveolar lesions. (**e**) Extensive viral antigen expression at the nasal mucosa on day 3 pi in KUTK-4-infected ferret. (**f**) Most of the lung was not affected by viral infection in KUTK-4-infected ferrets. (**g**) Most of the peribronchial gland appeared normal in KUTK-4-infected ferret lungs at day 6 pi. Colors: green, severe lung lesions where alveolar spaces were filled with edema fluid, inflammatory cells, or cell debris; brown, severe lung lesions containing moderate to many viral antigen-positive cells.

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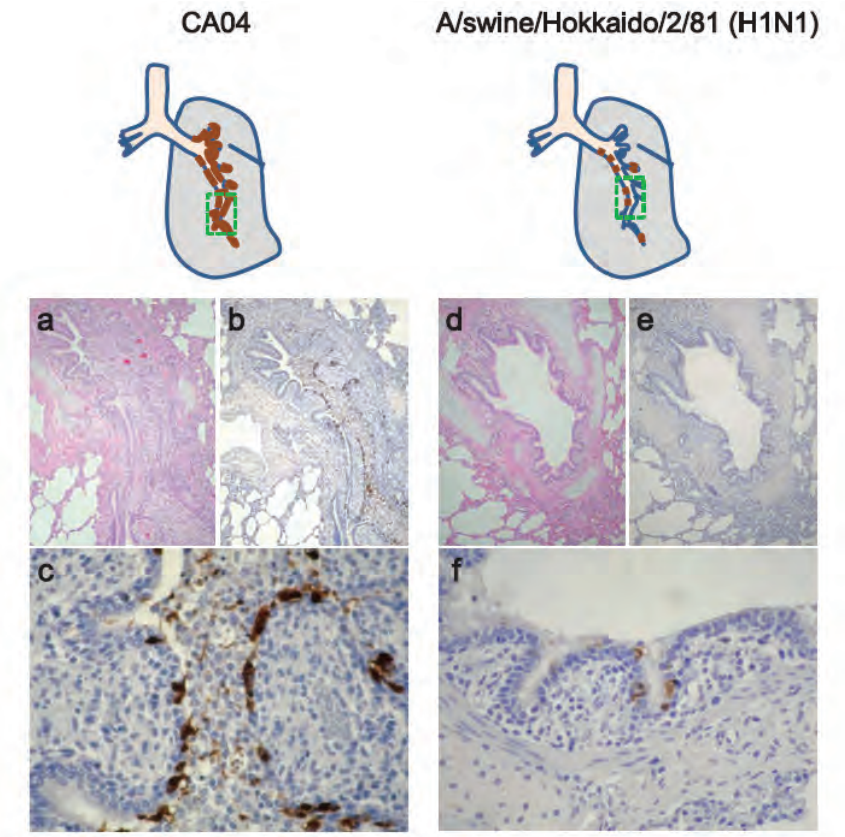

FIGURE A5-14 Pathological findings in infected miniature pigs. Shown are representative pathological findings for the lungs of miniature pigs on day 3 post infection with CA04 (miniature pig #1, **a-c**) or A/swine/Hokkaido/2/81 (H1N1) (miniature pig #5, **d-f**). The distribution of viral antigen (brown) is shown in the schematic figures. (**a**) The lumens of the bronchus and bronchioles were filled with inflammatory infiltrates. (**b**) Viral antigen was detected along bronchus and bronchiole. (**c**) Viral antigen was mainly detected in epithelial cells and desquamated cells. (**d**) The bronchial lumen remained clear with limited inflammatory reactions. (**e**) and (**f**) Few antigen-positive cells were detected at the epithelium, with minimum inflammatory reaction. The areas delineated by green boxes in the schematic diagrams correspond to the histopathological sections.

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TABLE A5-2 Virus Titres in Organs of Infected Mice[a]

		Virus titres (mean $\log_{10}$ PFU ± SD/g) in:	
Virus		Nasal turbinates	Lungs
A/California/04/09 (H1N1)	Day 3	6.6±0.2	7.8±0.03
	Day 6	5.4±0.6	6.8±0.01
A/Netherlands/603/09 (H1N1)	Day 3	6.6±0.2	6.8±0.3
	Day 6	5.5±0.2	6.2±0.2
A/Wisconsin/WSLH049/09 (H1N1)	Day 3	6.7±0.2	7.2±0.2
	Day 6	6.3±0.2	6.5±0.1
A/Wisconsin/WSLH34939/09 (H1N1)	Day 3	7.1±0.2	7.7±0.2
	Day 6	5.9±0.3	6.9±0.5
A/Osaka/164/09 (H1N1)	Day 3	6.3±0.7	7.2±0.1
	Day 6	3.8±1.3	6.5±0.4
A/Kawasaki/UTK-4/09 (H1N1)	Day 3	6.3±0.2	6.4±0.3
	Day 6	5.0±0.3	4.6±0.4

[a]BALB/c mice were intranasally infected with 10^5 PFU (50 µl) of virus. Three mice from each group were euthanized on days 3 and 6 pi for virus titration. None of the viruses tested was recovered from the spleens, kidneys, brains, colons, or livers of infected animals.

TABLE A5-3 Virus Titres in Respiratory Swabs from Infected Cynomolgus Macaques[a]

		Virus titre ($\log_{10}$ PFU/ml) of animals infected with:											
		A/California/04/09 (H1N1)					A/Kawasaki/UTK-4/09 (H1N1)						
Animal ID		#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12
Nasal swab	Day 1	5.8	1.0	1.5	4.7	4.5	2.6	3.0	2.9	1.6	3.6	2.4	3.6
	Day 3	5.2	2.1	2.5	3.7	2.6	3.3	2.8	3.2	2.4	4.1	1.5	3.3
	Day 5				4.7	4.6	3.4				1.3	3.6	2.5
	Day 7				—[b]	3.5	—				—	—	5.0
Tracheal swab	Day 1	3.4	2.3	3.6	2.3	3.5	2.0	1.3	1.3	—	2.0	2.3	2.1
	Day 3	4.3	—	2.6	2.6	2.4	2.0	1.0	1.8	—	4.0	—	—
	Day 5				3.5	2.5	3.7				5.6	—	—
	Day 7				—	2.0	—				3.4	—	2.6
Bronchial brush	Day 1	2.9	2.4	3.7	2.2	3.3	—	1.5	—	—	—	—	—
	Day 3	3.5	—	—	3.1	—	—	—	1.5	—	—	—	—
	Day 5				4.4	2.4	1.8				4.4	—	1.3
	Day 7				—	—	—				1.5	—	4.4

[a]Cynomolgus macaques were inoculated with $10^{7.4}$ PFU of virus (6.7 ml) through multiple routes. Nasal and tracheal swabs and bronchial brush samples were collected every other day for virus titration.

[b]—. virus not detected (detection limit: 1.0 $\log_{10}$ PFU/ml).

Blank: not applicable, animals euthanized on day 3 pi.

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TABLE A5-4 Virus Titres in Respiratory Organs of Infected Ferrets[a]

Virus		Virus titres (mean $\log_{10}$ PFU ± SD/g) in: Nasal turbinates	Trachea	Lungs
A/California/04/09 (H1N1)	Day 3	6.7±0.7	5.9±0.4	3.53, 4.12
	Day 6	2.40	3.1±0.1	2.95
A/Netherlands/603/09 (H1N1)	Day 3	7.3±0.6	6.0±1.7	5.15
	Day 6	3.26, 4.77	4.36, 5.14	—[b]
A/Wisconsin/WSLH049/09 (H1N1)	Day 3	7.8±0.6	6.0±0.9	6.49, 3.23
	Day 6	4.3±1.1	4.57, 3.40	5.48
A/Wisconsin/WSLH34939/09 (H1N1)	Day 3	8.3±0.1	4.6±0.3	4.5±1.8
	Day 6	4.5±1.0	3.8±1.4	3.6±1.1
A/Osaka/164/09 (H1N1)	Day 3	6.9±1.0	6.4±1.0	6.8±0.8
	Day 6	—	—	—
A/Kawasaki/UTK-4/09 (H1N1)	Day 3	6.5±0.5	2.45, 3.81	—
	Day 6	—	3.18	—

[a]Ferrets were intranasally infected with 10^6 PFU (500 µl) of virus. Three ferrets from each group were euthanized on days 3 and 6 pi for virus titration. When virus was recovered from all three animals, average titres are presented. When virus was not recovered from all three ferrets, individual titres were recorded. None of the viruses tested was recovered from the spleens, kidneys, brains, intestines, or livers of infected animals.

[b]—. virus not detected (detection limit: 2.3 $\log_{10}$ PFU/g).

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TABLE A5-5 Virus Titres in Nasal Swabs of Inoculated and Contact Ferrets[a]

Virus			Virus titres (mean $\log_{10}$ PFU/ml) in nasal swabs				
			Day 1	Day 3	Day 5	Day 7	Day 9
A/California/04/09 (H1N1)	Pair 1	*i*	7.1	4.0	—[b]	—	—
		c	—	6.8	4.3	—	—
	Pair 2	*i*	7.1	5.3	3.4	—	—
		c	—	6.2	4.0	—	—
	Pair 3	*i*	5.9	5.3	3.9	—	—
		c	—	6.4	5.9	2.1	—
A/Kawasaki/UTK-4/09 (H1N1)	Pair 4	*i*	6.6	5.3	4.3	—	—
		c	—	5.0	4.5	2.5	—
	Pair 5	*i*	6.1	5.9	1.3	—	—
		c	—	—	—	—	—
A/Victoria/03/75 (H3N2)	Pair 6	*i*	6.3	3.9	2.0	—	—
		c	—	—	6.0	3.7	2.5
	Pair 7	*i*	5.8	2.3	—	—	—
		c	—	—	—	—	2.3
A/duck/Alberta/35/76 (H1N1)	Pair 8	*i*	—	2.8	2.6	—	—
		c	—	—	—	—	—
	Pair 9	*i*	—	2.3	—	—	—
		c	—	—	—	—	—
	Pair 10	*i*	—	4.9	3.7	4.0	—
		c	—	—	—	—	—

[a]For pairs of ferrets, one animal was intranasally inoculated with 10^6 PFU of virus (500 µl) (inoculated ferret, *i*) and one day later, a naïve ferret was placed in an adjacent cage (contact ferret, *c*). Nasal swabs were collected from inoculated and contact ferrets every other day for virus titration.

[b]—. virus not detected (detection limit: 1.3 $\log_{10}$ PFU/ml).

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TABLE A5-6 Virus Titres in Organs of Infected Miniature Pigs[a]

	Virus titres (log_{10} PFU/g) of infected animals with:			
	A/California/04/09 (H1N1)		A/swine/Hokkaido/2/81 (H1N1)	
Animal ID	#1	#2	#5	#6
Nasal mucosa	6.7	5.0	5.1	4.8
Oro/nasopharynx	3.1	3.3	6.8	5.0
Tonsil	3.2	—[b]	4.5	4.4
Trachea	6.3	5.5	5.8	5.3
Bronchus (right)	5.6	6.1	5.9	6.5
Bronchus (left)	6.7	6.5	5.4	6.3
Lung (upper right)	7.8	6.6	6.1	4.5
Lung (middle right)	7.5	6.7	6.1	5.5
Lung (lower right)	6.4	6.8	5.3	4.5
Lung (upper left)	6.8	6.4	6.8	5.1
Lung (middle left)	8.0	7.6	4.7	5.5
Lung (lower left)	6.2	7.4	5.5	4.7
Ileum	—	—	3.5	—
Jejunum	—	—	2.8	—

[a]Specific-pathogen free miniature pigs were intranasally infected with $10^{6.2}$ PFU (1 ml) of virus. Two animals from each group were euthanized on day 3 pi for virus titration. No virus was recovered from heart, spleen, kidneys, liver, duodenum, rectum, bladder, cerebrum, cerebellum, or brain stem.

[b]—. virus not detected (detection limit: 2.0 log_{10} PFU/g).

TABLE A5-7 Virus Titres in Nasal Swabs from Infected Miniature Pigs[a]

		Virus titers (log_{10} PFU/ml) of infected animals with:							
		A/California/04/09 (H1N1)				A/swine/Hokkaido/2/81 (H1N1)			
Animal ID		#1	#2	#3	#4	#5	#6	#7	#8
	Day 1	5.6	6.5	6.4	6.1	6.3	5.3	3.6	4.1
	Day 2	6.5	6.5	7.4	6.7	5.5	5.5	5.1	5.6
	Day 3	5.7	5.3	7.2	5.3	5.0	4.4	4.7	5.5
	Day 4			3.7	3.6			4.9	4.6
	Day 5			4.5	5.4			2.7	3.2
	Day 6			4.3	5.3			2.8	3.2
	Day 7			3.3	3.4			1.3	1.6
	Day 8			—[b]	—			—	—
	Day 9			—	—			—	—

[a]Miniature pigs were intranasally infected with $10^{6.2}$ PFU of virus (1 ml) of virus.

[b]—. virus not detected (detection limit: 1.0 log_{10} PFU/ml).

Blank: not applicable, animals euthanized on day 3 pi.

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TABLE A5-8 Virus Susceptibility to Antiviral Compounds in Cell Culture

	IC_{90}		
	A/California/04/09 (H1N1)	A/Kawasaki/UTK-4/09 (H1N1)	A/Kawasaki/UTK-23/08 (H1N1)
Oseltamivir carboxylate[a]	10.56[c]	2971.30	5.58
Zanamivir	17.67	42.33	21.93
R-125489[b]	4.24	11.70	10.17
T-705	0.16	0.23	0.13

[a]Oseltamivir carboxylate is the active form of oseltamivir.
[b]R-125489 is the active form of CS-8958.
[c]IC_{90} value: mean μg/ml or nM of triplicate reactions for T-705 and other compounds tested, respectively.

TABLE A5-9 Virus Sensitivity in Neuraminidase Assays

	IC_{50}			
	A/California/04/09 (H1N1)	A/Osaka/164/09 (H1N1)	A/Kawasaki/UTK-4/09 (H1N1)	A/Kawasaki/UTK-23/08 (H1N1)
Oseltamivir carboxylate[a]	0.96[c]	1.6	1313	1.88
Zanamivir	0.32	0.43	0.79	0.36
R-125489[b]	0.41	0.44	0.34	0.20

[a]Oseltamivir carboxylate is the active form of oseltamivir.
[b]R-125489 is the active form of CS-8958.
[c]IC_{50} value: mean nM of duplicate reactions.

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A6

ESTIMATION OF THE REPRODUCTIVE NUMBER AND THE SERIAL INTERVAL IN EARLY PHASE OF THE 2009 INFLUENZA A/H1N1 PANDEMIC IN THE USA[42]

Laura Forsberg White,[43] Jacco Wallinga,[44,45] Lyn Finelli,[46] Carrie Reed,[46] Steven Riley,[47] Marc Lipsitch,[48] Marcello Pagano[49]

Introduction

In April 2009, the general public became aware of an outbreak of a novel influenza strain, now termed novel influenza A/H1N1 that had been affecting Mexico. Due to high travel volumes throughout the world, particularly the United States, the disease has been spreading rapidly worldwide, leading the WHO to raise the pandemic alert to a level 5 in May 2009, indicating that a pandemic is likely imminent and signaling world health organizations and governments to finalize planning and preparation for responding to such an event. On June 11, WHO declared a pandemic had begun.

While most cases have been relatively mild outside of Mexico (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009), a number of uncertainties remain about the severity of this virus on a per-case basis; moreover, higher-than normal attack rates expected from an antigenically novel virus may lead to substantial population-level severe morbidity and mortality even if the case-fatality ratio remains low (Lipsitch *et al*., 2009). Regardless of the severity now, legitimate concerns exist over the potential impact that this viral strain might have in the coming influenza season. Indeed during the high mortality pandemic of 1918–1919, much of the northern hemisphere saw a mild outbreak in the late spring of 1918 that preceded the much more severe outbreaks of the fall and winter of 1918–1919 (Andreasen *et al*., 2008; Barry *et al*., 2008). For

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[42]Reprinted from *Influenza and Other Respiratory Viruses* 3(6):267-276 (2009).

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these reasons, continuing scientific and public health attention to the spread of this novel virus is essential.

As officials prepare and plan for the growth of this pandemic, estimates of epidemiological parameters are needed to mount an effective response. Decisions about the degree of mitigation that is warranted – and public compliance with efforts to reduce transmission – depend in part on estimates of individual and population risk, as measured in part by the frequency of severe and fatal illness. Knowledge of the serial interval and basic reproductive number are crucial for understanding the dynamics of any infectious disease, and these should be reevaluated as the pandemic progresses in space and time (Fraser *et al*. 2004). The basic reproductive number R_0 is defined as the average number of secondary cases per typical case in an otherwise susceptible population, and is a special case of the more general reproductive number, which may be measured even after some of the population is immune. R_0 quantifies the transmissibility of an infection: the higher the R_0, the more difficult it is to control. The distribution of the serial interval, the time between infections in consecutive generations, determines, along with R_0, the rate at which an epidemic grows. Estimates of these quantities characterize the rates of epidemic growth and inform recommendations for control measures; ongoing estimates of the reproductive number as control measures are introduced can be used to estimate the impact of control measures. Previous modeling work has stated that a reproductive number exceeding two for influenza would make it unlikely that even stringent control measures could halt the growth of an influenza pandemic (Hallroan *et al*., 2008).

Prior work has placed estimates for the serial interval of seasonal influenza at 3.6 days (Cowling *et al*., 2009) with a SD of 1.6 days. Other work has estimated that the serial interval is between 2.8 and 3.3 days (White and Pagano, 2008a). Analysis of linked cases of novel A/H1N1 in Spain yields an estimate of a mean of 3.5 days with a range from 1 to 6 days (Surveillance Group for New Influenza A (H1N1) Virus Investigation and Control in Spain, 2009). Fraser *et al*. (2009) estimate the mean of the serial interval to be 1.91 days for the completed outbreak of respiratory infection in La Gloria, Mexico, which may have resulted from the novel H1N1 strain. There have been many attempts made to estimate the reproductive number. Fraser *et al.* (2009) estimate the reproductive number to be in the range of 1.4–1.6 for La Gloria but acknowledge the preliminary nature of their estimate. For the fall wave of the 1918 pandemic, others have estimated the basic reproductive number to be approximately 1.8 for UK cities (Ferguson *et al*., 2005), 2.0 for U.S. cities (Mills *et al*., 2004), 1.34–3.21 (depending on the setting) (White and Pagano, 2008a), and 1.2–1.5 (Andreasen *et al*., 2008). Additionally Andreasen *et al*. (2008) estimate, in contrast, that the reproductive number in the 1918 summer wave was between 2.0 and 5.4.

In what follows we employ a likelihood-based method previously introduced (White and Pagano, 2008a,b) to simultaneously estimate the basic reproductive number and the serial interval. We make use of data from the Centers for Disease

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Control (CDC) providing information on all early reported cases in the United States, including the date of symptom onset and report. Further, we illustrate the impact of the reporting fraction and temporal trends in the reporting fraction on estimates of these parameters.

Methods

Data

We use data from the Centers for Disease Control and Prevention (CDC) line list of reported cases of influenza A/H1N1 in the United States beginning on March 28, 2009. Information about 1368 confirmed and probable cases with a date of report on or before May 8, 2009 was used. Of the 1368 reported cases, 750 had a date of onset recorded. We include probable cases in the analysis as >90% of probable cases subsequently tested have been confirmed. After May 13 collection of individual-based data became much less frequent and eventually halted in favor of aggregate counts of new cases. The degree of case ascertainment early throughout this time period is unknown.

Statistical Analysis

We make use of the likelihood-based method of White and Pagano (White and Pagano, 2008a,b). This method is well suited for estimation of the basic reproductive number, R_0, and the serial interval in real time with observed aggregated daily counts of new cases, denoted by $\mathbf{N} = \{N_0, N_1, \ldots, N_T\}$, where T is the last day of observation and N_0 are the initial number of seed cases that begin the outbreak. The N_i are assumed to be composed of a mixture of cases that were generated by the previous k days, where k is the maximal value of the serial interval. We denote these as X_{ji}, the number of cases that appear on day i that were infected by individuals with onset of symptoms on day j. We assume that the number of infectees generated by infectors with symptoms on day $j, X_j = \sum_{i=j+1}^{j+k+1} X_{ji}$, follows a Poisson distribution with parameter $R_0 N_j$. Additionally, $X_j = \{X_{j,j+1}, X_{j,j+2}, \ldots, X_{j,j+k+1}\}$, the vector of cases infected by the N_j individuals, follows a multinomial distribution with parameters p, k and X_j. Here p is a vector of probabilities that denotes the serial interval distribution. Using these assumptions, we obtain the following likelihood, as shown in White and Pagano (2008b):

$$L\left(R_0, \mathrm{p} \middle| \mathrm{N}\right) = \prod_{t=1}^{T} \frac{\exp\left(-\varphi_1\right)\varphi_t^{N_t}}{\Gamma\left(N_t + 1\right)},$$

where $\varphi_t = R_0 \sum_{j=1}^{k} p_j N_{t-j}$ and $\Gamma(x)$ is the gamma function. Maximizing the likelihood over R_0 and p provides estimators for the reproductive number and serial interval. This method assumes that there are no imported cases, there is no miss-

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ing data and that the population is uniformly mixing. Assuming that there are imported cases (for example individuals who became infected in Mexico after the index case), denoted by $Y = \{Y_1,\ldots Y_T\}$, then the likelihood becomes

$$L\left(R_0, \mathbf{p}|\mathbf{N},\mathbf{Y}\right) = \prod_{t=1}^{T} \frac{\exp\left(-\varphi_1\right)\varphi_t^{N_t - Y_t}}{\Gamma\left(N_t - Y_t + 1\right)},$$

where ϕ_t is defined as before. We further modify this methodology to account for some of the imperfections of the current data.

Imputation of missing onset times First, we handle missing onset times by making use of the reporting delay distribution. Most cases have a date of report, but far fewer have a date of onset given. As our interest is in modeling the date of onset, we impute these missing dates for those with a date of report. Let r_{ti} be the reporting time, let o_{ti} be their time of onset, assuming it is observed, and let $d_{ti} = r_{ti} - o_{ti}$. We fit a linear regression model with the $\log(d_{ti})$ as the outcome and r_{ti} as the explanatory variable as well as an indicator of whether the case is an imported case or not, b_{ti}. For each person with a reported r_{ti} but missing o_{ti}, we obtain $\hat{o}_{ti}$ by predicting the value for the reporting delay from the model, denoted by $\hat{d}_{ti}\left(r_{ti}, b_{ti}\right)$ and generate a random variable, X_{ti}, as the exponential of a normally distributed random variable with parameter $\log\left(\hat{d}_{ti}\left(r_{ti}, b_{ti}\right)\right)$, and variance given by the prediction error obtained from the regression model. Then the imputed time of onset is: $\tilde{o}_{ti} = r_{ti} - [X_{ti}]$, where $[X_{ti}]$ is the rounded value. The data used in this analysis is $\tilde{N}_t = N_t + \tilde{n}_t$; where N_t is the number of observed onset times for day t and $\tilde{n}_t$ are the number of unobserved (and thus imputed) onset times on day *t*.

Augmentation of data for underreporting As observed in Figure A6-1, the onset times are rapidly declining as one approaches the final date of report. This is likely attributable to reporting lag and is addressed by inflating case counts to account for delayed reporting. Again using the reporting delay distribution, we can modify the number of cases with onset on day *t*, as $M_t = \tilde{N}_t \Big/ \sum_{j=1}^{\min(T-t,l)} q_j$, where q_j is the probability of a *j* day reporting delay and l is the length of the reporting delay distribution. Note that the M_t are often non-integer values since they are estimates of the true number of cases. We only consider M_t such that the augmented data represents no more than 95% of the imputed reported value.

Adjustment for changes in reporting fraction Further, we report on the impact of changes in reporting. Inevitably many cases will go undetected. It is reasonable to assume that the proportion that go undetected will initially decrease as an epidemic unfolds and the public becomes increasingly aware of the outbreak. It is estimated that during the exponential growth phase of the epidemic, the proportion of hospitalized persons among cases reported between April 13 and April 28, declined at a rate of 10% per day (data not shown). We interpret this as

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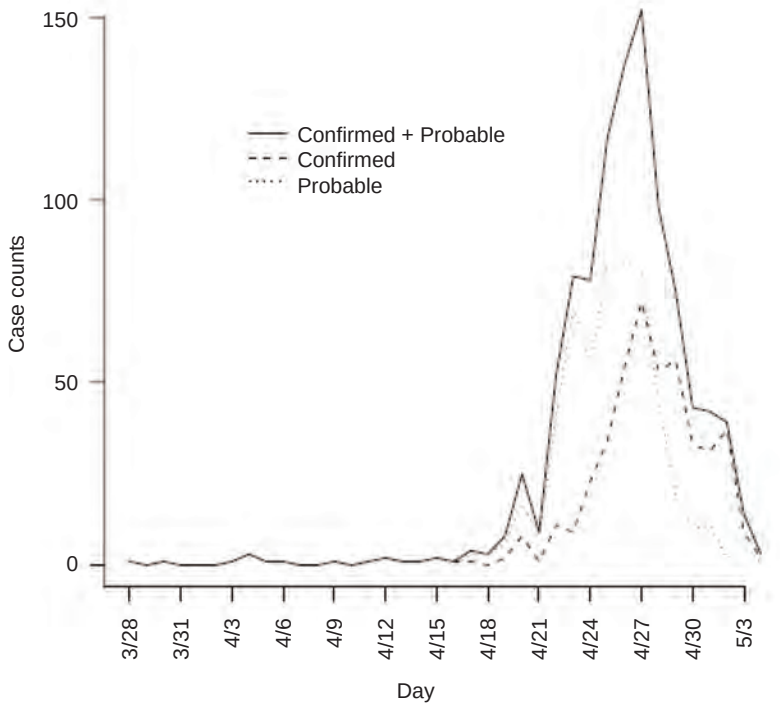

FIGURE A6-1 Confirmed and probable cases in the United States plotted by onset time. First date of onset is March 28, 2009.

an increase in the rate of ascertainment, i.e., the average severity of infections was not decreasing. Rather, the proportion of cases being ascertained was increasing with more mild cases being ascertained. Therefore, we estimate that the ratio of observed cases on consecutive days was 90% of the ratio of the true number of cases during this time. If s_t of the true cases are reported on day t and N_t cases are observed on that day, then

$$\frac{N_t}{N_{t-1}} = 0.9\left(\frac{N_t/s_t}{N_{t-1}/s_{t-1}}\right)$$

This implies that $s_t = (1/0.9)s_{t-1}$ will be reported on day t, representing a 11% increase in reporting with time. In the analysis, we modify the likelihood by inflating expected counts by $1/s$, $s = \{s_1,\ldots,s_T\}$ per day, but do not take account of the binomial variation in reported cases that is associated with less than perfect reporting. We assume that $s_t = 0.15$ for $t = 1,\ldots,15$ (i.e., March 28 to April 13) and thereafter $s_t = 1.11\ s_{t-1}$. We report on sensitivity to these assumptions.

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Spectral analysis of the cyclical component of the epidemic curve As an independent check of our joint estimation of R_0 and the serial interval, we used an alternative method to estimate the serial interval from the observed epidemiological curve. The idea is that we decompose the observed epidemiological curve into a trend component, which is essentially a moving average over d days, and a cyclical component, which is the difference between the observed number of cases and the trend. We expect that if there are a few cases in excess over the trend at day t, these cases will result in secondary cases that form an excess over the trend near day $t + \mu$, and tertiary cases that form an excess over the trend near day $t + 2\mu$ and so on. Therefore, we expect to see positive autocorrelation in the cyclical component of the epidemiological curve with a characteristic period equal to the mean of the serial interval μ. The characteristic period can be extracted using spectral analysis. Here we used the spectrum() command with modified Daniell smoothers as encoded in the R package. We expect the characteristic period of μ days to show up as a dominant frequency of $(1/\mu)$ (per day).

Interquartile ranges for the estimates were obtained by using a parametric bootstrap; 1000 simulated datasets were generated using the parameter estimates and constrained to have a total epidemic size within 2% of the actual epidemic size. The 0.025 and 0.975 quantiles obtained from the simulated data are reported as the confidence interval. All analyses were performed using R 2.6.1.

Results

The data are shown in Figure A6-1 by date of onset. There were 1368 confirmed or probable cases with a recorded date of report. Of these, there were 750 with a recorded date of onset. The first date of onset is March 28, 2009. The last date of onset is May 4, 2009 making 38 days of data used in the analysis. Over this period of time 117 of the reported cases had recently traveled to Mexico and are considered imported cases in our analysis. We report results for four separate datasets: all data with an onset date on or before April 25, 26, 27, or 29. Further, by the end of April knowledge of the epidemic was widespread in the United States and reporting mechanisms began to change, such that cases began to be reported in batches and were less likely to include individual information on the date of onset.

Estimation of R_0 and the Serial Interval

Reporting delays by day of onset for cases with known date of onset are shown in Figure A6-2A. The results from the regression indicate that a reporting date that is 1 day later is associated with a 5% increase in the reporting delay ($P < 0.001$).

We first show the results from imputing and then augmenting the data to obtain $\tilde{N}_t$ and M_t in Figure A6-2. Our initial interest is in determining the optimal value for k (the maximum serial interval category) to be used in the analysis.

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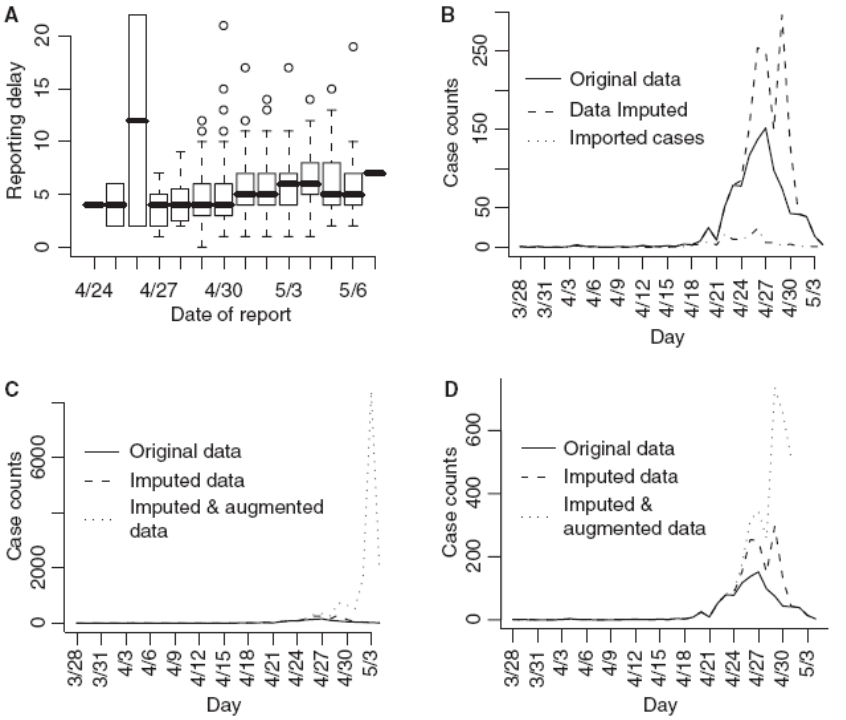

FIGURE A6-2 (A) Reporting delay by the date of report. (B) Imputed data and original data. (C) All data (right frame), (D) only augmented data where at least 5% of the data is observed.

We allow k to vary between 4 and 7 days and obtain the estimates for the serial interval using data with onset times on or before the 27th day of the epidemic (April 24, 2009). In interpreting the serial interval curves in Figure A6-3, it should be noted that the final category represents the probability of a serial interval of k days or longer. On the basis of these results, we set k to four since the log likelihood values for the varying values of k are nearly indistinguishable and in all cases the major mass (on average 88% for the original data and 93% for the augmented data) of the serial interval lies in the first 3 days.

We obtain estimates using the original data (N_t), the imputed data ($\tilde{N}_t$) and the augmented data (M_t) shown in Table A6-1 and Figure A6-4. Clearly using all available data will lead to biased results since significant underreporting is occurring from April 29 onward when the epidemic curve begins to plummet. In Figure A6-4 we show results using data with onset dates up to and including each day from April 21, 2009 through May 4, 2009. The reliability of the

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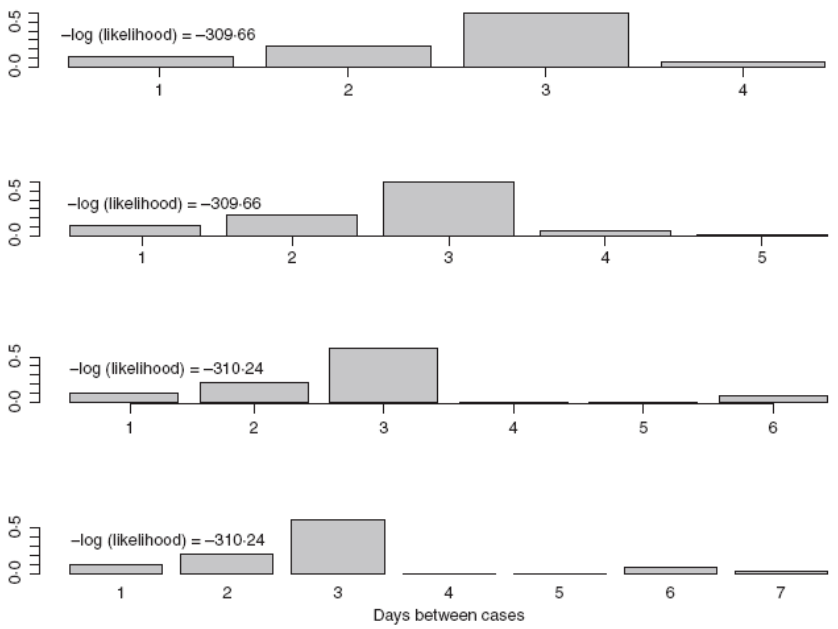

FIGURE A6-3 Serial interval estimates for k = 4, 5, 6, and 7 days with –log(likelihood) values.

results using the actual data is questionable since so many issues in the data have not been accounted for. Augmenting and imputing the data appears to stabilize the estimates substantially. We further note in the final pane of Figure A6-4 the dependence between the estimates. Using data from simulated outbreaks, we estimate the bivariate density of the basic reproductive number and the mean of the serial interval using a bivariate kernel density estimator. Not surprisingly this illustrates the positive correlation between the basic reproductive number and the mean of the serial interval.

Using the observed data when the peak number of incident cases is observed, we obtain the serial interval estimates shown in Figure A6-5. The estimated mean of the serial interval tends to be between 2.5 and 2.6 days for all the data, with a mode of 3 days. R_0 is estimated to be between 2.3 and 2.5 for data ending between April 25 and April 27. We observe growth rates, r, between 0.34 and 0.43, depending on the data used (Table A6-1).

Additionally, we observe that when we account for increases in the reporting fraction, the estimates of the reproductive number drop substantially ($\hat{R}_0$ = 1.7 – 1.8) and the estimates of the mean serial interval decrease by about 10% (2.2–2.3 days, see Table A6-1). We note the sensitivity of these estimates

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TABLE A6-1 Estimates Obtained from the Original, Imputed, and Augmented Data

	4/25	4/26	4/27	4/28
$\hat{R}_0$ (Range)				
Original	2.27 (1.41, 2.48)	1.95 (1.27, 2.14)	1.59 (1.12, 1.66)	1.51 (1.14, 1.60)
	1.66 (1.41, 2.14)	*1.56 (1.21, 1.82)*	*1.40 (0.93, 1.39)*	*1.32 (0.86, 1.30)*
Imputed	2.25 (1.37, 2.85)	2.19 (1.38, 2.96)	2.36 (1.51, 2.94)	2.31 (1.60, 3.02)
	1.66 (1.37, 2.51)	*1.68 (1.35, 2.04)*	*1.75 (1.42, 2.17)*	*1.68 (1.43, 1.98)*
Augmented	2.26 (1.32, 2.51)	2.27 (1.38, 2.51)	2.51 (1.51, 2.88)	2.52 (1.70, 2.83)
	1.68 (1.37, 2.21)	*1.73 (1.39, 2.12)*	*1.84 (1.48, 2.29)*	*1.81 (1.53, 2.21)*
μ (Range)				
Original	2.55 (1.87, 3.30)	2.45 (1.65, 3.27)	2.20 (1.53, 3.13)	2.15 (1.59, 3.08)
	2.21 (1.88, 3.17)	*2.17 (1.61, 3.15)*	*2.04 (1.43, 3.01)*	*2.00 (1.39, 2.98)*
Imputed	2.49 (1.74, 3.33)	2.47 (1.71, 3.31)	2.54 (1.71, 3.30)	2.60 (1.96, 3.24)
	2.17 (1.67, 3.15)	*2.18 (1.68, 3.17)*	*2.21 (1.71, 3.17)*	*2.28 (1.90, 3.18)*
Augmented	2.48 (1.68, 3.28)	2.48 (1.74, 3.32)	2.55 (1.77, 3.34)	2.61 (2.00, 3.32)
	2.16 (1.75, 3.16)	*2.18 (1.71, 3.13)*	*2.21 (1.73, 3.21)*	*2.30 (1.94, 3.14)*
$\eth^2$ (Range)				
Original	0.60 (0.21, 1.25)	0.77 (0.25, 1.48)	0.80 (0.24, 1.59)	0.79 (0.28, 1.59)
	0.88 (0.22, 1.15)	*0.94 (0.24, 1.49)*	*0.91 (0.24, 1.59)*	*0.89 (0.24, 1.59)*
Imputed	0.64 (0.20, 1.52)	0.67 (0.21, 1.41)	0.67 (0.22, 1.37)	0.57 (0.21, 1.17)
	0.88 (0.22, 1.31)	*0.94 (0.22, 1.46)*	*0.91 (0.23, 1.33)*	*0.89 (0.21, 1.17)*
Augmented	0.66 (0.21, 1.52)	0.65 (0.21, 1.54)	0.67 (0.20, 1.36)	0.60 (0.20, 1.26)
	0.89 (0.23, 1.34)	*0.88 (0.23, 1.34)*	*0.90 (0.23, 1.29)*	*0.85 (0.23, 1.15)*
Imported cases				
Original	58	72	96	102
	10	*14*	*24*	*6*
Imputed	60	80	106	115
	11	*20*	*26*	*9*
Augmented	65.4	93.4	139.1	160.0
	13.4	*27.9*	*45.7*	*20.9*
Growth rate, *r*				
Original	0.34	0.34	0.33	0.31
Imputed	0.34	0.37	0.40	0.37
Augmented	0.34	0.39	0.43	0.41
New cases				
Original	78	117	137	152
Imputed	85	153	254	251
Augmented	91.6	176.3	314.9	344.4
Total cases				
Original	275	392	529	681
Imputed	282	435	689	940
Augmented	295.0	471.3	786.3	1130.6

Bootstrap confidence intervals are shown. Italicized results reflect results accounting for an 11% per day increase in reporting fraction starting April 13.

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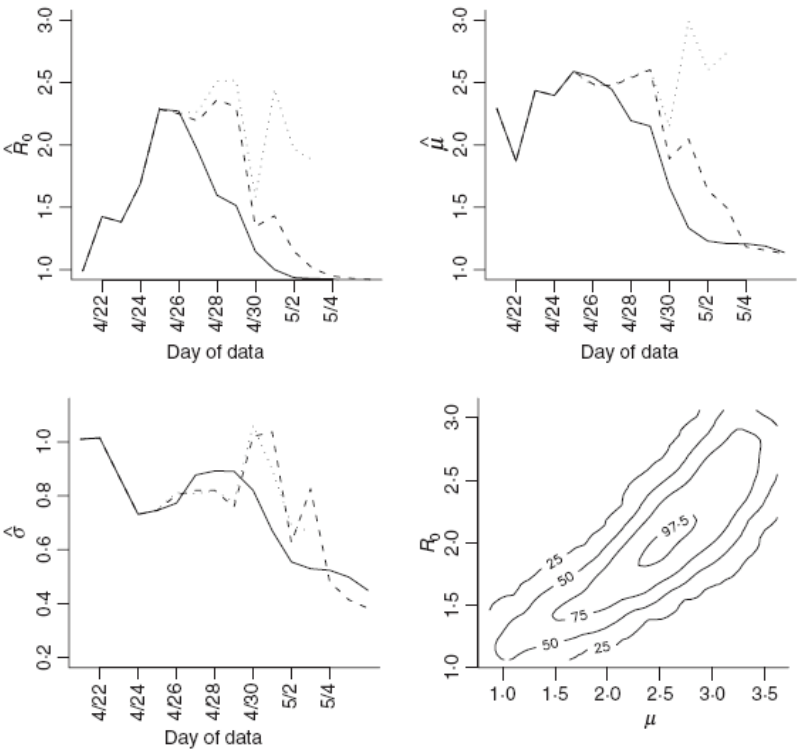

FIGURE A6-4 Estimates for the reproductive number, mean, and variance of the serial interval. The results using the original data (solid line), imputed data (dashed line), and augmented data (dotted line) are all shown using data with onset date no later than the value in the *x*-axis. Augmented data estimates are not shown after April 30, 2009 since less than 5% of the data is original data. These results correspond, in part, to those shown in Table A6-1. The fourth plan shows the contour plot of the joint density estimate of the mean of the serial interval and the basic reproductive number for imputed data up to and including April 27. The values of the contours correspond the estimated 25th, 50th, 75th, and 97.5th percentiles of the joint density.

to the assumed reporting distribution and report these sensitivities for estimates obtained on April 27 using the imputed data where $\hat{R}_0 = 1.75$ and $\hat{\mu} = 2.21$. Given a reporting fraction increase of 11% per day, if the initial reporting fraction varies between $s_0 = 0.01$ and $s_0 = 0.20$ then $\hat{R}_0$ will range between 1.91 ($s_0 = 0.01$) and 1.71 ($s_0 = 0.20$) and the estimated mean serial interval will vary between 2.19 ($s_0 = 0.01$) and 2.22 ($s_0 = 0.20$). If the daily rate of change in the reporting ratio varies from 11% to values between 8% and 14% and we hold $s_0 = 0.15$, then $\hat{R}_0$

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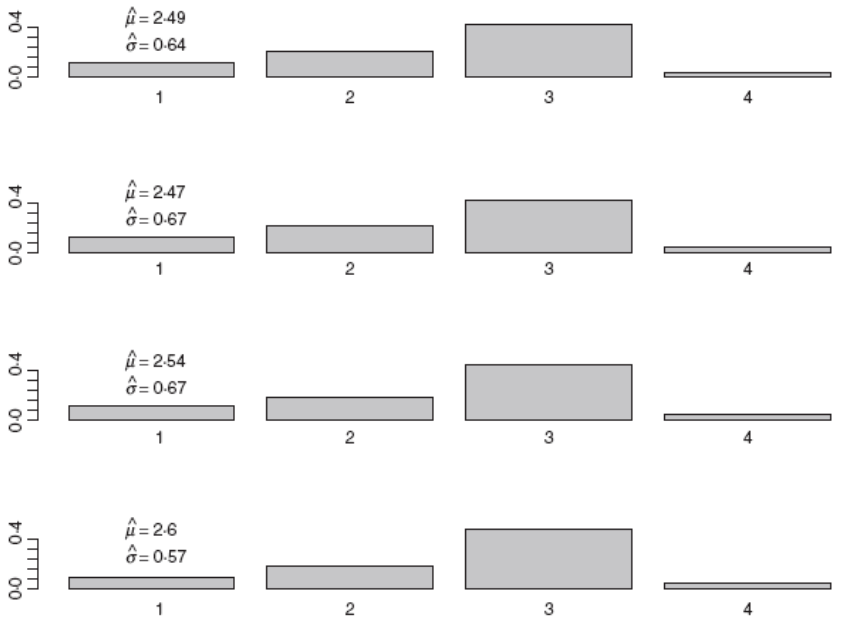

FIGURE A6-5 Serial interval estimate using data up to and including 4/25/2009 (top figure), 4/26/2009 (second), 4/27/2009 (third), and 4/28/2009 (bottom figure).

ranges between 1.98 (8%) and 1.63 (14%) and $\hat{\mu}$ is estimated to be between 2.28 (8%) and 2.16 (14%).

Finally, we assess the trend component of the epidemiological curve using a moving average over $d = 4$ days, and we assess the cyclical component as the deviation between the observed number of cases and the trend. We only use data up to April 28, 2009. For the original data we find a dominant frequency of 0.4, suggesting a serial interval of 2.5 days. Repeating this with the imputed data suggests a serial interval of 2.67 days, and the augmented data suggests a serial interval of 3.2 days. These results are similar to the findings on the modal serial interval (3 days) from maximum likelihood estimation, though slightly higher than the estimated mean serial interval. This suggests that the estimated values for serial intervals are based on regularities in deviations from the trend in the epidemiological curve. There were no indications of weekly periodicity or a weekday effect.

Estimation of R_0 Alone

Estimates for the serial interval in a different setting have recently been provided by Cowling *et al*. (2009) and Fraser *et al*. (2009). The first is for

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seasonal influenza and obtained using household transmission data. The authors fit the observed serial interval estimates to a Weibull distribution with a mean of 3.6 days and standard deviation of 1.6 days. This estimate is consistent with that obtained by the Spanish surveillance group (Surveillance Group for New Influenza A (H1N1) Virus Investigation and Control in Spain, 2009) for the current influenza A/H1N1 outbreak. Fraser *et al*. (2009) estimate the mean of the serial interval to be 1.91 days for the present virus in La Gloria, Mexico. While both serial interval and reproductive number are likely to depend on the virus and also on the population, we consider a sensitivity analysis in which we assume previously measured serial interval distributions and estimate the reproductive number alone (Table A6-2). To use the Fraser *et al*. estimate, we assume that the standard deviation is 1 day and that the serial interval follows a discretized gamma distribution. We also use a discretized gamma distribution while preserving the mean and standard deviation of the Cowling *et al*. estimate (2009). In both cases we set k to 6.

Our results are as expected and indicate that the estimated reproductive number varies dramatically depending on the estimate of the serial interval used. For the longer estimate of Cowling *et al*., the estimates ranged between 3.25 and 4.67 using the observed data. For the serial interval estimate derived from Fraser *et al*., the estimates are much lower, and are between 1.92 and 2.52.

The italicized entries in Table A6-2 provides estimates of the reproductive number under the same circumstances as previously stated but also taking into account the possibility that reporting increased by 11.1% each day starting April 13. Unsurprisingly, estimates decline under this assumption. For the Fraser *et al*. serial interval, the estimated reproductive number falls to between 1.5 and 2.0, whereas for the Cowling *et al*. estimate the value is between 2.0 and 3.0.

These estimates were similarly sensitive to assumptions on the initial reporting fraction and its rate of change starting April 13. For values of the initial reporting fraction from 0.01 to 0.20 for the imputed data on April 27, the estimate of R_0 will range between 3.03 and 2.70 for the Cowling serial interval and 2.03 and 1.81 for the Fraser serial interval. Varying the daily rate of change in the reporting fraction from 8% to 14% rather than being fixed at 11% means the estimates would range between 3.19 and 2.54 for the Cowling estimate and 2.06 and 1.75 for the Fraser estimate. The larger the initial reporting fraction or the larger the increase in the reporting ratio, the greater proportion of cases that are reported throughout the time of observation. This increase in reporting leads to a decrease in the estimate of the reproductive number.

Discussion

We obtain estimates of the reproductive number and the serial interval. These estimates, along with information on population susceptibility and risk of severe disease, help to inform public health policy, such as potential utility or success

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TABLE A6-2 Estimates of the Reproductive Number the Mean of the Serial Interval (SI) Is 3.6 Days with SD of 1.6 Days (Cowling *et al.*, 2009) or Mean of 1.91 Days and SD of 1 Days (Fraser *et al.*, 2009).

	4/25/2009	4/26/2009	4/27/2009	4/28/2009
$\hat{R}_0$ (confidence interval); mean SI = 3-6 days				
Original data	3.48 (2.88, 3.72)	3.29 (2.85, 3.47)	2.87 (2.55, 3.06)	2.59 (2.31, 2.77)
	2.57 (2.39, 3.13)	*2.48 (2.30, 2.81)*	*2.25 (2.04, 2.46)*	*2.05 (1.80, 2.16)*
Imputed data	3.56 (2.90, 3.80)	3.65 (3.10, 3.88)	3.83 (3.46, 4.12)	3.53 (3.23, 3.70)
	2.61 (2.43, 3.19)	*2.68 (2.50, 3.14)*	*2.78 (2.69, 3.23)*	*2.61 (2.47, 2.86)*
Augmented data	3.62 (2.94, 3.89)	3.79 (3.27, 4.05)	4.11 (3.74, 4.42)	3.94 (3.72, 4.22)
	2.66 (2.48, 3.23)	*2.79 (2.61, 3.26)*	*2.97 (2.88, 3.45)*	*2.88 (2.79, 3.19)*
$\hat{R}_0$ (confidence interval); mean SI = 1.91 days				
Original data	1.99 (1.77, 2.26)	1.86 (1.71, 2.08)	1.72 (1.55, 1.90)	1.63 (1.51, 1.80)
	1.76 (1.64, 2.11)	*1.66 (1.54, 1.88)*	*1.54 (1.39, 1.71)*	*1.45 (1.32, 1.59)*
Imputed data	2.03 (1.79, 2.31)	2.05 (1.85, 2.30)	2.22 (2.11, 2.53)	2.04 (1.97, 2.28)
	1.80 (1.68, 2.17)	*1.78 (1.68, 2.09)*	*1.87 (1.85, 2.23)*	*1.74 (1.70, 2.00)*
Augmented data	2.05 (1.80, 2.35)	2.11 (1.95, 2.38)	2.34 (2.27, 2.66)	2.20 (2.18, 2.45)
	1.82 (1.69, 2.16)	*1.84 (1.75, 2.14)*	*1.97 (1.97, 2.32)*	*1.87 (1.85, 2.08)*
Num cases				
Original data	275	392	529	681
Imputed data	282	435	689	940
Augmented data	295.0	471.3	786.3	1130.6

Italicized results reflect results accounting for an 11% per day increase in reporting fraction starting April 13.

of different community mitigation strategies, and help to characterize the spread of the disease. Our estimates of the early reproductive number of novel influenza A/H1N1 in the United States are higher than those obtained in another published study of data from the Netherlands (Hahne *et al*., 2009) and Mexico (Fraser *et al*., 2009). Our estimates are slightly smaller than those obtained from an initial analysis of the outbreak in Japan (Nishiura *et al*., 2009) and an alternative analysis of data from Mexico (Boelle *et al*., 2009). There are several possible explanations for this. First, the prior estimates were based on a completed outbreak of a respiratory infection in La Gloria, Mexico and on virus genetic data, whereas our study uses the early phase of the epidemic curve from the United States as a whole. Each of these datasets has various uncertainties associated with it; we have highlighted and attempted to correct for changes in reporting, reporting delays, and missing dates of onset, but these corrections will only be approximate. Indeed, all datasets for an infection with a spectrum of severity and changing ascertainment patterns will be imperfect in these ways. Second, we have used a different approach (White and Pagano, 2008a,b) from that used in the Mexico data; results reported here use a method focused on a period of exponential growth of the epidemic, while the prior

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estimates used either viral sequence coalescence estimates or analysis of a whole epidemic curve, including the declining phase, in the case of La Gloria. Finally, our estimate of the serial interval from the data is longer than that obtained for La Gloria, though somewhat shorter than that obtained from contact tracing in Spain (Surveillance Group for New Influenza A (H1N1) Virus Investigation and Control in Spain, 2009). As expected, if we assume a serial interval distribution, rather than estimate it, our estimate of the reproductive number shifts to adjust, as a consequence of the relationship between these two quantities (Lipsitch and Bergstrom, 2004; Anderson and May, 1991).

The results presented here should be interpreted with the following caveats in mind. First the data are not from a closed system, and clearly there are imported cases, such as individuals who acquired the illness in Mexico after March 28. Although we account for cases that are known to be imported, it is likely that the data we have is incomplete and several other infections could have been imported. Misclassification of cases that were truly imported will bias reproductive number estimates upwards. Second, incomplete reporting is a feature of nearly all data on the novel influenza A/H1N1, and certainly of any datasets large enough to estimate temporal trends in case numbers. If underreporting were consistent over time, it would have only a minor effect on our point estimates (which depend mainly on the growth rate and on cyclical signals in the data) but would increase uncertainty around these estimates. More likely, as we have noted, there are trends in reporting, with increasing reporting as awareness grows, and declining reporting as public health workers become unable to obtain and report detailed information on each case. One might argue for analyzing only a subset of cases during the time period with optimal reporting or by only looking at hospitalizations, which might be more accurately recorded. However, in the first case, we ignore a large number of initial cases that will undoubtedly lead to gross errors in the estimates. In this case all secondary cases after the first day that is analyzed will be attributable to that day. By only considering hospitalizations, we violate the assumption of a closed system and assume that all cases that are hospitalized are attributable to another hospitalized case. The results from such an analysis would be challenging to interpret. Instead, we have accounted for these changes by imputation of onset dates, augmentation of data to account for reporting delays, and adjustments for an estimated upward trend in reporting of the early data. We feel that such adjustments, while still imperfect, are superior to ignoring information in incomplete data. In all analyses of such data, the statistical confidence intervals obtained should not be interpreted as measuring all of the uncertainty in estimates; additional uncertainty comes from unmeasured changes in reporting.

We have also noted the impact of the assumed reporting distribution on the estimates with a sensitivity analysis. While we have estimated the rate of increase in the reporting fraction through time from our data, our estimate of the initial reporting fraction is not based on data. We have illustrated the impact of variation in these quantities on our estimates and note that while our estimates do change

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as these quantities vary the changes are not dramatic. In fact if we assume that the initial reporting fraction is as low as 1% rather than our assumed 15%, then the estimate of the reproductive number increases from 1.75 to 1.90. The impact that the difference in these two estimates will have on policy is minimal. We also note that under the same circumstances, the estimated mean of the serial interval changes very little (from 2.21 to 2.19), illustrating the robustness of the mean to variations in this quantity. What these results mean is that as fewer of the cases are reported, our estimates of the reproductive number are likely to be overly conservative if we do not properly adjust for this underreporting.

We have discussed the impact of the assumed serial interval on the estimates of the reproductive number. It is clear that assuming a form of the serial interval directly impacts the estimates of the reproductive number. External estimates of the serial interval distribution have the advantage that they are directly observed rather than inferred from properties of the epidemic curve; on the other hand, pairs of cases with known infector and infectee are nonrepresentative of the overall pattern of transmission in a population. For our baseline results, we estimate the serial interval non-parametrically rather than imposing a shape on it. We have also incorporated previous estimates of serial interval to test the sensitivity of our conclusions.

The difference between our low estimates (when assuming increased reporting fraction and using Fraser *et al*. (Fraser *et al*., 2009) serial interval distribution from La Gloria) and our high estimates (when ignoring increased reporting and using the serial interval distribution of Cowling *et al*. for seasonal influenza [2009]) is the difference between an epidemic that is readily controlled and one that is virtually uncontrollable according to existing models of pandemic interventions (Halloran *et al*., 2008; Ferguson *et al*., 2005; Germann *et al*., 2006). It is clear that more precise estimates of the serial interval in various contexts for this virus are essential to reduce the uncertainty of estimates of the reproductive number; similarly, it is essential to estimate growth rates in a variety of contexts where reporting fractions can be better understood, possibly at local levels where a single reporting system is used.

Finally, it should be remembered that neither serial interval (Kenah *et al*., 2008; Svensson, 2007) nor reproductive number is a constant of nature; each depends on the population, the state of control measures and behavior, and other factors. Continued monitoring of the growth of the pandemic in various settings will be required to define the range of reproductive numbers achieved by this virus and their possible dependence on geography, population, season, and changes in the virus.

Acknowledgements

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Conflict of Interest

Marc Lipsitch has received consulting fees from the Avian/Pandemic Flu Registry (Outcome Sciences), which is funded in part by Roche.

References

Anderson RM, May RM. Infectious Diseases of Humans. Oxford, UK: Oxford University Press; 1991.

Andreasen V, Viboud C, Simonsen L. Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. J Infect Dis 2008; 197(2):270–278.

Barry JM, Viboud C, Simonsen L. Cross-protection between successive waves of the 1918-1919 influenza pandemic: epidemiological evidence from US army camps and from Britain. J Infect Dis 2008; 198(10):1427–1434.

Boelle PY, Bernillon P, Desenclos JC. A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March–April 2009. Euro Surveill 2009; 14(19):19205.

Cowling BJ, Fang VJ, Riley S, Malik Peiris JS, Leung GM. Estimation of the serial interval of influenza. Epidemiology 2009; 20(3):344–347.

Ferguson NM, Cummings DA, Cauchemez S *et al*. Strategies for containing an emerging influenza pandemic in southeast Asia. Nature 2005; 437(7056):209–214.

Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci USA 2004; 101(16):6146–6151.

Fraser C, Donnelly CA, Cauchemez S *et al*. Pandemic potential of a strain of influenza A (H1N1): early findings. Science 2009; 324: 1557–1561.

Germann TC, Kadau K, Longini IM Jr, Macken CA. Mitigation strategies for pandemic influenza in the United States. Proc Natl Acad Sci USA 2006; 103(15):5935–5940.

Hahne S, Donker T, Meijer A *et al*. Epidemiology and control of influenza A(H1N1)v in the Netherlands: the first 115 cases. Euro Surveill 2009; 14(27):19267.

Halloran ME, Ferguson NM, Eubank S *et al*. Modeling targeted layered containment of an influenza pandemic in the United States. Proc Natl Acad Sci USA 2008; 105(12):4639–4644.

Kenah E, Lipsitch M, Robins JM. Generation interval contraction and epidemic data analysis. Math Biosci 2008; 213(1):71–79.

Lipsitch M, Bergstrom CT. Invited commentary: real-time tracking of control measures for emerging infections. Am J Epidemiol 2004; 160:517–519; Discussion 520.

Lipsitch M, Riley S, Cauchemez S, Ghani AC, Ferguson NM. Managing and reducing uncertainty in an emerging influenza pandemic. N Engl J Med 2009; 361: 112–115.

Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. Nature 2004; 432(7019):904–906.

Nishiura H, Castillo-Chavez C, Safan M, Chowell G. Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan. Euro Surveill 2009; 14(22):19227.

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009; 360: 2605–2615.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Surveillance Group for New Influenza A (H1N1) Virus Investigation and Control in Spain. New influenza A (H1N1) virus infections in Spain, April–May 2009. Euro Surveill. 2009;14(19). Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19209 (Accessed on 9 June 2009).

Svensson A. A note on generation times in epidemic models. Math Biosci 2007; 208(1):300–311.

White LF, Pagano M. Transmissibility of the influenza virus in the 1918 pandemic. PLoS ONE 2008a; 3(1):e1498. doi:10.1371/journal. pone.0001498. (Accessed on 6 June 2009).

White LF, Pagano M. A likelihood-based method for real-time estimation of the serial interval and reproductive number of an epidemic. Stat Med 2008b; 27(16):2999–3016.

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A7

THE SEVERITY OF PANDEMIC H1N1 INFLUENZA IN THE UNITED STATES, FROM APRIL TO JULY 2009: A BAYESIAN ANALYSIS[50]

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Abstract

Background

Accurate measures of the severity of pandemic (H1N1) 2009 influenza (pH1N1) are needed to assess the likely impact of an anticipated resurgence in the autumn in the Northern Hemisphere. Severity has been difficult to measure because jurisdictions with large numbers of deaths and other severe outcomes have had too many cases to assess the total number with confidence. Also, detection of severe cases may be more likely, resulting in overestimation of the severity of an average case. We sought to estimate the probabilities that symptomatic infection would lead to hospitalization, ICU admission, and death by combining data from multiple sources.

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Methods and Findings

We used complementary data from two US cities: Milwaukee attempted to identify cases of medically attended infection whether or not they required hospitalization, while New York City focused on the identification of hospitalizations, intensive care admission or mechanical ventilation (hereafter, ICU), and deaths. New York data were used to estimate numerators for ICU and death, and two sources of data—medically attended cases in Milwaukee or self-reported influenza-like illness (ILI) in New York—were used to estimate ratios of symptomatic cases to hospitalizations. Combining these data with estimates of the fraction detected for each level of severity, we estimated the proportion of symptomatic patients who died (symptomatic case-fatality ratio, sCFR), required ICU (sCIR), and required hospitalization (sCHR), overall and by age category. Evidence, prior information, and associated uncertainty were analyzed in a Bayesian evidence synthesis framework. Using medically attended cases and estimates of the proportion of symptomatic cases medically attended, we estimated an sCFR of 0.048% (95% credible interval [CI] 0.026%–0.096%), sCIR of 0.239% (0.134%–0.458%), and sCHR of 1.44% (0.83%–2.64%). Using self-reported ILI, we obtained estimates approximately 7–9 × lower. sCFR and sCIR appear to be highest in persons aged 18 y and older, and lowest in children aged 5–17 y. sCHR appears to be lowest in persons aged 5–17; our data were too sparse to allow us to determine the group in which it was the highest.

Conclusions

These estimates suggest that an autumn–winter pandemic wave of pH1N1 with comparable severity per case could lead to a number of deaths in the range from considerably below that associated with seasonal influenza to slightly higher, but with the greatest impact in children aged 0–4 and adults 18–64. These estimates of impact depend on assumptions about total incidence of infection and would be larger if incidence of symptomatic infection were higher or shifted toward adults, if viral virulence increased, or if suboptimal treatment resulted from stress on the health care system; numbers would decrease if the total proportion of the population symptomatically infected were lower than assumed.

Please see later in the article for the Editors' Summary.

Introduction

The H1N1 2009 influenza (pH1N1) pandemic has resulted in over 209,000 laboratory-confirmed cases and over 3,205 deaths worldwide as of 11 September 2009 (http://www.who.int/csr/don/2009_09_11/en/index.html, accessed 14 Sep-

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tember 2009), but national and international authorities have acknowledged that these counts are substantial underestimates, reflecting an inability to identify, test, confirm, and report many cases, especially mild cases. Severity of infection may be measured in many ways, the simplest of which is the case-fatality ratio (CFR), the probability that an infection causes death. Other measures of severity, which are most relevant to the burden a pandemic exerts on a health care system, are the case-hospitalization and case-intensive care ratios (CHR and CIR, respectively), the probabilities that an infection leads to hospitalization or intensive care unit (ICU) admission. In the absence of a widely available and validated serologic test for infection, it is impossible to estimate these quantities directly, and in this report we instead focus on the probabilities of fatality, hospitalization, and ICU admission per *symptomatic* case; we denote these ratios sCFR, sCHR, and sCIR respectively.

Although it is difficult to assess these quantities, estimates of their values and associated uncertainty are important for decision making, planning, and response during the progression of this pandemic. Initially, some national and international pandemic response plans were tied partly to estimates of the CFR, but such plans had to be modified in the early weeks of this pandemic, as it became clear that the CFR could not at that time be reliably estimated (Lipsitch et al., 2009a). Costly measures to mitigate the pandemic, such as the purchase of medical countermeasures and the use of disruptive social distancing strategies may be acceptable to combat a more severe pandemic but not to slow a milder one. While past experience (Jordan et al., 1958) and mathematical models (Ferguson et al., 2006; Halloran et al., 2008; Mills et al., 2004) suggest that between 40% and 60% of the population will be infected in a pandemic with a reproduction number similar to those seen in previous pandemics, the number of deaths and the burden on the health care system also depend on the age-specific severity of infection, which varies by orders of magnitude between pandemics (Miller et al., 2008) and even between different waves in the same pandemic (Andreasen et al., 2008). Reports from the Southern Hemisphere suggest that a relatively small fraction of the population experienced symptomatic pH1N1 infection (7.5% in New Zealand, for example; Baker et al., 2009), although these numbers are considered highly uncertain (Baker et al., 2009). On the other hand, primary care utilization for influenza-like illness (ILI) has been considerably higher than in recent years (Baker et al., 2009), and anecdotal reports in the Southern Hemisphere have indicated that some intensive care units (ICUs) have been overwhelmed and surgery postponed due to a heavy burden of pH1N1 cases (Bita, 2009; Newton, 2009).

The problem of estimating severity of pH1N1 infection includes the problem of estimating how many of the infected individuals in a given population and time period subsequently develop symptoms, are medically attended, hospitalized, admitted to ICU, and die due to infection with the virus. No large jurisdiction in the world has been able to maintain an accurate count of total pH1N1 cases once

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the epidemic grew beyond hundreds of cases, because the effort required to confirm and count such cases is proportionate to the size of the exponentially growing epidemic (Lipsitch et al., 2009b), making it impossible to reliably estimate the frequency of an event (e.g., death) that occurs on the order of 1 in 1,000 patients or fewer. As a result, simple comparisons of the number of deaths to the number of cases suffer from underascertainment of cases (making the estimated ratio too large), and underascertainment of deaths due to inability to identify deaths caused by the illness and due to delays from symptom onset to death (making the estimated ratio too small; Lipsitch et al., 2009a). Imperfect ascertainment of both numerator and denominator will lead to biased estimates of the CFR. Estimating the number of persons at these varying levels of severity therefore depends on estimating the proportion of true cases that are recognized and reported by existing surveillance systems. Similar problems affect estimates of key parameters for other diseases, such as HIV. In HIV, a solution to this problem—which now forms the basis for the UK's annual HIV prevalence estimates published by the Health Protection Agency (Health Protection Agency Centre for Infections, 2009a, b)—has been to synthesize evidence from a variety of sources that together provide a clearer picture of incidence, prevalence, and diagnosis probabilities. This synthesis is performed within a Bayesian framework that allows each piece of evidence, with associated uncertainties, to be combined into an estimate of the numbers of greatest interest (Goubar et al., 2008; Presanis et al., 2008).

Here we use a similar framework to synthesize evidence from two cities in the United States—New York and Milwaukee—together with estimates of important detection probabilities from epidemiologic investigations carried out by the US Centers for Disease Control and Prevention (CDC) and other data from CDC. We estimate the severity of pH1N1 infection from data from spring–summer 2009 wave of infections in the United States. The New York City and Milwaukee health departments pursued differing surveillance strategies that provided high-quality data on complementary aspects of pH1N1 infection severity, with Milwaukee documenting medically attended cases and hospitalizations, and New York documenting hospitalizations, ICU/ventilation use, and fatalities. These are the numerators of the ratios of interest.

The denominator for these ratios is the number of symptomatic pH1N1 cases in a population, which cannot be assessed directly. We use two different approaches to estimate this quantity. In the first (Approach 1), we use self-reported rates of patients seeking medical attention for ILI from several CDC investigations to estimate the number of symptomatic cases from the number of medically attended cases, which are estimated from data from Milwaukee. In the second (Approach 2), we use self-reported incidence of ILI in New York City, and making the assumption that these ILI cases represent the true denominator of symptomatic cases, we directly estimate the ratio between hospitalizations, ICU admissions/mechanical ventilation, and deaths (adjusting for ascertainment) in New York City. Each of these two methods provides estimates for the general

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population, and also for broad age categories 0–4, 5–17, 18–64, and 65+ years. The result of each approach is a tiered severity estimate of the pandemic.

Methods

Methods Overview

The overall goal of this study was to estimate, for each symptomatic pH1N1 case, the probability of hospitalization, ICU admission or mechanical ventilation, or death, overall and by age group. The challenge is that in any population large enough to have a significant number of patients with these severe outcomes, there is no reliable measure of the number of symptomatic pH1N1 cases. This problem was approached in two ways. Approach 1 was to view the severity of infection as a "pyramid" (Garske et al., 2009), with each successive level representing greater severity; to estimate the ratio of the top level to the base (symptomatic cases), we estimated the ratios of each successive level to the one below it (Figure A7-1, left side). Thus we broke down (for example) the sCFR (Figure A7-1, black), i.e., the probability of death per symptomatic case, into components for which data were available – the probability of a case coming to medical attention given symptomatic infection (CDC survey data); the probability of being hospitalized given medical attention (Milwaukee data); and the probability of dying given hospitalization (New York data, including a correction for those who died of pH1N1 but were not hospitalized). Approach 2 was to use the self-reported incidence of ILI from a telephone survey in New York City as the estimate of total symptomatic pH1N1 disease, and the total number of confirmed deaths in New York City as the estimate of the deaths (after accounting for imperfect ascertainment, in this case due to possibly imperfect viral testing sensitivity). In each case, prior distributions were used to quantify information on the probability that cases at each level of severity were detected; these prior distributions reflected the limited data available on detection probabilities and associated uncertainty.

All of these estimates were combined within a Bayesian evidence synthesis framework. This framework permits the estimation of probabilities for the quantities of interest (the sCFR, sCIR, and sCHR) and associated uncertainty (expressed as credible intervals [CIs]). These credible intervals appropriately reflect the combined uncertainties associated with each of the inputs to the estimate—mainly, the true numbers of cases at each level of severity, after accounting for imperfect detection—as well as the uncertainties due to sampling error (chance).

Study Populations

Data were obtained from enhanced pandemic surveillance efforts by the City of Milwaukee Health Department and the New York City Department of Health and Mental Hygiene (DOHMH). Details of testing policies, data acquisition, and

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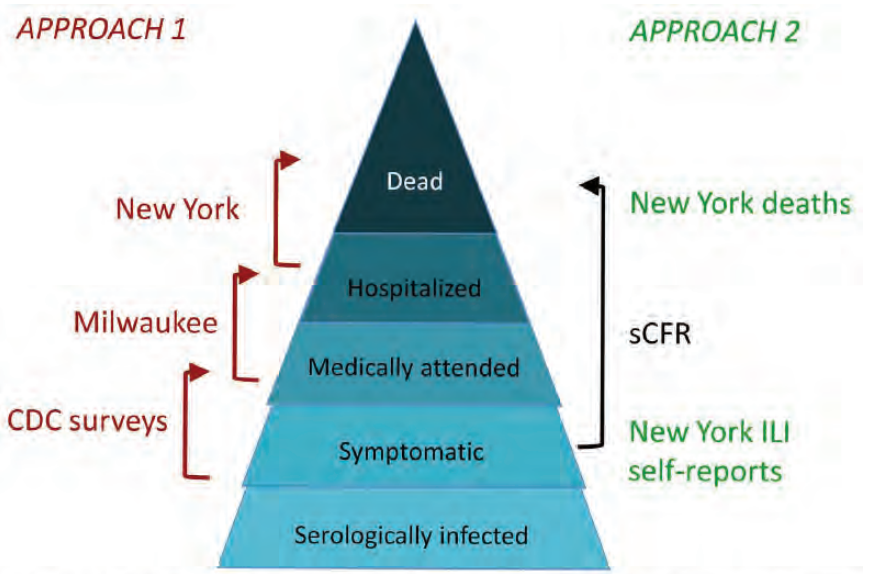

FIGURE A7-1 Diagram of two approaches to estimating the sCFR. Approach 1 used three datasets to estimate successive steps of the severity pyramid. Approach 2 used self-reported IU for the denominator, and confirmed deaths for the numerator, both from New York City. Both approaches used prior distributions, in some cases informed by additional data, to inform the probability of detecting (confirming and reporting) cases at each level of severity (not shown in the diagram; see text S1). The Bayesian evidence synthesis framework was used as a formal way to combine information and uncertainty about each level of severity into a single estimate and associated uncertainty that reflected all of the uncertainty in the inputs.

analysis are given in Text S1. All data were analyzed first in aggregate and then by age category.

Milwaukee Data

Between April 6 and July 16, 2009, Milwaukee recorded 3,278 confirmed cases and four deaths due to pH1N1, reflecting sustained efforts to test patients reporting ILI and their household contacts from the start of the epidemic in April until mid-July. On April 27, Milwaukee initiated protocols including recommendations for testing persons with influenza symptoms and travel history to areas reporting novel H1N1 cases, using a reverse transcriptase polymerase chain reaction (RT-PCR) test specific for pH1N1. By May 7, Milwaukee issued testing guidance updated to recommend testing persons with moderate to severe symptoms, except that test-

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ing continued to be recommended for health care workers with mild, moderate or severe symptoms. We used a line list dated July 21, and in a preliminary analysis examined the frequency of hospitalization among cases by "episode date" (the earliest date in their case report). The proportion of confirmed cases hospitalized was stable around 3% up to May 20, after which it increased markedly to 6%–8% in the following weeks. We judged that this change reflected reduced testing of mild cases and limited our analysis (used to inform the ratio of hospitalizations to medically attended cases) to the 763 cases with an episode date up to or including May 20. While Milwaukee data were not the main source of estimates of ICU admission or death probabilities, we did employ hospitalized cases up to an episode date of June 14 to contribute to estimates of the ratio of deaths or ICU admissions to hospitalizations, since these should not be affected by failure to test mild cases.

New York Case Data

New York City maintained a policy from April 26 to July 7, 2009 of testing hospitalized patients with ILI according to various criteria. These criteria evolved up to May 12, from which point they remained as follows: all hospitalized ILI patients received a rapid influenza antigen test. Those patients who tested positive on rapid test (which is known to have low sensitivity for seasonal influenza (Uyeki et al., 2009) and for pH1N1 (CDC, 2009)), and any patient in the ICU or on a ventilator, regardless of rapid test result, received RT-PCR tests for pH1N1. We obtained a line list of confirmed or probable hospitalized cases dated July 7, and found in a preliminary analysis that all patients in this line list had a date (onset or admission) in their record no later than June 30, 7 d prior to the date of the line list. Given that >90% of hospitalizations were reported in New York within 7 d, we used this entire line list without accounting for delays in reporting of hospitalizations. Also, given that 98% of admissions occurred after May 12, we did not attempt to account for changes in testing practices before May 12. This line list included a field indicating whether the patient had been admitted to the ICU or ventilated; patients were not followed up after admission to determine if this status changed. However, a chart review of 99 hospitalized cases indicated that none had been admitted to the ICU after admission, so no effort was made to account for this limitation.

Separately, we obtained a list of 53 patients whose deaths were attributed to pH1N1, of whom 44 (83%) had been hospitalized before dying. All patients with known influenza or unexplained febrile respiratory illness at the time of death had postmortem samples and/or samples taken before they died sent for PCR testing.

New York Telephone Survey Data

To estimate levels of ILI in New York City, DOHMH conducted 1,006 surveys between May 20 and May 27, 2009, and 1,010 between June 15 and

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June 19. Interviews lasted 5 min and were conducted with households in both English and Spanish. The survey used a random-digit dialing (RDD) telephone sampling methodology to obtain data from a random sample of residential households in New York City. A nonrandom individual from each selected household was interviewed and provided information about all household members. Sampled numbers were dialed between five and 15 times to contact and interview a household, or until the sampled number was determined to be nonworking.

To account for this design, the data were weighted to the 2007 American Community Survey (ACS); respondents were weighted to householders by borough, age, gender, and race/ethnicity, and the population was weighted by age to the borough of residence.

The survey's RDD sampling methodology gave a useful overview of ILI in the community, but it has limitations. The design does not include individuals living in households only reachable by cellular telephone but not by a landline telephone number, and it omitted those living in group or institutional housing. Although households were randomly selected, for the sake of efficiency the interviewed adult was not. Instead, an available adult in the household provided information about all household members and themselves, which may have introduced bias. The results of the survey are being compiled for publication elsewhere. Here, we use summaries of these results by age group (see Text S1) as one means to provide denominators of symptomatic cases.

Data on Detection Probabilities from CDC Investigations

Sources of data include two community surveys on ILI and health-seeking behavior, and two field investigations conducted during early outbreaks of pH1N1 in the US. These sources are described in further detail elsewhere (Reed et al., 2009), but are summarized here briefly. In 2007, the Behavioral Risk Factor Surveillance Survey (BRFSS), an RDD telephone survey, included a module on ILI in nine states. This module included questions to assess the incidence of ILI, health-seeking behavior, physician diagnosis of influenza, and treatment of influenza with antiviral medications during the annual 2006–2007 influenza season. In May 2009, following the emergence of pH1N1, an RDD telephone survey sampled similar to the BRFSS was conducted in the same nine states using only the ILI module from the 2007 BRFSS and limited demographic questions. In addition, some data were available from field investigations conducted during large outbreaks of pH1N1 in one community in Chicago and a university campus in Delaware. Investigations of these outbreaks consisted of household interviews in a Chicago neighborhood and an online survey of students and faculty in Delaware. These data were used to inform detection probabilities. In addition, these data were used to inform a prior distribution on the ratio between symptomatic and medically attended cases, $c_{M|S}$: these surveys estimated that between 42% and 58% of symptomatic ILI patients sought medical attention (Reed et al., 2009).

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Analysis

Estimation of the probabilities of primary interest, $c_{H|S}$, $c_{I|S}$, and $c_{D|S}$, respectively the sCHR, sCIR, and sCFR, was undertaken using a Bayesian evidence synthesis framework (Goubar et al., 2008). Details are given in Text S1, and a schematic illustration of the model is given in Figure A7-2. Briefly, in this framework, prior information about the quantities of interest (including the uncertainty associated with this prior information) is combined with the information coming from the observed cases at each severity level to derive a *posterior distribution* on these quantities. This posterior distribution fully reflects all information about the quantities of interest that is contained in the prior distribution and the observed data. Specifically, it was assumed that detected cases *O* at each level of severity—medically attended (*M*), hospitalized (*H*), ICU-admitted (*I*), and fatal (*D*)—represented binomially distributed samples from the true number of cases *N* at the corresponding level of severity, in the given location (New York, abbreviated *N* or Milwaukee, abbreviated *W*), with probability equal to the probability of detection at each level (*d*). The probability *d* for each level was informed by evidence on the probability of testing at each level of severity (which may have depended on the sensitivity of the rapid test if this was required for PCR testing) and the sensitivity of the PCR test (Table A7-1). Thus, for example, we defined

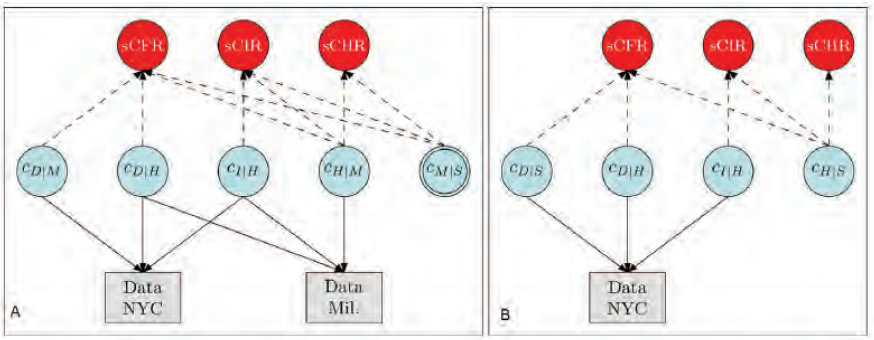

FIGURE A7-2 Schematic illustration of the relationship between the observed data (rectangles) and the conditional probabilities (blue circles). The key quantities of interest, sCHR, sCIR, and sCFR, are products of the relevant conditional probabilities. (A) Approach 1, synthesizing data from New York City and Milwaukee. Note that $c_{M/S}$ (double circle) is informed by prior information (Reed et al., 2009) rather than observed data. (B) Approach 2, using data from New York City only, including the telephone survey. Variables: $c_{D/M}$: the ratio of non-hospitalized deaths to medically-attended cases; $c_{D/H}$: the ratio of deaths to hospitalized cases; $c_{I/H}$: the ratio of cases admitted to intensive care or using mechanical ventilation to hospitalized cases; $c_{H/M}$: the ratio of hospitalized cases to medically attended cases; $c_{M/S}$: the ratio of medically attended cases to symptomatic cases; $c_{D/S}$: the ratio of deaths to symptomatic cases; $c_{H/S}$: the ratio of hospitalized cases to symptomatic cases.

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TABLE A7-1 Detection Probabilities and Their Prior Distributions

Detection Probability	Components	Distributions	Rationale
d_M Medically attended illness	d_{M1} probability of testing, follow-up, and reporting among medically attended patients	Uniform (0.2,0.35)	Data from CDC epi-aids in Delaware and Chicago (Reed et al., 2009)
$d_M = d_{M1}d_{M2}$	d_{M2} PCR test sensitivity	Uniform (0.95,1)	Assumption (Reed et al., 2009)
d_{HW} Hospitalization (Milwaukee)	d_{HW1} probability of testing, follow-up, and reporting among hospitalized patients	Uniform (0.2,0.4)	Assumption (Reed et al., 2009)
$d_{HW} = d_{HW1}d_{HW2}$	d_{HW2} PCR test sensitivity	Uniform (0.95,1)	Assumption (Reed et al., 2009)
d_{IW} ICU admission (Milwaukee)	d_{IW1} probability of testing, follow-up, and reporting among hospitalized patients	Uniform (0.2,0.4)	Assumption (Reed et al., 2009)
$d_{IW} = d_{IW1}\ d_{IW2}$	d_{IW2} PCR test sensitivity	Uniform (0.95,1)	Assumption (Reed et al., 2009)
d_{DW} Deaths (Milwaukee)	PCR test sensitivity and other detection	Beta (45,5)	Assumption (Reed et al., 2009) (mean 0.9, standard deviation 0.05)
d_{HW} Hospitalization (New York City)	d_{HN1} probability of oerforming PCR (rapid A positive or ICU/ventilated)	0.27+0.73 (Uniform (0.2,0.71))	27% of test cases were ICU-admitted so received PCR test; remainder were tested if rapid A positive, which has a sensitivity of 0.2 (Uyeki et al., 2009) to 0.71 (sensitivity among ICU patients in NYC)
$d_{HN} = d_{HN1}d_{HN2}$	d_{HN2} PCR test sensitivity	Uniform (0.95,1)	Assumption (Reed et al., 2009)
d_{IN} ICU/ventilation (New York City)	PCR test sensitivity	Uniform (0.95,1)	Assumption (Reed et al., 2009)
d_{DN} Deaths (New York City)	PCR test sensitivity and other detection	Beta (45,5)	Assumption (Reed et al., 2009)

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the probability of detecting a hospitalized case in New York as $d_{HN} = d_{HN1}d_{HN2}$, where d_{HN1} was the probability of performing an RT-PCR–based test and d_{HN2} was the sensitivity of that test. Hence, the observed number of hospitalized patients in New York, O_{HN}, was assumed to be distributed as $Binomial(N_{HN},d_{HN})$.

We noted that the ratios $c_{H|S}$, $c_{I|S}$, and $c_{D|S}$ can be built up multiplicatively from simpler components: for instance, the ratio of deaths to symptomatic infections may be expressed as $c_{D|S} = c_{D|H}c_{H|M}c_{M|S}$, the product of the ratios of deaths: hospitalizations, of hospitalizations:medically attended cases, and of medically attended cases:symptomatic cases. These ratios of increasing severity are similar to conditional probabilities but are not strictly so in all cases, since for example some deaths in New York City occurred in persons who were not hospitalized. For this reason we model deaths separately among hospitalized and nonhospitalized patients, i.e., $c_{D|S} = c_{D|H}c_{H|M}c_{M|S} + c_{D|M}c_{M|S}$. For each observed level of severity (medically attended, hospitalized, ICU, death), the true number of cases was modeled as a binomial sample from the true number of cases at an appropriate lower level, hence

$$N_{Mk} \sim Binomial\ (N_{Sk},c_{M|S});$$
$$N_{Hk} \sim Binomial\ (N_{Mk},c_{H|M});$$
$$N_{Ik} \sim Binomial\ (N_{Hk},c_{I|H});$$
$$N_{Dk} \sim Binomial\ (N_{Hk},c_{D|H}) + Binomial\ (N_{Mk},c_{D|M}),$$

where the first subscript indicates severity and the second indicates the population (New York, Milwaukee to May 20, Milwaukee to June 14).

In Approach 1 (New York and Milwaukee data combined), for the unobserved level of severity (symptomatic cases) we used a prior distribution of $c_{M|S} \sim Beta$ (51.5,48.5) to represent uncertainty between 42% and 58% (Reed et al., 2009); this distribution has 90% of its mass in this range, with a mean of 0.515. The main analysis of this first approach was performed using prior information to inform the detection probabilities. An additional "naïve" analysis was performed, in which the detection probabilities *d* were set equal to 1 at all levels of severity. Our prior distributions for the number of symptomatic cases in New York (overall and by age) were taken as ranging uniformly between zero and the proportion reporting ILI in the telephone survey (with the upper bound of that distribution itself having a prior distribution reflecting the confidence bounds of the survey results; details in Text S1). For Milwaukee, the prior distribution on symptomatic cases was taken as uniform between 0 and 25% of the population.

In Approach 2 (New York case data and telephone survey data), we made the assumption that self-reported ILI cases represented symptomatic pH1N1 infection, and used the mean and 95% confidence intervals from that survey to define a prior distribution on the number of symptomatic cases overall and by age group. We then used observed hospitalizations, ICU/ventilator use, and fatalities along with prior distributions on detection probabilities as above to inform estimates

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of true numbers of hospitalizations, ICU/ventilator use, and fatalities, and these in turn were used to estimate sCHR, sCIR, and sCFR.

The evidence was synthesized through a full probability model in a Bayesian framework, implemented in the OpenBUGS software (Thomas et al., 2006), which uses Markov chain Monte Carlo to sample from the posterior distribution.

Results

Table A7-2 shows the numbers of medically attended cases, hospitalizations, ICU admissions, and deaths in the two cities, with the Milwaukee data separated into the period (to May 20) for which we believe medically attended cases were consistently detected, and the period (to June 14) for which we consider only hospitalized cases, ICU admissions, and deaths.

Approach 1

We considered two alternatives to estimate the ratios of interest from the combined New York and Milwaukee data, using self reported rates of seeking medical attention to establish the denominator. First, we obtained a naïve estimate of the ratios of deaths to hospitalizations, ignoring differences in detection across levels of severity; and second, we obtained an estimate that incorporated evidence and expert opinion on the detection probabilities at each level of severity.

The naïve estimate would suggest a median (95% CI) ratio of deaths to hospitalizations ($c_{D|H}$) of 4.3% (95% CI 3.2%–5.5%), of ICU admissions to hospitalizations ($c_{I|H}$) of 25% (95% CI 22%–27%), and of hospitalizations to medically attended cases ($c_{H|M}$) of 3.1% (95% CI 2.0%–4.4%). The ratio of deaths outside of hospitals to medically attended cases ($c_{D|M}$) is estimated to be 0.03% (95% CI 0.01%–0.06%). Incorporating the prior evidence that 42%–58% of symptomatic ILI is medically attended, this would imply a naïve estimate of the sCFR ($c_{D|S} = c_{D|H}c_{H|M}c_{M|S} + c_{D|M}c_{M|S}$) of 0.081% (95% CI 0.049%–0.131%), a corresponding estimate of the sCIR ($c_{I|S} = c_{I|H}c_{H|M}c_{M|S}$) of 0.38% (95% CI 0.24%–0.58%), and an estimate of the sCHR ($c_{H|S} = c_{H|M}c_{M|S}$) of 1.55% (95% CI 0.98%–2.32%). If one assumes that detection probabilities are no worse at higher levels of severity than at lower levels, then these figures would be reasonable *upper bounds* on the symptomatic CFRs and CIRs.

Incorporating prior evidence of the detection probabilities at each level of severity, and thus accommodating structural and statistical uncertainties in these probabilities, we estimated that ratio of deaths to hospitalizations ($c_{D|H}$) of 2.7% (95% CI 1.8%– 3.8%) of ICU admissions to hospitalizations ($c_{I|H}$) of 17% (95% CI 12%–21%) and of hospitalizations to medically attended cases ($c_{H|M}$) of 2.9% (95% CI 1.6%–5.0%). The ratio of deaths outside of hospitals to medically attended cases ($c_{D|M}$) is estimated to be 0.02% (95% CI 0.01%–0.04%).

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TABLE A7-2 Cases at Each Level of Severity

		Severity				
		Medically Attended	Hospitalized		ICU-admitted	Dead
Location	Age Group	to May 20	to May 20	to Jun 14	to Jun 14	to Jun 14
Milwaukee	0-4	126 (16%)	7 (28%)	27 (18%)	5 (20%)	0
	5-17	470 (60%)	6 (24%)	29 (20%)	7 (26%)	2 (50%)
	18-64	189 (24%)	12 (48%)	87 (59%)	14 (52%)	2 (50%)
	65+	3 (0.4%)	0	4 (13%)	1 (4%)	0
	Total	788	25	147	25	4
	Age Group	Medically Attended	Hospitalized		ICU-admitted	Dead (total)/Dead but not hospitalized
New York	0-4	—	225 (23%)		44 (17%)	2 (4%)/2
	5-17	—	197 (20%)		51 (20%)	2 (4%)/2
	18-64	—	518 (52%)		147 (57%)	46 (87%)/6
	65+	—	56 (6%)		15 (6%)	3 (6%)/0
	Total	—	996		257	53/9

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Table A7-3 shows the estimates for the quantities of primary interest, overall and by age group, in the analysis that incorporated prior evidence of detection probabilities. Here, the posterior median estimate for the sCFR is 0.048% (95% CI 0.026%–0.096%) and for the sCIR is 0.239% (95% CI 0.134%–0.458%). The sCHR is estimated as 1.44% (95% CI 0.83%–2.64%).

Estimates of each of these severity measures vary dramatically by age group, with the lowest severity by each measure in the 5–17 year age group. Comparing the two groups for which we have the most data, the relative risk of death for a symptomatic 18–64-year-old compared to a symptomatic 5- to 17-year-old is 15 (95% CI 5– 57). The corresponding relative risks of ICU admission and hospitalization are 5 (95% CI 2–13) and 5 (95% CI 2–12) respectively. The Bayesian framework provides a natural way to estimate confidence (measured as the posterior probability) that one rate is higher than another. The probability that severity is higher in the 18- to 64-y age group than in the 5–17 age group is >99.9%, for each of fatality, ICU admission, and hospitalization respectively. The data are too sparse to say with confidence whether adults over 65 or under 65 have greater severity. For example, among the four age groups, the symptomatic case-fatality ratio is highest in the 18- to 64-y age group with posterior probability 62%, and in those 65 and over with probability 38%. The symptomatic case-ICU admission ratio is highest in 18- to 64-year-olds with posterior probability 51% and in those over 65 with posterior probability 38%. The sCHR is highest in 18- to 64-year-olds with posterior probability 37% and in those over 65 with posterior probability 37%.

TABLE A7-3 Posterior Median (95% CI) Estimates of the sCFR, sCIR, and sCHR, by Age Group, Based on a Combination of Data from New York City and Milwaukee, and Survey Data on the Frequency of Medical Attendance for Symptomatic Cases

Age	sCFR	sCIR	sCHR
0-4	0.026% (0.006%-0.092%)	0.321% (0.133%-0.776%)	2.45% (1.10%-5.56%)
5-17	0.010% (0.003%-0.031%)	0.106% (0.043%-0.244%)	0.61% (0.27%-1.34%)
18-64	0.159% (0.066%-1.471%)	0.542% ((0.230%-1.090%)	3.00% (1.35%-5.92%)
65+	0.090% (0.008%-1.471%)	0.327% (0.035%-4.711%)	1.84% (0.21%-25.38%)
Total	0.048% (0.026%-0.096%)	0.239% (0.134%-0.458%)	1.44% (0.83%-2.64%)

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Approach 2

Table A7-4 shows the estimates for the sCFR, sCIR, and sCHR, by age group, when self-reported ILI is used as the denominator for total symptomatic cases. Overall these estimates are: sCFR= 0.007% (95% CI 0.005%–0.009%), sCIR =0.028% (95% CI 0.022%–0.035%) and sCHR =0.16% (95% CI 0.12%–0.26%). Compared to Approach 1, these estimates are nearly an order of magnitude smaller, and the age distribution differs. The relative risks for each severity in the 18- to 64-year-old group compared to the 5- to 17-year-old group are 7 (95% CI 3–25) for fatalities, 1.5 (95% CI 0.9–2.5) for ICU admissions, and 1.4 (95% CI 0.9–2.1) for hospitalizations. The CFR is highest in the 18–64 y group with posterior probability 52%. In contrast to Approach 1, the CIR is highest among 0- to 4-year-olds, with posterior probability 79%, and the CHR is highest among 0- to 4-year-olds, with posterior probability 99%.

Discussion

We have estimated, using data from two cities on tiered levels of severity and self-reported rates of seeking medical attention, that approximately 1.44% of symptomatic pH1N1 patients during the spring in the US were hospitalized; 0.239% required intensive care or mechanical ventilation; and 0.048% died. Within the assumptions made in our model, these estimates are uncertain up to a factor of about 2 in either direction, as reflected in the 95% credible intervals associated with the estimates. These estimates take into account differences in detection and reporting of cases at different levels of severity, which we believe, based on some evidence, to be more complete at higher levels of severity. With-

TABLE A7-4 Posterior Median (95% CI) Estimates of the sCFR, sCIR, and sCHR by Age Group, Using Self-Reported ILI as the Denominator of Symptomatic Cases

Age	sCFR	sCIR	sCHR
0-4	0.004% (0.001%-0.011%)	0.044% (0.026%-0.078%)	0.33% (0.21-0.63%)
5-17	0.002% (0.000%-0.004%)	0.019% (0.013%-0.027%)	0.11% (0.08%-0.18%)
18-64	0.010% (0.007%-0.016%)	0.029% (0.021%-0.040%)	0.15% (0.11%-0.25%)
65+	0.010% (0.003%-0.025%)	0.030% (0.016%-0.055%)	0.16% (0.10%-0.30%)
Total	0.007% (0.005%-0.009%)	0.028% (0.022%-0.035%)	0.16% (0.12%-0.26%)

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out such corrections for detection and reporting, estimates are approximately two-fold higher for each level of severity. Using a second approach, which uses self-reported rates of influenza-like illness in New York City to estimate symptomatic infections, we have estimated rates approximately an order of magnitude lower, with a symptomatic sCHR of 0.16%, an sCIR of 0.028%, and an sCFR of 0.007%. In both approaches, the sCFR was highest in adults (in Approach 1, 18–64 y, while Approach 2 cannot distinguish whether it is higher in that group or in those 65y and older) and lowest in school-aged children (5–17 y). Data on children 0–4 and adults 65 and older were relatively sparse, making statements about their ordering more difficult. Nonetheless, these findings, along with surveillance data on the age specific rates of hospitalization and death in this pandemic (http://www.cdc.gov/vaccines/recs/ACIP/downloads/mtg-slidesoct09/12-2-flu-vac.pdf), indicate that the burden of hospitalization and mortality in this pandemic falls on younger individuals than in seasonal influenza (Thompson et al., 2009). A shift in mortality toward nonelderly persons has been observed in previous pandemics and the years that immediately followed them (Simonsen et al., 1998).

These estimates are valuable for attempting to project, in approximate terms, the possible severity of a fall–winter wave of pH1N1, under the assumption that the virus does not change its characteristics. In the 1957 and 1968 pandemics, it appears that perhaps 40%–60% of the population was serologically infected, and that of those, 40%–60% were symptomatic (Jordan et al., 1958; Clarke et al., 1958; Davis et al., 1970; Foy et al., 1976). Current estimates of the transmission of pH1N1 range between about 1.4 and about 2.2, consistent with estimates of the reproduction numbers from prior pandemics (Boelle et al., 2009; Fraser et al., 2009; Nishiura et al., 2009a; White et al., 2009; Pourbohloul et al., 2009). To convert our estimates into population impacts, one needs to make an assumption about the attack rate and its age distribution. For each 10% of the US population symptomatically infected (with the same age distribution observed in the spring wave), our Approach 1 estimates suggest that approximately 7,800–29,000 deaths (3–10 per 100,000 population), 40,000–140,000 intensive care admissions (13–46 per 100,000 population), and 250,000–790,000 hospitalizations (170–630 per 100,000 population) will occur. These estimates scale up or down in proportion to the attack rate; for example, they should be doubled if 20% of the population were symptomatic, producing for example 15,000–58,000 deaths (6–20 per 100,000 population). Approach 2 suggests much smaller figures (for each 10% of the population symptomatic) of 1,500–2,700 deaths (0.5–0.9 per 100,000), 6,600–11,000 ICU admissions/uses of mechanical ventilation (22–35 per 100,000), and 36,000–78,000 hospitalizations (12–26 per 100,000). Again, these numbers should be scaled in proportion to the attack rate.

To date, symptomatic attack rates seem to be far lower than 25% in both the completed Southern Hemisphere winter epidemic and the autumn epidemic in progress in the US; severe outcomes seem to be considerably less numerous than those described for Approach 1 with a 25% attack rate. In New Zealand, just

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under 2% of the population consulted a general practitioner (GP) for ILI during the winter wave of the pandemic (http://www.moh.govt.nz/moh.nsf/indexmh/influenza-a-h1n1-update-138-180809), which is consistent with an attack rate significantly lower than 25%, though somewhat higher than the GP consultation rate observed in severe seasonal flu outbreaks such as those in 2003 and 2004 (http://www.surv.esr.cri.nz/PDF_surveillance/Virology/FluWeekRpt/2004/FluWeekRpt200444.pdf).

The level of severity estimated for the United States reflects in part the availability of antiviral treatment and other medical interventions that will not be available in all populations. Oseltamivir use was common in Milwaukee (Milwaukee Department of Health, unpublished data), and although the health care system was put under strain in both cities studied, there was no shortage of intensive care or other life-saving medical resources. In a situation of greater stress on the health system, as has been observed in certain locations in the Southern Hemisphere (Bita, 2009; Newton, 2009); http://www.capegateway.gov.za/eng/your_gov/3576/news/2009/aug/185589), or in areas that lack a high-quality health care system, severity might increase in proportion to decreased availability of adequate medical attention. Worryingly, our estimates of the proportion of symptomatic cases requiring mechanical ventilation or ICU care was approximately 4–5 × our estimate of the sCFR. It is possible that a substantial proportion of those admitted to ICUs could have died without intensive care. In populations without widespread access to intensive care, our results suggest that the same burden of disease could lead to a death rate 4–5 × higher. Likewise, a change in the virus to become more virulent or resistant to existing antiviral drugs, or the emergence of more frequent bacterial coinfections, could increase the severity of infection compared to that observed so far.

Estimates of severity for an infection such as influenza are fraught with uncertainties (Lipsitch et al., 2009a). Our analysis has accounted for many of these uncertainties, including imperfect detection and reporting of cases, bias due to delays between events (such as the delay from illness onset to death), and the statistical uncertainties associated with limited numbers of cases, hospitalizations, and deaths. Another major source of difficulty is the spatial and temporal variation in reporting effort for mild and severe cases; for example, most jurisdictions in the US stopped reporting mild cases on or before the second week of May, but this change varied by jurisdiction. We have attempted to avoid this difficulty by focusing on individual jurisdictions—New York and Milwaukee—for which the approach to reporting was relatively stable over time. One limitation is that Milwaukee changed its guidance during our surveillance period from testing of all symptomatic cases to testing of all symptomatic health care workers but only moderate-tosevere cases in non-health care workers. We believe that testing policies did not change dramatically during this period, because the proportion of hospitalized cases remained fairly constant; however, the sample size before this change in guidance was

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small. Thus, our estimates should be seen as being the risk of severe outcome among persons with symptoms, possibly biased somewhat toward those with more severe symptoms.

Despite our efforts to account for sources of uncertainty, several others remain and have not been accounted for in our analysis. First, we have assumed that for each level of severity (from medically attended up to fatal), case reporting was equal across age groups; for example, we assumed that medically attended cases were as likely to be reported for young children as for adults. It is possible that this is not the case, for example that mild cases were more likely to come to medical attention if they occurred in children than if they occurred in adults. If this were true, our conclusion that severity was higher in adults than children could be partly a result of differential reporting.

Second, the overall estimates of severity (not stratified by age group) reflect the age composition of cases in the sample we studied, especially the age composition of the lowest level of severity examined, medically attended illness. Among medically attended cases in Milwaukee, 60% were in the 5–17 y age group, the one in which severe outcomes were the least likely. A preponderance of cases within this age group may be typical of the early part of influenza epidemics, and while it has been argued that there is a shift from younger to older age groups in seasonal influenza (Brownstein et al., 2005) as the epidemic progresses, there is evidence, at least from the 1957 pandemic, that attack rates remain higher in children than adults throughout the course of the epidemic (Jordan et al., 1958). Since severity of pH1N1 influenza appears to be considerably higher in adults, a shift in the burden of disease from children to adults as the epidemic progresses would lead to an increase in average severity.

We note that the association between age and severity may also affect observed trends in the characteristics of cases. The World Health Organization has noted worldwide a shift from younger to older mean age among confirmed cases (http://www.who.int/csr/ disease/swineflu/notes/h1n1_situation_20090724/en/index.html). If severity is lowest among children, this upward shift in age distribution may partially reflect a shift toward detection of more severe cases, rather than a true shift in the ages of those becoming infected.

Third, the symptomatic CFR, CIR, and CHR are dependent upon our estimates of the true number of symptomatic cases, N_{iSk}, and hence are sensitive to the choice of prior distribution for these, as well as to our prior assumptions on the detection probabilities. In particular, if the probability that symptomatic patients seek medical attention and are confirmed is lower than we assume in our prior distributions, then there are more cases than are inferred by our model, and severity is correspondingly lower than our estimates. If the probability of detecting severe outcomes (hospitalizations, deaths, ICU) is lower than our prior distributions reflect, then there are more severe outcomes than our model infers, so severity is correspondingly higher.

Finally, the small sample sizes in some age groups, the over-65 year olds in

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particular, lead to large uncertainty in the age-specific estimates. This level of uncertainty is reflected in the wide 95% credible intervals for the estimates.

Our two approaches yield estimates that differ by almost an order of magnitude in the severity of the infection, on each of the three measures considered. How should planners evaluate these contrasting estimates? The lower estimates, using the denominator of self-reported ILI in New York City, may reasonably be considered lower bounds on the true ratios. ILI is thought to be relatively rare in May–June, hence true ILI was probably largely attributable to pH1N1 during this period in New York City. However, self-reported ILI is notoriously prone to various biases, most of which suggest that true rates are probably lower than selfreported rates. A previous telephone survey conducted in New York City found that 18.5% of New Yorkers reported ILI in the 30 d prior to being surveyed in late March 2003 (Metzger et al., 2004), which represented a period of above-baseline but declining influenza activity nationally and no known influenza outbreaks in New York City (Metzger et al., 2004). The survey was repeated in October–November 2003, prior to the appearance of significant influenza activity, and 20.8% reported ILI in the 30 d prior (Metzger et al., 2004). If these surveys represent a baseline level of self-reported ILI in the absence of significant influenza activity, then the approximately 12% self-reported ILI in the telephone survey is substantially lower than this out-of-season baseline, suggesting that it likely overstates the total burden of symptomatic pH1N1 disease. The lower estimates are also broadly consistent with estimates from New Zealand, which has experienced a nearly complete influenza season (Baker et al., 2009), and from Australia (http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm/$FILE/ozflu-no14-2009.pdf). The higher estimates, on the other hand, were obtained using ratios of hospitalizations to confirmed medically attended cases and self-reported rates of seeking medical attention for ILI, which have been consistently measured in the range of about 40%–60%. It is possible that the special efforts of the New York City health department to identify pH1N1-related fatalities (including those not hospitalized) provides a fuller picture of the total number of deaths from this infection. Interestingly, New York City reports about the same number of hospitalizations for our study period (996) as New Zealand reports up to mid-August (972), but 3.5 × as many deaths (53 versus 16) (Baker et al., 2009). If this discrepancy reflects more complete ascertainment of deaths in New York City, it may account for much of the difference between our higher estimates of case-fatality ratios and those from New Zealand. Given the number of uncertainties cataloged above (which apply also to other jurisdictions within and outside the US), we believe that our two approaches probably bracket the reasonable range of severity for the US spring wave.

Age-specific severity patterns as estimated here are largely consistent with those one would obtain by simply comparing the incidence of confirmed cases, hospitalizations, and deaths in the US as a whole for a similar period (Reed et al., 2009), although the estimates for persons over age 65 are highly uncertain,

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with 95% credible intervals spanning several orders of magnitude, due to the very small number of individuals in our sample from that age group.

The estimates provided here may be compared to those for seasonal influenza. Compared to seasonal influenza, these estimates (assuming a 25% symptomatic attack rate) suggest a number of deaths in the US that could range from about half the number estimated for an average year to nearly twice the number estimated for an average year (Thompson et al., 2003) (Approach 1), or a range about 10-fold lower than that (Approach 2); however, the deaths would be expected to occur in younger age groups, compared to the preponderance of deaths in persons over 65 in seasonal influenza. Such a shift in age distribution is typical for pandemics and the years that follow them (Simonsen et al., 1998). Under Approach 1, and assuming a typical pandemic symptomatic attack rate of 25%, the estimated number of hospitalizations for an autumn–winter pandemic wave is considerably more than the approximately 300,000 estimated for typical seasonal influenza (Thompson et al., 2004), whereas Approach 2 suggests a number between 1/3 and 2/3 of that observed in typical seasonal influenza. It should be noted that most hospitalizations, and about 90% of deaths attributed to seasonal influenza, are categorized as respiratory and circulatory, not including the more specific diagnoses of pneumonia and influenza; that is, they are due to myocardial infarction, stroke, and other proximate causes, but are nonetheless likely initially caused by influenza infection (Reichert et al., 2004). The deaths included in our study may have reflected more directly influenza-related causes and may not reflect these indirect causes of influenza-related death. Indeed, it is unclear whether the proportion of indirect respiratory and circulatory causes of death and hospitalization will be as high in this pandemic year, given the younger ages involved in most severe cases. Given these differences between the estimates here based on virologically confirmed deaths and the ecological statistical approach to estimating influenza-attributable deaths and hospitalizations for seasonal influenza, it will be difficult to interpret comparisons between the two types of estimates until (after the pandemic has finished) comparisons can be made between the ecological and the confirmed-case approach to estimating burden of hospitalization and deaths.

Our estimate of the sCFR is lower than those provided by Garske et al. (2009), which ranges from 0.11% to 1.47% overall, and between 0.59% and 0.78% in the US, but which was based on confirmed plus probable (rather than symptomatic) cases. Nishiura et al. (2009b) estimate that between 0.16% and 4.48% of confirmed cases in the United States and Canada were fatal. Our Approach 1 includes a probability of approximately 1/8 (~50% probability of symptomatic patients seeking care × ~28% probability of testing and report for a symptomatic × ~97% test sensitivity, with associated ranges for each; Table A7-1) to convert symptomatic into medically attended cases, and this factor accounts for most of the difference between our estimates and the earlier estimates based on confirmed or confirmed plus probable cases. Wilson and

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Baker (2009), on the other hand, use a denominator of infections (rather than symptomatic or confirmed cases) and estimate a range of CFR from 0.0004% up to 0.6%. Our estimates fall in the middle part of this range. More recently, Baker et al. (2009) used their estimates of the total incidence of symptomatic disease in New Zealand to estimate an sCFR of 0.005%, equal to the lower end of the credible interval for our Approach 2 estimate, and considerably below our Approach 1 estimate. The generally downward trend in the estimates of severity reflects early ascertainment of more severe cases (e.g., mainly hospitalized cases in the early Mexican outbreak); the authors of each of these earlier reports recognized and discussed the issue of ascertainment and its potential biasing effect on severity estimates.

While we have been careful to highlight uncertainties in the estimates of severity, our results are sufficiently well-resolved to have important implications for ongoing pH1N1 pandemic planning. The estimated severity indicates that a reasonable expectation for the autumn–winter pandemic wave in the US is a death toll less than or equal to that which is typical for seasonal influenza, though possibly with considerably more deaths in younger persons. If attack rates in the autumn match those of prior pandemics and hospitalization rates are comparable to our estimates using Approach 1, the surge of ill individuals and subsequent burden on hospitals and intensive care units could be large. However, using Approach 2, estimates of hospitalizations and ICU admissions are considerably lower. Either set of estimates places the epidemic within the lowest category of severity considered in pandemic planning conducted prior to the appearance of pH1N1 in the United States, which considered CFRs up to 0.1% (http://www.flu.gov/professional/community/community_mitigation.pdf).

Continued close monitoring of severity of pandemic (H1N1) 2009 influenza is needed to assess how patterns of hospitalization, intensive care utilization, and fatality are varying in space and time and across age groups. Increases in severity might reflect changes in the host population—for example, infection of persons with conditions that predispose them to severe outcomes—or changes in the age distribution of cases—for example a shift toward adults, in whom infection is more severe. Changes in severity might also reflect changes in the virus or variation in the access and quality of care available to infected persons.

Supporting Information

Text S1 Supplementary methods.
Found at: doi:10.1371/journal.pmed.1000207.s001 (0.43 MB DOC)

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Author Contributions

ICMJE criteria for authorship read and met: AMP DDA TNYCSFIT AH CR SR BSC LF PB ML. Agree with the manuscript's results and conclusions: AMP DDA TNYCSFIT AH CR SR BSC LF PB ML. Designed the experiments/the study: TNYCSFIT SR BSC LF ML. Analyzed the data: AMP LF ML. Collected data/did experiments for the study: TNYCSFIT AH LF PB. Enrolled patients: TNYCSFIT AH. Wrote the first draft of the paper: ML. Contributed to the writing of the paper: AMP DDA TNYCSFIT AH CR SR BSC LF PB. Contributed to model development: AMP. Contributed to model development and assessment: DDA. The New York City Swine Flu Investigation Team, who designed the surveillance for NYC, collected, cleaned, and did initial analyses of the data, is responsible for the data integrity of the NYC data and shared it with the other authors, and played a significant role in revising the paper and thinking through the analyses.

Editor's Summary

Background

Every winter, millions of people catch influenza—a viral infection of the airways—and about half a million people die as a result. In the US alone, an average of 36,000 people are thought to die from influenza-related causes every year. These seasonal epidemics occur because small but frequent changes in the virus mean that an immune response produced one year provides only partial protection against influenza the next year. Occasionally, influenza viruses emerge that are very different and to which human populations have virtually no immunity. These viruses can start global epidemics (pandemics) that kill millions of people. Experts have been warning for some time that an influenza pandemic is long overdue and in, March 2009, the first cases of influenza caused by a new virus called pandemic (H1N1) 2009 (pH1N1; swine flu) occurred in Mexico. The virus spread rapidly and on 11 June 2009, the World Health Organization declared that a global pandemic of pH1N1 influenza was underway. By the beginning of November 2009, more than 6,000 people had died from pH1N1 influenza.

Why Was This Study Done?

With the onset of autumn—drier weather and the return of children to school help the influenza virus to spread—pH1N1 cases, hospitalizations, and deaths in the Northern Hemisphere have greatly increased. Although public-health officials have been preparing for this resurgence of infection, they cannot be sure of its impact on human health without knowing more about the severity of pH1N1 infections. The severity of an infection can be expressed as a case-fatality ratio

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(CFR; the proportion of cases that result in death), as a case-hospitalization ratio (CHR; the proportion of cases that result in hospitalization), and as a case-intensive care ratio (CIR; the proportion of cases that require treatment in an intensive care unit). Because so many people have been infected with pH1N1 since it emerged, the numbers of cases and deaths caused by pH1N1 infection are not known accurately so these ratios cannot be easily calculated. In this study, the researchers estimate the severity of pH1N1 influenza in the US between April and July 2009 by combining data on pH1N1 infections from several sources using a statistical approach known as Bayesian evidence synthesis.

What Did the Researchers Do and Find?

By using data on medically attended and hospitalized cases of pH1N1 infection in Milwaukee and information from New York City on hospitalizations, intensive care use, and deaths, the researchers estimate that the proportion of US cases with symptoms that died (the sCFR) during summer 2009 was 0.048%. That is, about 1 in 2,000 people who had symptoms of pH1N1 infection died. The "credible interval" for this sCFR, the range of values between which the "true" sCFR is likely to lie, they report, is 0.026%–0.096% (between 1 in 4,000 and 1 in 1,000 deaths for every symptomatic case). About 1 in 400 symptomatic cases required treatment in intensive care, they estimate, and about 1 in 70 symptomatic cases required hospital admission. When the researchers used a different approach to estimate the total number of symptomatic cases—based on New Yorkers' self-reported incidence of influenza-like-illness from a telephone survey—their estimates of pH1N1 infection severity were 7- to 9-fold lower. Finally, they report that the sCFR and the sCIR were highest in people aged 18 or older and lowest in children aged 5–17 years.

What Do These Findings Mean?

Many uncertainties (for example, imperfect detection and reporting) can affect estimates of influenza severity. Even so, the findings of this study suggest that an autumn–winter pandemic wave of pH1N1 will have a death toll only slightly higher than or considerably lower than that caused by seasonal influenza in an average year, provided pH1N1 continues to behave as it did during the summer. Similarly, the estimated burden on hospitals and intensive care facilities ranges from somewhat higher than in a normal influenza season to considerably lower. The findings of this study also suggest that, unlike seasonal influenza, which kills mainly elderly adults, a high proportion of deaths from pH1N1 infection will occur in nonelderly adults, a shift in age distribution that has been seen in previous pandemics. With these estimates in hand and with continued close monitoring of the pandemic, public-health officials should now be in a better position to plan effective strategies to deal with the pH1N1 pandemic.

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Additional Information

Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1000207.

- The US Centers for Disease Control and Prevention provides information about influenza for patients and professionals, including specific information on pandemic H1N1 (2009) influenza
- Flu.gov, a US government Web site, provides access to information on H1N1, avian and pandemic influenza
- The World Health Organization provides information on seasonal influenza and has detailed information on pandemic H1N1 (2009) influenza (in several languages)
- The UK Health Protection Agency provides information on pandemic influenza and on pandemic H1N1 (2009) influenza
- More information for patients about H1N1 influenza is available through Choices, an information resource provided by the UK National Health Service

References

Andreasen V, Viboud C, Simonsen L (2008) Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: Implications for pandemic control strategies. J Infect Dis 197: 270–278.

Baker MG, Wilson N, Huang QS, Paine S, Lopez L, et al. (2009) Pandemic influenza A(H1N1)v in New Zealand: The experience from April to August 2009. Euro Surveill 14: pii: 19319. Available: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId= 19319. Accessed: 15 September 2009.

Bita N (2009 August 04) No bed for swine flu man on life support. The Australian.

Boelle PY, Bernillon P, Desenclos JC (2009) A preliminary estimation of the reproduction ratio for new influenza A(H1N1) from the outbreak in Mexico, March-April 2009. Euro Surveill 14: pii =19205.

Brownstein JS, Kleinman KP, Mandl KD (2005) Identifying pediatric age groups for influenza vaccination using a real-time regional surveillance system. Am J Epidemiol 162: 686–693.

CDC (2009) Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States, 2009. MMWR Morb Mortal Wkly Rep 58: 826–829.

Clarke SK, Heath RB, Sutton RN, Stuart-Harris CH (1958) Serological studies with Asian strain of influenza A. Lancet 1: 814–818.

Davis LE, Caldwell GG, Lynch RE, Bailey RE, Chin TD (1970) Hong Kong influenza: The epidemiologic features of a high school family study analyzed and compared with a similar study during the 1957 Asian influenza epidemic. Am J Epidemiol 92: 240–247.

Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, et al. (2006) Strategies for mitigating an influenza pandemic. Nature 442: 448–452.

Foy HM, Cooney MK, Allan I (1976) Longitudinal studies of types A and B influenza among Seattle schoolchildren and families, 1968-74. J Infect Dis 134: 362–369.

Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, et al. (2009) Pandemic potential of a strain of influenza A (H1N1): early findings. Science 324: 1557–1561.

Garske T, Legrand J, Donnelly CA, Ward H, Cauchemez S, et al. (2009) Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ 339: b2840.

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Goubar A, Ades AE, De Angelis D, McGarrigle CA, Mercer CH, et al. (2008) Estimates of human immunodeficiency virus prevalence and proportion diagnosed based on Bayesian multiparameter synthesis of surveillance data. J R Stat Soc Ser A 171: 1–27.

Halloran ME, Ferguson NM, Eubank S, Longini IM Jr, Cummings DA, et al. (2008) Modeling targeted layered containment of an influenza pandemic in the United States. Proc Natl Acad Sci U S A 105: 4639–4644.Jordan WS Jr, Denny FW Jr, Badger GF, Curtiss C, Dingle JH, et al. (1958) A study of illness in a group of Cleveland families. XVII. The occurrence of Asian influenza. Am J Hyg 68: 190–212.

Health Protection Agency Centre for Infections (2009) HIV in the United Kingdom: 2008 Report. Available: http://www.hpa.org.uk/hivuk2008. Accessed: 15 September 2009.

Health Protection Agency Centre for Infections (2009) Sexually transmitted infections and men who have sex with men in the United Kingdom: 2008 report. Available: http://www.hpa.org.uk/hivmsm2008. Accessed: 15 September 2009.

Jordan WS Jr, Denny FW Jr, Badger GF, Curtiss C, Dingle JH, et al. (1958) A study of illness in a group of Cleveland families. XVII. The occurrence of Asian influenza. Am J Hyg 68: 190–212.

Lipsitch M, Riley S, Cauchemez S, Ghani AC, Ferguson NM (2009a) Managing and reducing uncertainty in an emerging influenza pandemic. N Engl J Med 361: 112–115.

Lipsitch M, Hayden FG, Cowling BJ, Leung GM (2009b) How to maintain surveillance for novel influenza A H1N1 when there are too many cases to count. Lancet 374: 1209–1211.

Metzger KB, Hajat A, Crawford M, Mostashari F (2004) How many illnesses does one emergency department visit represent? Using a population-based telephone survey to estimate the syndromic multiplier. MMWR Morb Mortal Wkly Rep 53 Suppl: 106–111.

Miller MA, Viboud C, Olson DR, Grais RF, Rabaa MA, et al. (2008) Prioritization of influenza pandemic vaccination to minimize years of life lost. J Infect Dis 198: 305–311.

Mills CE, Robins JM, Lipsitch M (2004) Transmissibility of 1918 pandemic influenza. Nature 432: 904–906.

Newton K (2009 July 18) Swine flu puts hold on surgery. The Dominion Post Wellington, NZ.

Nishiura H, Castillo-Chavez C, Safan M, Chowell G (2009a) Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan. Euro Surveill 14: pii: 19227. Available: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId= 19205. Accessed: 1 November, 2009.

Nishiura H, Klinkenberg D, Roberts M, Heesterbeek JA (2009b) Early epidemiological assessment of the virulence of emerging infectious diseases: a case study of an influenza pandemic. PLoS One 4: e6852. doi:10.1371/ journal.pone.0006852.

Pourbohloul B, Ahued A, Davoudi B, Meza R, Meyers LA, et al. (2009) Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respi Viruses 3: 215–222.

Presanis AM, De Angelis D, Spiegelhalter DJ, Seaman S, Goubar A, et al. (2008) Conflicting evidence in a Bayesian synthesis of surveillance data to estimate human immunodeficiency virus prevalence. J R Stat Soc Series A Stat Soc 171:915–937.

Reed C, Angulo F, Swerdlow D, Lipsitch M, Meltzer M, et al. (2009) Estimating the burden of pandemic influenza A/H1N1–United States, April-July 2009. Emerg Infect Dis. In press.

Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, et al. (2004) Influenza and the winter increase in mortality in the United States, 1959–1999. Am J Epidemiol 160: 492–502.

Simonsen L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, et al. (1998) Pandemic versus epidemic influenza mortality: A pattern of changing age distribution. J Infect Dis 178: 53–60.

Thomas A, O'Hara B, Ligges U, Sturtz S (2006) Making BUGS Open. R News 6: 12–17.

Thompson WW, Weintraub E, Dhankhar P, Cheng PY, Brammer L, et al. (2009) Estimates of US influenza-associated deaths made using four different methods. Influenza Other Respi Viruses 3: 37–49.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, et al. (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289: 179–186.

Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, et al. (2004) Influenza-associated hospitalizations in the United States. JAMA 292: 1333–1340.

Uyeki TM, Prasad R, Vukotich C, Stebbins S, Rinaldo CR, et al. (2009) Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis 48: e89–92.

White LF, Wallinga J, Finelli L, Reed C, Riley S, et al. (2009) Estimation of the reproductive number and the serial interval in the current influenza A/H1N1 outbreak. Influenza Other Respi Viruses 3: 267–276.

Wilson N, Baker MG (2009) The emerging influenza pandemic: estimating the case fatality ratio. Euro Surveill 14: pii: 19255. Available: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId = 19255. Accessed 15 September, 2009.

SUPPLEMENTARY METHODS: THE SEVERITY OF PANDEMIC H1N1 INFLUENZA IN THE UNITED STATES, APRIL – JULY 2009

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1. Introduction

In this Supplementary Material we provide additional details about the statistical model employed (Section 2), the data (Section 3), the detection probabilities (Section 4), the relationship between medically attended and symptomatic illness (Section 5), and the software implementation of our model (Section 6).

2. Model

Of ultimate interest is to estimate three quantities:

1) the case-fatality ratio, defined as the ratio of the true number of H1N1pdm-attributable deaths to the true number of H1N1pdm infections; we denote this $c_{D|Inf}$ because it is a conditional probability, Pr{death | infection};

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2) the case-ICU admission ratio, defined as the ratio of the true number of H1N1pdm -attributable ICU admissions to the true number of H1N1pdm infections; we denote this $c_{I|Inf}$ = Pr{ICU | infection}; and
3) the case-hospitalization ratio, defined as the ratio of the true number of H1N1pdm-attributable hospitalizations to the true number of H1N1pdm infections; this is denoted $c_{H|Inf}$ = Pr{hospitalization | infection}.

Ascertainment of all infections, whether symptomatic or not, requires serological surveys, which are not yet available for H1N1pdm. Without such surveys, it is not possible to estimate the relationship between infection and more severe outcomes. We therefore attempt to estimate the ratio of severe outcomes to *symptomatic* infection: namely, the symptomatic case-fatality ratio $c_{D|S}$ = Pr{death | symptomatic infection}, the symptomatic case-ICU admission ratio $c_{I|S}$ = Pr{ICU admission | symptomatic infection} or the symptomatic case-hospitalization ratio $c_{H|S}$ = Pr{hospitalization | symptomatic infection}.

No jurisdiction in the United States conducted case-based surveillance for a long enough period, in a large enough population to estimate this quantity directly; in particular, jurisdictions with intensive case-finding (such as Milwaukee) did not have enough deaths or ICU admissions to make a statistically robust estimate, while jurisdictions with enough deaths and ICU admissions (such as New York) had too many cases to pursue intensive case-finding for the period over which deaths and ICU visits were registered.

Given that we do not have data on all severity levels for both locations, we aim to estimate $c_{D|S}$, $c_{I|S}$ and $c_{H|S}$, using two approaches. First, we combine data from both Milwaukee and New York on medically attended symptomatic cases, hospitalizations, ICU admissions and deaths, together with information from the Centers for Disease Control (CDC) on ascertainment probabilities and proportions of symptomatic cases seeking medical attention, to estimate the ratios $c_{D|S}$, $c_{I|S}$ and $c_{H|S}$, assuming the conditional probabilities are equal, but age-specific, across the two jurisdictions. Second, we use data on hospitalizations, ICU admissions and deaths just from New York City, together with data on self-reported incidence of influenza-like illness (ILI) in New York, assuming that these ILI cases represent the true number of symptomatic cases, to estimate $c_{D|S}$, $c_{I|S}$ and $c_{H|S}$.

2a. Severity Model

Approach 1 We start from the simple assumption that the following hierarchy in the severity level holds: death $\subseteq$ hospital admission $\subseteq$ medical attendance $\subseteq$ symptomatic case, and similarly, ICU admission $\subseteq$ hospital admission $\subseteq$ medical attendance $\subseteq$ symptomatic case, where $\subseteq$ represents inclusion. Under this assumption,

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$c_{D|S}$ = Pr {death | symptoms}
= Pr {death | hospital}Pr{hospital | medical attendance} Pr{medical attendance | symptoms},
= $c_{D|H}c_{H|M}c_{M|S}$

$c_{I|S}$ = Pr{ICU | symptoms}
= Pr{ICU | hospital} Pr{hospital | medical attendance} Pr{medical attendance | symptoms}
= $c_{I|H}c_{H|M}c_{M|S}$

and

$c_{H|S}$ = Pr{hospital | symptoms}
= Pr{hospital | medical attendance} Pr{medical attendance | symptoms}
= $c_{H|M}c_{M|S}$

where $c_{D|H}$ and $c_{I|H}$ are the probabilities of true H1N1pdm-attributable deaths or ICU admissions, respectively, conditional on true H1N1pdm-attributable hospitalizations; $c_{H|M}$ is the probability of true H1N1pdm-attributable hospitalization, conditional on being a true H1N1-positive medically attended case, and $c_{M|S}$ is the probability of being a true H1N1pdm-positive medically attended case, conditional on true symptomatic infection with H1N1pdm.

Clearly, these subset relations may not strictly hold. Indeed, in New York, data are available on H1N1pdm-attributable deaths which occur outside of hospital. So we instead make the assumption that

$c_{D|S}$ = Pr {death | symptoms}
= Pr {death among hospitalized ∪ death among medically attended but not hospitalized | symptoms}
= Pr{death among hospitalized | symptoms} + Pr{death among medically attended but not hospitalized | symptoms}
= $c_{D|H}c_{H|M}c_{M|S} + c_{D\cap\bar{H}|M}c_{M|S}$

(see Figure A7-3).

We consider age-group specific values for all of these conditional probabilities so all carry a subscript *i* for age group and we denote the actual number of people who reached a given level of severity in a given jurisdiction by N_s for symptomatic cases, N_M for medically attended cases, N_H for hospitalizations, N_I

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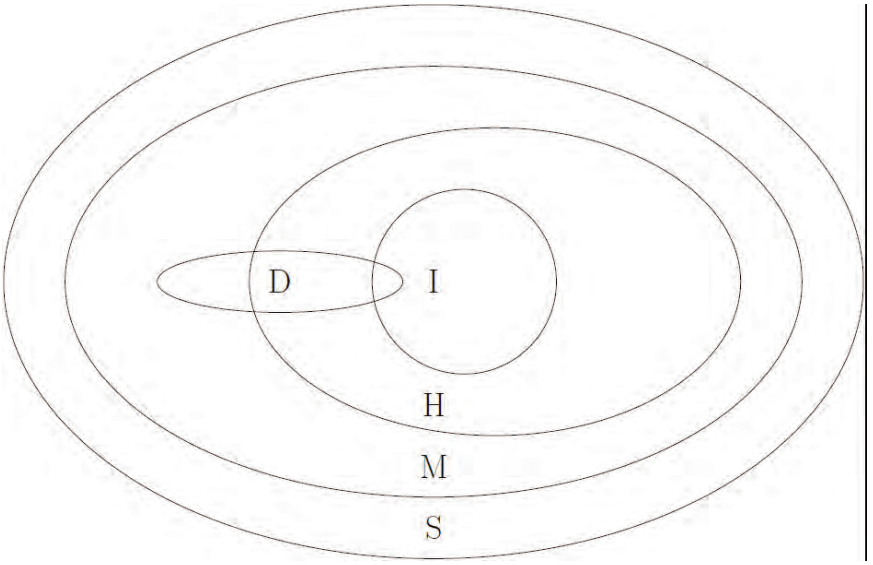

FIGURE A7-3 Assumed severity hierarchy.

for ICU admissions and N_D for deaths. Each of these true numbers also varies by age group i and location k (Milwaukee, $k = W$ or NYC, $k = N$). We assume that in each age group, for each level of severity, the true number of persons at that level of severity is binomially distributed based on the corresponding conditional probability and the true number at the preceding level of severity:

$$
\begin{aligned}
&N_{iMk} \sim Binomial\left(N_{iSk}, c_{iM|S}\right)\\
&N_{iHk} \sim Binomial\left(N_{iMk}, c_{iH|M}\right)\\
&N_{iIk} \sim Binomial\left(N_{iHk}, c_{iI|H}\right)\\
&N_{iD\cap Hk} \sim Binomial\left(N_{iHk}, c_{iD|H}\right)\\
&N_{iD\cap \bar{H}k} \sim Binomial\left(N_{iMk}, c_{iD\cap \bar{H}|M}\right)
\end{aligned}
\qquad (1a)
$$

N_{iSk} is given a prior reflecting our uncertainty about the number of symptomatic cases (see details in section on symptomatic vs. medically attended infection).

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Approach 2 For the NYC only analysis, we do not consider the medically attended level, such that

$$c_{D|S} = c_{D|H} c_{H|S} c_{D \cap \bar{H}|S},$$
$$c_{I|S} = c_{I|H} c_{H|S}$$

$c_{H|S}$ is given by

$$\begin{aligned} N_{iH} &\sim Binomial\left(N_{iS}, c_{iH|S}\right) \\ N_{iI} &\sim Binomial\left(N_{iH}, c_{iI|H}\right) \\ N_{iD \cap H} &\sim Binomial\left(N_{iH}, c_{iD|H}\right) \\ N_{iD \cap \bar{H}} &\sim Binomial\left(N_{iS}, c_{iD \cap \bar{H}|S}\right) \end{aligned} \quad \text{(1b)},$$

and $N_{iS} \sim Binomial\ (N_{iP}, c_{iS|P})$ where N_{iP} is the NYC population size (considered constant), and $c_{iS|P}$ are given priors, to reflect estimates from the NYC telephone survey, see section on symptomatic vs. medically attended infection.

2b. Observation Model

For a variety of reasons, detection at each level of severity will be imperfect, and thus the true values N are not observed. However, we do observe detected medically attended cases O_{iMW} and detected hospitalizations O_{iHW} in Milwaukee, and we observe detected hospitalizations O_{iHN}, detected ICU stays O_{iIN}, and detected deaths O_{iDN} in New York City. We assume that these observations O are related to the true numbers N as follows:

$$\begin{aligned} O_{iMk} &\sim Binomial\ (N_{iMk}, d_M) \\ O_{iHk} &\sim Binomial\ (N_{iHk}, d_H) \\ O_{iIk} &\sim Binomial\ (N_{iIk}, d_I) \\ O_{iDk} &\sim Binomial\ (N_{iDk}, d_D) \end{aligned} \quad \text{(2)}$$

where for each level of severity j, d_j is the detection probability, i.e. the probability that a case enters our database.

2c. Combining the models—a Bayesian approach

Given (1a) or (1b) and (2), we wish to estimate the values of the age-specific c_{ij}, which can then be multiplied appropriately to estimate the age-specific (symptomatic) case-hospitalization, case-ICU and case-fatality ratios.

Figure A7-4 is a schematic representation of the relationship between the quantities we wish to estimate and the quantities we observe. The figure shows only a small part of the whole model in approach 1, for one generic age group and

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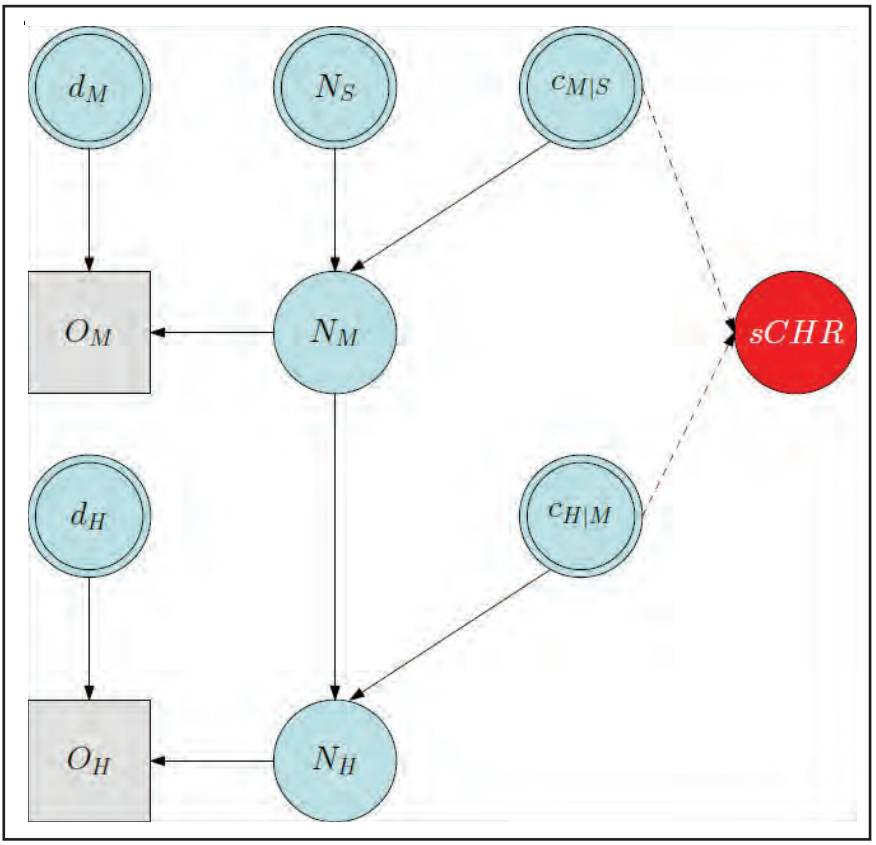

FIGURE A7-4 Simplified directed acyclic graph displaying the dependencies in part of the model.

location, and for the first three levels of severity (symptomatic to hospitalized). Circles denote parameters, double circles denote parameters for which we have prior information, and squares denote observations. Solid lines denote distributional relationships and dashed lines denote functional relationships. The arrows represent the process by which the parameters, if known, would generate the data. In our case, the problem is reversed, i.e. to infer the values of the parameters given the available information. The figure provides an illustration of the flow of information from the observations and prior distributions to the unknown parameters. So for example, the information on O_H (the observed number of hospitalizations) together with the prior on d_H gives information on N_H, the true number of hospitalizations. Note that estimation of the parameters of primary interest (e.g. *sCHR*, the symptomatic case-hospitalization ratio) is informed indirectly

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by the combination of prior and sample information on intermediate but related parameters (O_H and O_M, together with d_M, d_H, N_S and $c_{M|S}$, via the true numbers N and the conditional probabilities c).

More generally, the complete set of unknown parameters is $\underline{\theta} = (c_{ij}, d_{jk}, N_{ijk}, sCHR, sCIR, sCFR)$, and we have observations $\underline{O} = (O_{ijk})$. Inference is then carried out in a Bayesian setting using the prior information, $P(\underline{\theta})$, and the likelihood of the observations given the parameters, $L(\underline{O}|\ \underline{\theta})$ to obtain, via Bayes' Theorem, the posterior distribution $P(\underline{\theta}|\underline{O}) \propto P(\underline{\theta})L(\underline{O}|\underline{\theta})$ of the parameters.

3. Data

3a. Milwaukee

On April 27th, Milwaukee sent out messaging to local healthcare providers recommending testing anyone presenting with signs and symptoms characteristic of influenza (fever >100 degrees, cough or sore throat, myalgia) and travel to an area with documented H1N1. By May 7th more than 100 confirmed cases had been identified, and testing guidance was updated to recommend testing persons with moderate to severe symptoms (temperature of > 101.5 and significant respiratory symptoms and significant constitutional symptoms). Testing of persons with mild symptoms was limited to health care workers. On June 15th providers were told to begin testing on a fee-for-service basis. Throughout the outbreak, healthcare providers have been asked to report any suspect, probable or confirmed case of H1N1. Providers were advised about concerns regarding the accuracy of rapid flu tests and urged to use PCR as the preferred method for analysis. All confirmed and probable cases were entered into a line list on a rolling basis, and we used a line list dated July 21.

Because our primary focus for Milwaukee was on hospitalization probabilities, in a preliminary analysis we plotted the frequency of hospitalization by week of "episode date," the earliest date (of illness onset, report or hospitalization) in an individual record. The hospitalization frequency was around 3% overall with no temporal trend up to an episode date of May 20, after which there was a dramatic upward trend in the proportion hospitalized, with 8.2%, 6.0%, and 7.0% hospitalized in the weeks that followed. We interpreted this increased hospitalization rate as evidence of declining ascertainment of mild cases, and we therefore restricted our attention to cases with illness onset date up to and including May 20. This also obviated the need to deal with censoring, as the date of the line list was two months later, far longer than the delay in reporting for nearly all cases. This created a data set of 763 cases, of whom 25 (3%) were hospitalized.

While the main source of data on the probability of ICU admission or death was New York City, such data were available, albeit in small numbers, for

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Milwaukee. To inform the ratio of ICU+ventilation:hospitalization and death:-hospitalization, we used a larger subset of the data, on the assumption that the change in ascertainment after May 20 was due to reduced ascertainment of mild cases, not changes in ascertainment of hospitalized or more severe cases. Therefore, we considered the 147 hospitalizations with episode date up to and including June 14. Again, this was more than 30 days prior to the close of the line list, so we did not correct for censoring. Of these 147 hospitalizations, 25/147 (17%) were admitted to the ICU and/or ventilated, and 4 (3%) died.

3b. New York City

From April 26 to July 7, 2009, New York City maintained a policy of testing hospitalized patients with influenza-like illness (ILI) under various criteria. Criteria for testing varied up to May 12, after which point all hospitalized patients with influenza-like illness (ILI) were tested with a rapid influenza antigen test. Those patients who tested positive, and also any patient on a ventilator or in an intensive care unit (ICU) regardless of rapid test result, were tested for H1N1pdm by PCR. We obtained a line list of confirmed cases dated August 24, 2009, including 996 hospitalizations, of whom 882 had a known date of onset. Preliminary analysis indicated that >99% of hospitalizations were reported within 21 days of symptom onset. Since the last date of admission in the data set was July 6, 49 days prior to the date of the line list (August 24), we did not restrict this data set. Also, >97% of admissions in the data set were after May 12, so we did not attempt to account for differences in testing prior to May 12.

Separately, we obtained a list of 53 deaths attributed to H1N1pdm, of whom 44 (83%) had been hospitalized before dying. The dates of death ranged from 17 May to 19 July, but the dates of case report to New York City ranged from 13 May to 4 July; hence, these cases were all included within the time frame in which hospitalizations were being investigated. Based on the time-to-death distribution and the timing of hospitalizations, we estimated that >99.9% of deaths which would be reported from the hospitalized cases had already been reported. We therefore made no effort to account for censoring of deaths.

The data are shown in Table A7-1 of the main text.

4. Detection Probabilties

We require information on the detection probabilities, d_M, d_H, d_I, d_D. In general, these are assumed location-specific, and may consist of multiple components. We present below the evidence or prior assumptions available to inform estimates of these detection probabilities.

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4a. Detection of medically attended illness

The detection probability for medically attended (M) illness (in Milwaukee), d_{MW}, may be expressed as

d_{MW} = Pr{specimen collected & tested | true M case already M} Pr{test positive | specimen collected & tested for a true M case}
$= d_{MW1}d_{MW2}$

where d_{MW2} is the sensitivity of the PCR-based tests recommended for use in Milwaukee. We assume $d_{MW1} \sim Uniform(.2,.35)$, $d_{MW2} \sim Uniform(.95,1)$, and that the probability of censoring is 0, for the reasons described in Section 3. These assumptions are based on estimates from Reed et al. (2009), using data from seasonal influenza and from Epi-Aids in Delaware and Chicago and are not Milwaukee-specific. Unlike Reed et al., we do not assume a separate probability for specimens being sent for confirmatory testing, since Milwaukee recommended against use of rapid antigen testing for screening (which would have led to false negatives and reduced detection) and since Milwaukee recommended testing of all persons with moderate to severe symptoms.

4b. Detection of hospitalizations (Milwaukee)

We define d_{HW}, the detection probability for hospitalization (in Milwaukee) as

d_{HW} = Pr{report hosp case | test pos} Pr{test pos | true hosp case already hosp and tested}Pr{tested | true hosp case already hosp}
$= d_{HW1}d_{HW2}$

By using the July 21 line list but restricting analysis to cases with an episode date prior to or on May 20 (or June 14) we believe it reasonable to assume the probability of censoring is 0. We have no Milwaukee-specific data on the probability that some true hospitalizations go unreported, either because testing was not performed, or because a positive case was not reported. Hence we again follow Reed et al. in assuming

d_{HW1} = Pr{report hosp case | test pos} Pr{tested | true hosp case already hosp} $\sim Uniform(.2,.4)$ and $d_{HW2} \sim Uniform(.95,1)$ to account for imperfect PCR test sensitivity.

We assume the same priors for the detection probabilities in ICU admissions.

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4c. Detection of deaths (Milwaukee)

d_{DW} is the detection probability for deaths in Milwaukee. As with hospitalizations, we assume no censoring, since the date of the line list is a month after the last episode date in the data set we are considering (episode dates up to 14th June), so that d_{DW} = Pr{report death | true H1n1pdm-attributable death (already died)}. We have no data to assess the probability of a death being tested for H1N1pdm, hence we assume a prior reflecting failure to detect of $d_{DW} \sim Beta(45,5)$ giving a prior mean of 0.9 and standard deviation 0.05 (a range of 0.8 – 1, as in New York, see below), covering both test sensitivity and failure to detect.

4d. Detection of hospitalizations (New York)

d_{HN} is the detection probability for hospitalization (in New York). In New York, rapid antigen testing was used as a screen for most patients. From May 12, PCR testing for H1N1pdm was performed only on hospitalized patients who (a) tested positive on a rapid influenza A test, or (b) were in the ICU or on ventilator, regardless of their rapid influenza A status. Thus one component of d_{HN} is d_{HN1}, the probability of PCR testing. 27% (242/909) of hospitalized H1N1pdm patients in New York were in the ICU, so for these we assume that the probability of PCR testing was 1. For the other 73% we assume the probability of PCR testing was equal to the sensitivity of the rapid test, which we model as Uniform(.2,.71). Thus we model d_{HN1}~.27+.73(Uniform(.2,.71)). Finally we account for imperfect sensitivity of the PCR, $d_{HN2} \sim Uniform(.95,1)$. Because of active surveillance for hospitalized cases, we assume that testing was performed as advised and was reported in all cases; hence we do not assume a separate factor for failure to test or report. As noted above, we made no effort to account for censoring of hospitalized cases.

4e. Detection of ICU admissions, New York

Here we assume that detection is equal to the sensitivity of the PCR test, $d_{IN} \sim Uniform(.95,1)$, since rapid testing was not required for PCR testing. As with hospitalizations, we assume the probability of censoring is 0.

A limitation is that we only detect ICU admissions that are known by the time the hospitalized case is reported to the NYC Department of Health. Later admissions from the ward are not reported. Thus we will underestimate the proportion of ICU admissions among hospitalized cases. However, a chart review of 99 hospitalizations found that 24 (24%) were admitted to the ICU during their entire stay, a proportion indistinguishable from that in our overall dataset. Hence we conclude that this underestimation is not severe.

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4f. Detection of deaths, New York

New York had a policy of PCR testing all unexplained respiratory deaths involving fever. We have no data to assess the completeness of such testing. Given issues of PCR sensitivity and possible failure to test, we assume a prior distribution for ascertainment of deaths of, $d_{DN} \sim Beta(45,5)$ giving prior mean 0.9 and standard deviation 0.05), reflecting possible failure to detect H1N1pdm-attributable deaths.

5. Symptomatic vs. Medically Attended Infection

We have no direct data on the number of symptomatic but not medically attended H1N1pdm infections. However, multiple epidemiological investigations have estimated the proportion of influenza-like illness that is medically attended; these estimates range from 42% to 58% (Reed et al., 2009) and include data both from prior influenza seasons and from the spring 2009 H1N1pdm influenza period. Thus we model the conditional probability of being medically attended given symptomatic infection, $c_{M|S} \sim Beta(51.5,48.5)$ giving a mean of 0.515 and standard deviation 0.05, with 90% of the probability mass between 0.42 and 0.58.

For approach 1, we also require prior distributions for the true number of symptomatic infections, N_S. For Milwaukee, we assume $N_{iSW} \sim Uniform(H_{iMW}, 0.25 \times popn_{iW})$, i.e. a lower limit of the observed number of medically attended cases, with an upper limit of 25% of the population size. This implies a maximum clinical attack rate of 25%. For New York, we assume $N_{iSN} \sim Uniform(0, upper_{iN} \times popn_{iN})$: we have not observed medically attended cases in New York, so cannot use the observation as a lower limit. We used an upper bound of symptomatic infection in New York City based on the number of persons reporting ILI in a telephone survey conducted by the New York City Department of Health and Mental Hygiene covering a 30-day period in May-June at the height of the spring epidemic (NYC DOHMH, unpublished data):

$upper_{0\text{-}4,N} \sim Beta(18.2,72)$
$upper_{5\text{-}17,N} \sim Beta\ (50.4,178)$
$upper_{18\text{-}64,N} \sim Beta(38.7,338)$
$upper_{65+,N} \sim Beta(27.6,446)$
$upper_{all,N} \sim Beta(91.4,654)$

In approach 2, the telephone survey data is used directly to inform priors for the proportion of the NYC population with symptomatic infection, rather than an upper bound:

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$c_{0\text{-}4,S|P} \sim Beta(18.2,72)$
$c_{5\text{-}17,S|P} \sim Beta(50.4,178)$
$c_{18\text{-}64,S|P} \sim Beta(38.7, 338)$
$c_{65+,S|P} \sim Beta(27.6,446)$
$c_{All,S|P} \sim Beta(91.4,654)$

6. Implementation

The Bayesian model described in Section 2 used the data and priors as presented in Sections 3 to 5, and was implemented in the OpenBUGS software. This uses Markov chain Monte Carlo to obtain samples from the posterior distributions of the parameters of interest. Three chains of 1,000,000 iterations each were run, starting from different initial values. Summary statistics were based on the last 200,000 iterations of each chain, after discarding the first 800,000 as a burn-in period.

Convergence for the quantities of primary interest which were reported in the main text, the conditional probabilities c_{ij}, was assessed both visually and using Gelman-Rubin-Brooks plots and we are satisfied the chains converged for these in most age groups. In approach 1, the probability of hospitalization given medical attendance did not reach quite the same level of convergence as the other c_{ij}, particularly for the 65+ age group. This is due to the paucity of data available for this ratio: only data from Milwaukee is available, up till May 20th, the period for which ascertainment of mild cases was assumed constant over time. The observed numbers of hospitalizations in particular are very small, with 0 hospitalizations observed in the 65+ age group. This has a knock-on effect on the true numbers of medical attendances and symptomatic infections (N_{iSk} and N_{iMk}), so that their Markov chains also did not quite reach the same level of convergence as the chains for the true numbers of hospitalizations, ICU admissions and deaths.

The posterior estimates for the symptomatic case-fatality, case-ICU admission and case-hospitalization ratios are reliant on the estimates of N_{iSk}, the true number of symptomatic cases, and are hence sensitive to the choice of prior. Convergence for N_{iSk} improves as the upper limit for its prior is reduced, i.e. as the maximum clinical attack rate becomes smaller. However, it would not be reasonable to assume a maximum clinical attack rate of less than the telephone survey estimates for New York or less than 25% for Milwaukee, given our lack of prior knowledge on these. For this reason we do not report estimates of the total number symptomatic. Despite the uncertainty, there is some information available in the likelihood to update the estimates of the number symptomatic: the posteriors do not simply reflect the prior distributions (Figures A7-5 and A7-6).

In approach 2, we are satisfied that the chains converged for the conditional probabilities c_{ij} in all age groups.

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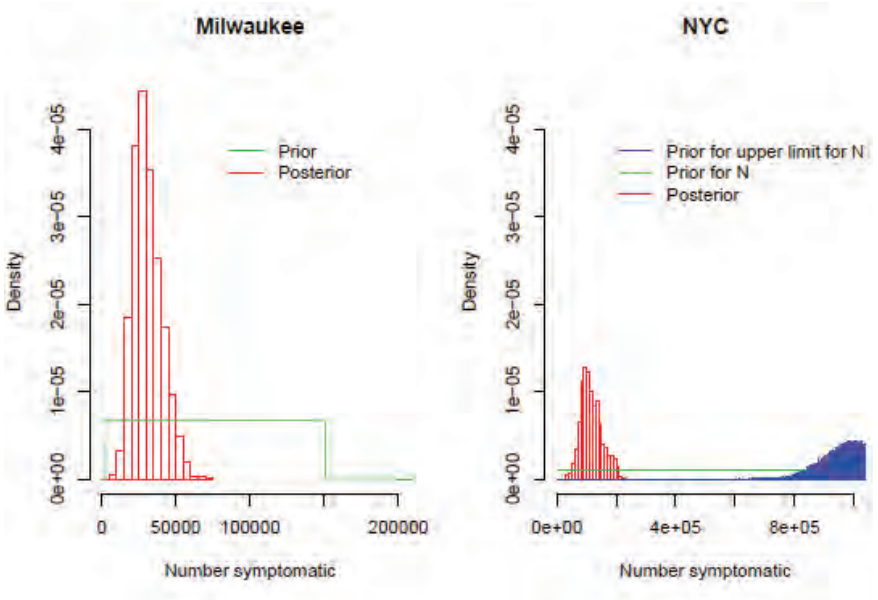

FIGURE A7-5 Prior versus posterior number of symptomatic infections, Approach 1.

Reference

Reed C, Angulo F, Swerdlow D, Lipsitch M, Meltzer M, et al. (2009) Estimating the burden of pandemic influenza A/H1N1—United States, April-July 2009. Emerg Infect Dis. In press. DOI: 10.3201/eid1512.091413

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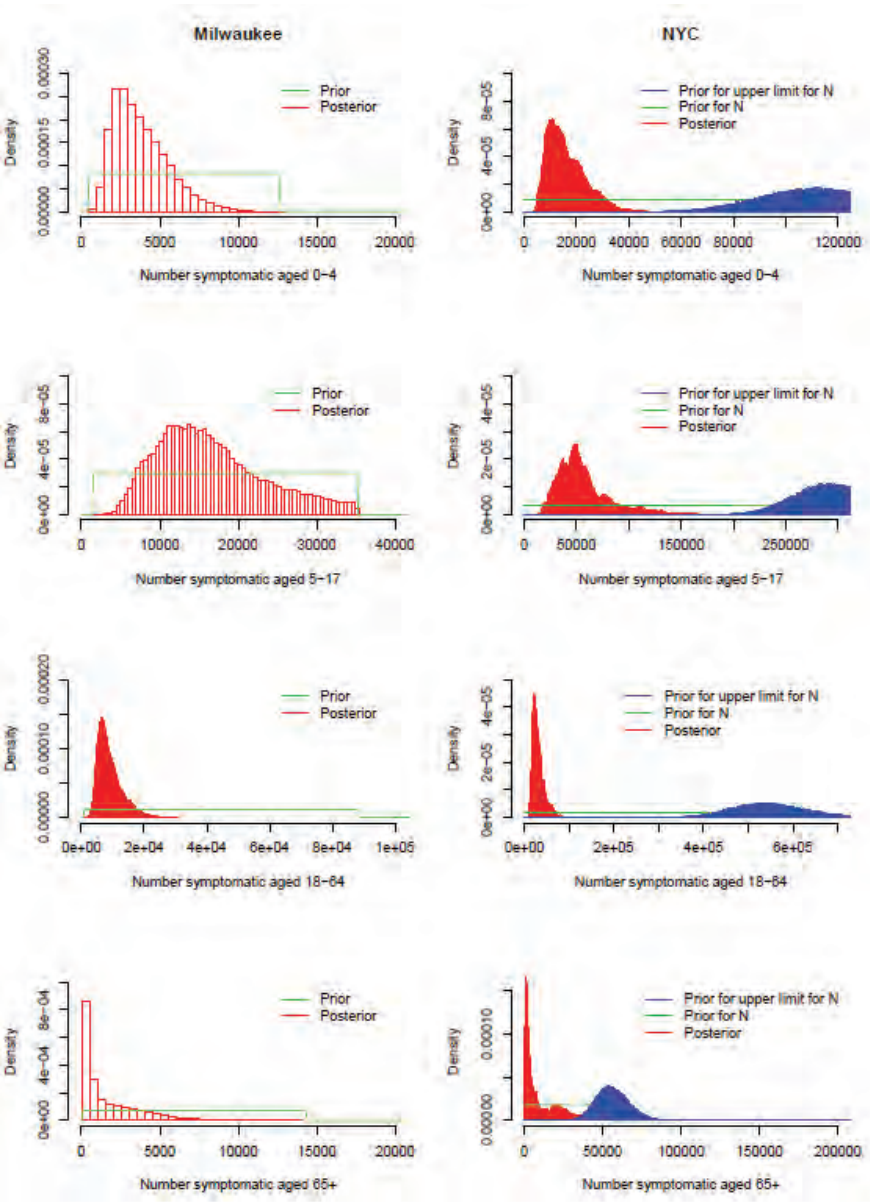

FIGURE A7-6 Prior vs posterior number of symptomatic infections, by age, Approach 1.

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A8

HARD CHOICES IN DIFFICULT SITUATIONS: ETHICAL ISSUES IN PUBLIC HEALTH EMERGENCIES

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During the past decade, the destruction of the World Trade Center, bioterrorism using inhalational anthrax, severe acute respiratory syndrome (SARS), and natural disasters such as Hurricane Katrina have dramatized the importance of effective responses to public health emergencies. Currently, preparedness for the 2009-H1N1 influenza A pandemic is a public health priority.

Public health emergencies differ markedly from ordinary clinical care in several ways. First, essential services may be threatened. Basic necessities such as safety, shelter, food, sanitation, and electricity may not be available to large sections of society. After Hurricane Katrina, essential services such as police protection, transportation, and medical care broke down in New Orleans. These disruptions fell most heavily on poor, primarily African American persons who could not evacuate because they did not have automobiles. Second, during a public health emergency there may be critical shortages of medical resources that far exceed surge capacity. In the 2009-H1N1 influenza A pandemic, vaccines may be in short supply because of production constraints. If the pandemic becomes severe, the number of people with respiratory failure, who require mechanical ventilation to survive, is projected to far exceed the available number of ventilators, critical care beds, personnel, and surge capacity of hospitals. Persons with respiratory failure who are not able to receive mechanical ventilation during a severe pandemic will almost certainly die. Such identifiable deaths, which might have been prevented, will distress families, health care workers, and the general public. Because the allocation of scarce resources during a public health emergency may have life-and-death consequences, the ethical rationale for these policies will be closely scrutinized and will need to be carefully justified.

This paper first analyzes the ethical principles that should guide public health policies during a declared public health emergency. Second, it analyzes how physicians should respond when patients challenge allocation priorities and request interventions for which they have low priority. Third, it discusss the importance of conducting research during a public health emergency and suggest steps to facilitate such research. Finally, this paper analyzes why some members of the public may be suspicious of emergency public health guidelines and suggests how public health officials can address such concerns.

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Ethical Principles During a Public Health Emergency

The goal of public health is to improve the health of a population or community rather than the well-being of an individual patient (Childress et al., 2002; Gostin, 2008; Gostin et al., 2003). Public health is utilitarian, seeking to improve aggregate measures of community health. During the 2009-H1N1 influenza A pandemic, the mission of public health is to prevent mortality and morbidity caused by influenza and to maintain essential societal functions. Because of this focus on population outcomes, public health officials may adopt measures that are not in the best interests of individual citizens and may restrict liberties. This section specifies the goals of public health during this pandemic, then discusses how to balance public health powers with individual liberty and fairness. Next, it analyzes how ethical principles for a declared public health emergency should be specified and balanced. When ethical principles are overridden, they are not ignored or voided but must be observed to the extent that is possible under the circumstances, consistent with the public health goals. Finally, this section illustrates how ethical principles have been invoked—either implicitly or explicitly—in federal guidelines to allocate vaccines, antiviral drugs, and ventilators during the 2009-H1N1 influenza A pandemic.

The Goals of Public Health Emergency Policies

When responding to an H1N1 pandemic, the public health system aims to prevent or reduce harms resulting from the pandemic. This goal is community-oriented and inherently utilitarian (IOM, 2009), seeking to minimize aggregate harms to society. "Utility" can be specified in many ways: for example, maximizing total lives saved, maximizing total number of life-years saved, minimizing new instances of infection, or minimizing societal harm by maintaining public functions. To be operationalized, public health goals need to be specified in more detail. This specification will depend on the particular public health intervention being considered.

One goal would be to prevent deaths from 2009-H1N1 influenza A; in other words, to save the most lives (IOM, 2009). This goal would be appropriate when allocating ventilators and other life-sustaining technologies during a severe pandemic. More broadly, the public health goal might focus on morbidity as well as mortality. The goal might be to prevent cases of severe influenza in order to reduce the aggregate morbidity and burden of disease. This goal would be appropriate if antivirals and vaccine were in short supply and needed to be allocated.

An even broader goal would be to minimize the total number of cases of influenza, including mild as well as severe cases. This would be an appropriate goal if there were no shortfall of vaccine, but a priority system still needs to be established in order to deliver the vaccine to the population.

During a severe pandemic, another goal might be to maintain essential functions of society. The image of basic services such as shelter and public safety

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breaking down in New Orleans after Hurricane Katrina has been seared into public memory. In a wave of a severe pandemic, a goal of public health efforts might be to ensure that police and fire departments continued to function, and that services such as housing sanitation, food, electricity, and communications were provided.

Finally, because a pandemic is global, the geographical scope of public health goals needs to be considered. Federal and state governments in the United States are developing national and state responses to the pandemic. Plans are under way to purchase and distribute vaccine and antivirals. Critics in developing countries charge that the available supply of vaccine is being rapidly purchased by developed nations, leaving inadequate supply to other countries (Bertozzi et al., 2009). Furthermore, many nations cannot afford to purchase vaccines for all citizens at increased risk for severe 2009-H1N1 influenza A infection. The world is interconnected, and the United States and other developed countries are affected by the course of the pandemic in less-developed countries. A large number of cases worldwide may increase the chances that the virus will mutate to a lethal variant. Moreover, the United States benefits from other countries sharing surveillance data and virus samples. However, resource-poor countries may be reluctant to engage in such scientific cooperation if they do not receive assistance with their public health efforts in return (Bertozzi et al., 2009).

Balancing Public Health Powers with Liberty and Fairness

Traditional public health laws, promulgated in the late nineteenth and early twentieth centuries, gave great deference to the "police powers" of the state to act in the common good (Colgrove and Bayer, 2005). During a declared public health emergency, public health officials have the authority take actions that would not be permissible in ordinary clinical care, including mandatory examination, isolation, and quarantine. These measures compel individual citizens to forego their basic rights.

In the late twentieth century, greater concern for civil rights was the background for attention to individual liberty during the AIDS epidemic. Mandatory public health measures were recognized as placing heavy burdens on individuals, restricting their liberty, causing economic losses, and sometimes leading to stigmatization (Fidler et al., 2007). Agreement developed that individual liberty may be restricted by public health officials only when several ethical requirements are met (Childress et al., 2002; Gostin, 2008; Gostin et al., 2002, 2003):

- The *threat* to public health must be *serious* and *likely*.
- The intervention should be *effective* in addressing the threat.
- The intervention should be the *least restrictive alternative* that addresses the threat.
- The burdens on those whose freedom is restricted must be acceptable.

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- *Procedural due process* should be available to persons deprived of their freedom and autonomy.
- Policies are *implemented equitably*. Even the perception that some groups are being treated unfairly may undermine public support for compulsory measures (Lo and Katz, 2005).

These standards for mandatory public health interventions struck a balance between protecting the public health and respecting the rights of individuals.

If the AIDS epidemic focused attention on individual rights, Hurricane Katrina riveted attention on how public health policies affect different groups within society. The public health response to Hurricane Katrina had an overwhelmingly disparate impact on social, economic, and racial groups. The poor, who were disproportionately African American, were unable to evacuate. Evacuation plans failed to anticipate that many people had no access to cars to leave the city. This discrepancy focused even more attention on the importance of fairness and protection of vulnerable groups during a public health emergency. In particular, these groups need to be engaged in the development of emergency plans, so that problems with implementation and access to services can be identified and ameliorated.

General and Specific Ethical Principles

Three recent national consensus reports have proposed ethical principles to guide public health policy during public health emergencies generally or, more specifically, during the 2009-H1N1 influenza A pandemic (Table A8-1).

Table A8-1 groups these principles under several broad headings: goals of public health policy during an emergency, balancing individual liberty with public health goals, fairness, the policy formation process, and the responsibility of public health officials and healthcare professionals.

The three reports have similarities and differences that can be characterized as a family resemblance. There is no set of principles that is common to all the reports, yet each report shares numerous features with the others. The reports all have something to say about each of the broad headings, although they differ in how they specify and balance principles. Each report also contains some principles that are not contained in the other reports.

Table A8-1 suggests that there is general agreement on many common ethical considerations regarding public health emergencies. This consensus includes the need to balance individual liberty with public health goals, the importance of fairness, and appropriate procedures for developing and implementing policies. These ideas provide a good starting point for discussions of ethical issues in the influenza pandemic.

Ethical principles are usually stated in a general manner, so that they apply to a broad range of situations. However, in order for principles to guide public

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TABLE A8-1 Ethical Considerations During a Declared Public Health Emergency

Ethical consideration \ Report	CDC, Ethical Guidance for Public Health Emergency Preparedness and Response (2009)[a]	CDC, Ethical Guideline for Pandemic Influenza (2007)[b]	IOM, Guidance for Establishing Standards of Care in Disaster Situations (2009)[c]
Goals of public health policy	Protect public safety, health, and well-being	Minimize serious influenza-associated complications	Duty to steward resources
		Preserve the functioning of society	Utilitarian goal of saving the greatest possible number of lives
Balance individual liberty with public health goals	Equal liberty and human rights. Respect the equal liberty, autonomy, and dignity of all persons	Balance individual liberty and community interests	Proportionality—public and individual requirements must be commensurate with the scale of the emergency and degree of scarce resources
Fairness	*Distributive justice*[d]		Maintaining the trust of patients and the community
Process of policy formation	Public accountability and transparency	Commitment to transparency	Standards recognized as fair by all those affected by them
		Public engagement and involvement	Transparency Consistency Accountability
		Procedural justice[e]	Community and provider engagement, education, and communication
Responsibility of public health and healthcare professionals	Recognize the special obligations of some public health professionals, and promote competency of and coordination among these professionals	Responsibility to maximize preparedness	Standards evidence based and responsive to specific needs of individuals and the population
		Base guidelines on the best available scientific evidence	Duty of compassion and care

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TABLE A8-1 Continued

Report / Ethical consideration	CDC, Ethical Guidance for Public Health Emergency Preparedness and Response (2009)[a]	CDC, Ethical Guideline for Pandemic Influenza (2007)[b]	IOM, Guidance for Establishing Standards of Care in Disaster Situations (2009)[c]
		Work with and learn from preparedness efforts globally	Clinicians must not abandon patients
Other	Community strength and resiliency		
	Responsible civic response		

[a]Jennings and Arras (in review).
[b]Kinlaw and Levine (2007).
[c]IOM (2009).
[d]Benefits and burdens imposed on the population by the emergency response measures and mitigations are shared equitably and fairly.
[e]Consistency in applying standards across people and time (treating like cases alike). Decision makers who are impartial and neutral. Those affected by the decisions have a voice in decision making and agree in advance to the proposed process. Treat those affected with dignity and respect. Decisions are adequately reasoned and based on accurate information. Communications and processes that are clear, transparent, and without hidden agendas. Processes to revise or correct approaches to address new information.

policy and individual actions, they need to be given more specificity. As we see in the following discussion, the manner in which principles are specified will lead to different policy emphases or recommendations.

For instance, fairness or justice is an ethical principle that seems intuitively clear and appealing. No one advocates unfairness in public health emergency policies. However, fairness or justice has many dimensions, and the reports in Table A8-1 specify the idea of justice in various ways.

Distributive justice requires us to distribute the benefits and burdens of the response to a public health emergency fairly or equitably across different groups in society. Public health emergency measures should not disproportionately disadvantage subgroups that already are vulnerable or disadvantaged and should reduce or eliminate existing public health disparities. Vulnerable or disadvantaged subgroups may also need special attention or protection. Policies that are neutral on their face may have a disparate impact on racial, economic, or social groups when they are applied in real-world settings. For example, communities with little public health or healthcare infrastructure may lack access to influenza vaccines or antivirals unless steps are taken to improve access.

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Impartiality requires that policies be applied without favoritism, bias, or discrimination.

Consistency requires us to treat in a similar manner people who are similar in all ethically pertinent characteristics. For each public health intervention and situation, it will need to be determined what characteristics are considered ethically relevant.

Procedural justice concerns the process by which public health policies in an emergency are developed and implemented. Decisions in public health emergencies are often contested because the evidence base is incomplete and uncertain and because people evaluate risks and burdens differently and have different values and priorities. Fair procedures help to establish the policies as legitimate.

The term procedural justice is not always defined clearly or consistently. It refers to a cluster of ideas that typically include

- Transparency. Literally, transparency refers to letting light through; not being opaque. Figuratively it means that decisions are made in the open: policies are available for all to see, together with the evidence and reasons supporting them and a description of the process by which they were developed.
- Engagement of stakeholders, including the public. Determining the views of stakeholders before policies are finalized ensures that their views and concerns are taken into account. It will also improve the policies because stakeholders may point out problems that were not apparent previously.
- Accountability. The root meaning is to count, enumerate, or calculate. An account is a reckoning or record of money received and spent. Thus, being accountable means that a person can be called upon to answer for conduct and responsibilities. Public health officials are accountable to the governor who appoints them and to the legislature, who may conduct hearings. Their decisions also can be appealed in the courts. These checks and balances increase accountability. Furthermore, good public health practice includes internal review and quality improvement procedures to try to improve policies and implementation.

Reciprocity is a more controversial interpretation of justice. Some people have jobs that benefit society but place them at increased risk of 2009-H1N1 influenza A infection. Examples include doctors, nurses, emergency first responders, and janitorial staff in hospitals. There is wide agreement that society needs to protect such workers by providing appropriate protective gear and giving them priority for vaccination. The extent of such reciprocity, however, may be contested. Some argue that doctors and nurses deserve priority for mechanical ventilators if they develop respiratory failure. However, others argue that it would be unfair to give a ventilator to a healthcare worker who has an extremely poor prognosis even

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with a ventilator as it will deprive another patient with a much better prognosis. Furthermore, it may seem self-serving for doctors writing guidelines to give themselves priority over others.

These different dimensions of fairness have implications regarding specific policies and actions. An emphasis on procedural justice will lead to calls for public engagement and consultations with healthcare workers and health care institutions. An emphasis on distributive justice will lead attention to vulnerable populations and how they will be impacted by emergency policies. Actions resulting from these different aspects of fairness often are interrelated. For example, one step toward reducing the disparate impact of policies is to engage vulnerable communities to better understand how they might be disproportionately affected by facially neutral policies.

Differences and Continuity Between Clinical Practice and Public Health Emergencies

The three reports in Table A8-1 differ in emphasizing the differences or similarities in the ethical principles that guide clinical care and responses to declared public health emergencies. During a public health emergency, public health officials and physicians have the authority to carry out actions that would not be permitted under ordinary circumstances, including mandatory examination, isolation, quarantine, and allocation of scarce healthcare resources. The justification for these actions is of utmost importance in gaining the acceptance and trust of the public.

The ethical basis for ordinary care is the best interests and autonomy of the individual patient. The competent, informed patient decides whether to accept or decline an intervention that the treating physician considers medically indicated. Best interests are determined according to the values and preferences of the individual patient, who may choose an option different than what the physician recommends. Ordinary care is centered on the individual patient, and patient autonomy is accorded great respect. The physician who disagrees with the patient's decision should act in the patient's best interest by educating and trying to persuade the patient (Lo, 2009a). However, the patient's informed decision is generally followed, unless the intervention is regarded as not medically indicated. Considerations of justice, including the allocation of healthcare dollars or the overall cost of care, ordinarily do not play a predominant role in decisions concerning ordinary care. In terms of ethical principles, patient autonomy and acting in the best interests of the individual patient are paramount, and justice is a subsidiary consideration.

In articulating ethical considerations during a public health emergency, the Centers for Disease Control and Prevention (CDC) guidance for allocation of vaccine, antiviral drugs, and nonpharmaceutical interventions emphasizes how these principles differ from the ethical principles governing clinical care:

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> During the course of a pandemic, the functioning of society may be threatened. Our moral tradition embodies an understanding that it may be ethically acceptable (or perhaps even ethically mandatory) to suspend some (but not all) ordinary moral rules in such circumstances. (Kinlaw and Levine, 2007)

The CDC report goes on to specify criteria that would justify such "suspensions of ordinary moral rules":

- Adopting the least restrictive practices that will allow the common good to be protected.
- Ensuring that restrictions are necessary and proportional to the need for protection.
- Attempting to ensure that those impacted by restrictions receive support from the community (Kinlaw and Levine, 2007).

The Institute of Medicine (IOM) report (IOM, 2009), in contrast, emphasized the continuity between ethical norms in usual healthcare practice and during a disaster. "Ethical norms in medical care do not change during disasters—health care professionals are always obligated to provide the best care they can under given circumstances" (IOM, 2009). The IOM committee recognized that during a disaster there will be "a substantial change in usual health care operations and the level of care it is possible to deliver" (IOM, 2009). The committee acknowledged that "core ethical precepts in medicine permit some actions during crisis situations that would not be acceptable under ordinary circumstances, such as implementing resource allocation protocols that could preclude the use of certain resources on some patients when others would derive greater benefit from them" (IOM, 2009). However, the primary duty of a healthcare professional "to the patient in need of medical care" still holds during disasters. The IOM committee declared:

> Recognizing that scarce resources may restrict treatment choices, clinicians must not abandon, and patients should not fear abandonment, when an ethical framework informs healthcare disaster policy.

It is important to try to reconcile these apparent disagreements over whether ethical principles differ during a public health emergency. Otherwise confusion and mistrust may result. Furthermore, analyzing these disagreements may lead to sounder policies for public health emergencies.

Broad statements such as "suspending ordinary moral rules" and "ethical norms in medical care do not change during disasters" may be misleading because of their high level of generality. It might be better to specify which particular moral rules do not change and which are suspended, under what circumstances, and with what limits.

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There are several ethical principles that physicians should follow. These different principles may conflict, and the tension between them cannot be resolved according to some hierarchical ordering of principles. Rather, they must be specified and balanced in the context of a particular situation. Principles like "fairness" are usually formulated in very general terms and often do not provide guides to action in specific situations. To provide an action guide, principles need to be specified—it needs to be spelled out how, by whom, and under what circumstances an action is to be carried out (Beauchamp and Childress, 2008). When countervailing ethical principles apply to a decision or situation, they need to be balanced. That is, reasons need to be provided for why one principle should be given more weight than another in the circumstances under consideration (Beauchamp and Childress, 2008). The balance among principles may be struck differently in usual care and public health emergencies.

The concept of "suspending" moral rules may also be misleading. It suggests that they are temporarily cancelled. A more helpful perspective may be that ethical principles may be overridden in certain circumstances. Ethical principles are not absolute but *prima facie* binding; that is, they may be overridden, but only for good reasons. Those reasons will depend on the particular situation at hand; the acceptable reasons and their weight may differ in ordinary clinical care and during public health emergencies. When a *prima facie* principle is outweighed by a countervailing principle in a particular situation, it is overridden, not simply discarded or overruled (Beauchamp and Childress, 2008). When overridden, a principle is still followed to the greatest extent possible consistent with following the dispositive principle. Ethical principles that are overridden leave "moral traces": physicians find it emotionally difficult not to follow them and regret that they cannot follow them in the situation at hand. Moreover, when overriding a moral principle, people have an obligation to mitigate the harm caused by violating the principle (Beauchamp and Childress, 2008).

Let us illustrate these ideas through the example of allocating ventilators during a severe influenza pandemic. Treating physicians will be constrained by public health emergency regulations to follow public health allocation policies. The ethical rationale is that during a public health emergency the aggregate benefit to society assumes paramount importance, and minimizing the number of avoidable deaths takes priority over the core ethical principles that underlie usual clinical care: respect for patient autonomy and the best interests of individual patients.

However, beneficence in the sense of acting in the best interests of the individual patient is overridden, not neglected or discarded. This has several specific implications. Beneficence to the individual patient is still required in the sense of fidelity to patients and nonabandonment. For example, after Hurricane Katrina, some physicians and nurses did not report for duty, leaving hospitals severely understaffed, and hospitals allegedly did not make plans to evacuate patients. Physicians not only should not abandon patients, but they also retain positive duties to relieve patient symptoms and emotional distress to the greatest

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extent possible under the circumstances. Moreover, IOM (2009) drew a clear limit to overriding the best interests of the individual patient, declaring it would be unacceptable to administer drugs to intentionally cause or hasten a patient's death.

Furthermore, when basic ethical principles are overridden during a declared public health emergency, procedural safeguards and constraints should be observed in order to ensure that there are good reasons for overriding them and that the new balancing of principles is carried out in a fair manner. According to the IOM, these procedural safeguards should include acceptance by those affected by the crisis standards of care, transparency, consistency, proportionality, accountability, community and provider engagement, education, and communication. The CDC reports refer to procedural justice. Although these reports differ in how they specify these procedural safeguards, they agree that safeguards are essential to gain public acceptance and trust.

Finally, the idea that principles are overridden suggests specific ways to organize health care during a public health emergency. To maintain the treating physician's fidelity to his or her patients, the decision as to whether a patient in respiratory failure would receive mechanical ventilation should be made by a designated triage officer, not by the treating physician. This separation of roles should help the treating physician better maintain his or her fiduciary role.

Allocation of Scarce Resources

During a severe pandemic, there may be shortages of key medical resources, and rules for allocation may be needed. In the case of 2009-H1N1 influenza A vaccine, shortages may be temporary, for example, when production of the 2009-H1N1 influenza A vaccine is scaling up and systems for delivering vaccination are set up. For ventilators, shortages cannot be avoided because during a severe pandemic the need is projected to far outstrip the supply; the cost of supplying enough ventilators and critical care beds for a worst-case scenario would be prohibitive, diverting resources from more basic public health emergency needs.

For allocating scarce resources during a public health emergency, ethical principles will need to be specified—that is, explained in much greater detail with regard to particular public health interventions and circumstances. Another way to view what is needed is to develop second-order ethical principles, which are more specific than the first-order principles, such as fairness, which we have previously discussed.

Shortages of ventilators in usual clinical care can be overcome by expanding surge capacity. Allocation of resources in this situation is commonly done according to several second-order principles or rules: first come, first served; and informed refusal by patients or their surrogates. In usual clinical care, no patient is denied access to mechanical ventilation who has a medical indication for it and consents to it. Furthermore, if there is a temporary shortage of ventilators or

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critical care beds that cannot be addressed through surge capacity, the first-come, first-served principle is followed. Patients are not removed from the ventilator against their wishes to make way for a patient with a much better prognosis.

During a dire shortage of a medical resource in a public health emergency, however, these second-order principles governing usual clinical care would not achieve the public health goals of minimizing avoidable deaths and maintaining essential societal functions. For example, an intensive care unit (ICU) patient with a very low probability of survival can often be kept alive for weeks on a ventilator, precluding the use of a ventilator for several patients with less severe, uncomplicated respiratory failure, who are highly likely to survive after only a few days of mechanical ventilation. What second-order ethical principles or rules should guide allocation decisions during a public health emergency? Several candidate rules allocating scarce resources during the 2009-H1N1 influenza A pandemic are discussed below, as well as an illustration of how they have influenced government guidelines.

Giving priority to those with the greatest medical need This is an intuitively plausible rule, often characterized as the "rule of rescue." In ordinary clinical care, this principle is used to triage patients in the emergency department. With regard to 2009-H1N1 influenza A, this principle has been cited in several federal recommendations. For vaccine allocation, pregnant women receive highest priority because they comprise a disproportionately large percentage of cases of severe 2009-H1N1 influenza A infection. Infants are also given high priority because they are at increased risk but cannot receive vaccination. In another example, for postexposure prophylaxis with antivirals, high priority is given to persons with compromised immunity or who are living in a residential setting (such as skilled nursing facilities), who are at increased risk for infection.

While this rule is plausible, in some circumstances it may undermine the goal of maximizing the total number of lives saved. In the case of mechanical ventilation during a severe pandemic, it would not make sense to allocate ventilators to patients who are so sick that they will have a very poor prognosis even if they receive the ventilator. More lives would be saved by the following rule.

Giving priority to those who are most likely to benefit from the scarce medical resource This rule would indeed maximize the number of lives saved. With regard to allocation of ventilators in a severe pandemic, this rule would give higher priority to those patients with respiratory failure who have the highest probability of survival if they receive mechanical ventilation. The utilitarian principle of maximizing the number of lives saved could be further refined. Rather than maximizing the number of lives saved, the aggregate utility might be characterized in other ways, for example maximizing the number of life-years saved. While theoretically attractive, however, it might be impractical to try to assess expected life-years when making allocation decisions in the emergency

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department. Still another refinement of the utilitarian public health goal might be to maximize the number of quality-adjusted life-years saved. However, in addition to the practical difficulties in assessing quality of life in emergency settings, assessments of quality of life can be criticized as discriminatory.

Giving priority to persons whose roles are vital for society as a whole This prioritization rule will help achieve the goal of preserving essential societal functions. For example, the Department of Health and Human Services (HHS) vaccine allocation policy gives priority to those needed in pandemic response and care (such as physicians, and first responders) and to those who provide essential services and security (such as police). It is important that these essential roles be specific for the type of intervention and emergency under consideration. Furthermore, this emergency- and intervention-specific prioritization should not be confused with general estimates of social worth, which have no place in public health emergency rules. Giving priority to healthcare workers makes sense for vaccinations, as they will subsequently be able to continue to provide medical care to patients who are sick with 2009-H1N1 influenza A. However, such priority makes less sense for mechanical ventilation, because healthcare workers who are so sick as to require mechanical ventilation are unlikely to recover their health in time to provide services to other patients during that wave of the pandemic.

Give priority to the fair distribution of benefits A general criticism of utilitarianism is that it ignores the distribution of benefits across society, which some consider to be important as well as the total amount of benefit to society. Several criteria have been proposed for distributing the benefits of scarce medical resources fairly.

Equal access to interventions Whatever prioritization rule is selected, it may exacerbate health disparities because certain groups may lack access to the public health intervention. For instance, HHS guidelines for 2009-H1N1 influenza A vaccination give priority to pregnant women. However, pregnant women who are poor, have low health literacy, and lack private health insurance and a primary care physician may have steep barriers to accessing vaccination services. The concern about worsening disparities is particularly acute because such women disproportionately will be women of color. Thus, in implementing prioritization rules, it will be essential that barriers to access be identified and ameliorated.

Life-cycle principle Some argue that everyone should have equal opportunity to live through all the stages of life (Emanuel and Wertheimer, 2006). Under this principle, children would have priority over elderly persons. This principle is consistent with the common belief that the death of a child or young adult is more tragic than the death of an elderly person who has already had the opportunity to have a family and career and grow old (Lo, 2009a).

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Reciprocity Another allocation principle that invokes the distribution of benefits is giving priority to persons whose work is essential in the pandemic response but puts them at increased risk for 2009-H1N1 influenza A. This priority might be viewed as reciprocity for assuming a duty to provide medical care and other services to infected persons. However, this principle may be regarded as self-serving, because physicians are drawing up priorities that put them at the head of the list.

Fair opportunities A more radical critique of utilitarianism rejects the goal of maximizing aggregate benefit to society. If there are relatively small differences in expected survival between two prioritization groups, some argue that it is not fair to those in the lower priority group to have no chance to survive. Philosophers have proposed a weighted lottery system, in which people in the lower priority group receive some small but nonzero chance of receiving the intervention (Daniels and Sabin, 2002). During a public health emergency, there would be many difficult challenges to a weighted lottery to allocate ventilators. Information on prognosis and outcomes is incomplete and uncertain, and it would be difficult to set weights for the lottery in an understandable manner. Allegations of bias would likely be made if a wealthy or famous person in a lower priority group received a ventilator. Finally, even if a trustworthy weighted lottery could be set up, it would be difficult to implement during a public health emergency.

Patient Challenges to Allocation Priorities

During public health emergencies, physicians in clinical practice will encounter patients who request or demand a scarce intervention even though they fall outside public health priorities for receiving it. Physicians' responses during a public health emergency will differ from their responses in usual clinical practice to patient requests for interventions that are not medically indicated. In usual practice, physicians generally attempt to persuade the patient that they are unnecessary. However, physicians often accede to such requests, as long as the intervention does not present undue medical risk to the patient (Lo, 2009a), is not futile in a strict sense, and does not deprive another identified patient who would benefit from the intervention. In contrast, during a public health emergency, it may not be appropriate or feasible to provide interventions that are in very short supply to persons who do not fit public health priorities (Lo, 2009a; Lo and Katz, 2005).

During an outbreak of severe pandemic influenza, a healthy 43-year-old lawyer asks his primary care physician for vaccination. "We've just bought a new house, started a new business, and had our second baby. I can't afford to get sick, and my family and employees can't afford to lose me" (Lo, 2009a). Current public health guidelines for 2009-H1N1 influenza A vaccination give low priority to healthy people of this age. Because of vaccine shortages at the time, they are unlikely to be vaccinated.

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Impact on Others

Unlike usual clinical care, during public health emergencies decisions for one patient regarding scarce interventions will likely have an impact on other patients. Public acceptance of priorities for allocating scarce resources during a public health emergency will be enhanced if the policies are perceived as fair. If many patients receive interventions even though they are not in high-priority groups, the press and Internet blogs are likely to report the story. In turn, people may believe that the guidelines are unfair or being unfairly implemented or that the magnitude of the threat is greater than officials acknowledge (Lo, 2009a). If some patients receive the vaccine even though they do not belong to a high-priority category, other patients in the low-priority categories will be less likely to accept the allocation plan.

Act in the Best Interests of the Patient

Physicians should maintain their usual role of acting in the best interests of the individual patient, insofar as it is possible while respecting emergency public health guidelines (Lo, 2009a).

Elicit and address patient concerns and emotions Fear and a sense of loss of control are natural human reactions to public health emergencies, and they need to be acknowledged. Also physicians should acknowledge the uncertainty inherent in an emergency. Patients may be more willing to pay attention to public health after their own needs are acknowledged. Trying to reassure people by telling them not to worry is unlikely to be effective during a declared public health emergency (Lo, 2009a).

Use the doctor-patient relationship to benefit patients The physician can explain other measures the patient can take to reduce the risk of infection, such as social distancing, frequent hand-washing, and telecommuting. The physician should explain that in the case of 2009-H1N1 influenza A vaccine, it is likely that individuals in lower priority groups will receive the vaccine, only at a later date. Patients often could be reassured if they are informed that they could see the physician promptly if they develop symptoms (Maunder et al., 2003). Also patients may be reassured by knowing what warning signs to watch for.

Advocate for appropriate exceptions to restrictions A particular case may be a justified exception to emergency public health policies or may show that a policy needs to be modified (Lo, 2009a). For example, a case could be made that, because of the number of reported cases of severe 2009-H1N1 influenza A influenza among young, healthy adults, they should receive higher priority for vaccination. Any exception should be fair in the sense that it would also apply to

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all other patients in a similar clinical situation, not just the particular patient at hand. If such a widespread exception would not be feasible from a public health perspective, it is difficult to justify making an exception for an individual patient (Lo, 2009a). It would be preferable for treating physicians to contact public health officials to ask that the rules be changed, rather than making an *ad hoc* exception that would not be consistently applied by other caregivers.

Research During a Public Health Emergency

Because the current 2009-H1N1 influenza A pandemic is novel, research will be needed to provide up-to-date information about the pandemic on which to base public health policy.

Public health officials have a legal responsibility to carry out surveillance and epidemiological studies during a public health emergency. This will require officials to collect information from patients, physicians, hospitals, and clinical laboratories and to investigate cases and outbreaks as needed. For such activities, which are routine public health practice, generally institutional review board (IRB) approval and individual patient consent are not required.

Beyond this, research will also be needed to determine what clinical strategies and treatment are optimal during this pandemic. For instance, several important questions about respiratory failure during a severe 2009-H1N1 influenza A pandemic need to be studied. One question is how best to assess the prognosis of patients with respiratory failure. The Sequential Organ Failure Assessment (SOFA) scoring system for patients in critical care units has not been prospectively validated in the setting of a 2009-H1N1 influenza A outbreak. As previously discussed, expected prognosis will be a key consideration in prioritizing patients who require mechanical ventilation if there is a dire shortage of ventilators. A second question concerns treatment for patients with 2009-H1N1 influenza A infection and refractory respiratory failure. Some critical care units have used extracorporeal membrane oxygenation (ECMO) for patients whose respiratory failure does not respond to mechanical ventilation and other critical care. Case series suggest that ECMO may be of benefit in this situation (Bertozzi et al., 2009). However, the efficacy and safety of ECMO when added to standard critical care in this setting can only be rigorously determined in a randomized controlled clinical trial (RCT). Randomization is the best way to ensure that the group receiving ECMO and the group receiving standard critical care are similar at baseline and to reduce the possibility that any observed difference in outcome between the two groups was due to some factor other than ECMO. Because ECMO is a scarce, labor-intensive resource, it is important to rigorously evaluate its effectiveness and safety, so that clinical standards regarding its use will be based on sound evidence and to ensure that scarce resources are prudently allocated. Additional novel clinical questions undoubtedly will arise during a severe pandemic.

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Carrying out research during a public health emergency presents formidable challenges that are best addressed in advance. Public health personnel will be stretched thin carrying out their duties during a wave of a severe pandemic and may have little time to plan and organize research studies and obtain IRB approval for them if needed. Delays in IRB approval may make it impossible to carry out studies in a timely manner, particularly multicenter studies, for which many IRBs need to give approval.

We offer several suggestions to facilitate research that will provide crucial information for setting public health policies and for clinical standards during a public health emergency:

1. The National Institutes of Health (NIH) and CDC should fund the preliminary design of such crucial clinical research as part of preparedness for a severe pandemic. If the design and planning for such studies begins only if and when the pandemic becomes severe, valuable time will be lost. Some investment now in research planning will allow more timely research if a severe pandemic occurs and ultimately more efficient use of scarce public health resources.
2. Researchers should design studies that have strong confidentiality and data security provisions. Many investigators will be contributing to a central database and accessing the data. NIH or CDC should also establish a system of secure access to identifiable data on a strict need-to-know basis when deidentified data will not suffice. This system should have strong confidentiality and security protections for identifiable data, such as password protection, encryption, and a prohibition on downloading identifiable data to laptops or portable storage devices.
3. Local IRBs should give priority to the review of studies that will provide crucial data to guide public health policies and clinical standards during a public health emergency. For example, studies designated as such by an NIH or CDC panel should be placed at the head of the queue for IRB scheduling.
4. NIH or CDC should set up a central IRB review process to review multisite 2009-H1N1 influenza A studies and encourage local IRBs at each site to defer to this centralized review instead of carrying out their own in-depth review. This centralized process should conduct coordinated scientific and ethics review. To facilitate review by individual sites and to gain public trust, the deliberations of this central IRB should be public. The transcript and minutes of this review should be publicly available on the Internet, so that local IRBs, investigators, and members of the public can readily access them. To facilitate acceptance of this central review by site IRBs, the central IRB should include IRB chairs from institutions that are expected to participate in these studies. The Centralized IRB established by the National Cancer Institute for multisite cancer clinical trials provides a model for such centralized review (Lo, 2009b).

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Different studies pose different ethics and human subject concerns. A multicenter study to validate SOFA as a prognostic tool in a 2009-H1N1 influenza A pandemic will be relatively straightforward in terms of human subjects protection, since it will use data that are already being collected for clinical and administrative purposes. It will not involve invasive interventions carried out solely for research purposes. The challenges will be to plan the study, protect confidentiality, and provide data security. It would be prudent to retain identifiers in order to allow long-term follow-up on participants. For example, long-term mortality could be readily determined through the National Death Registry, which requires identifying information on each participant.

A multicenter RCT of ECMO would present complex scientific, design, and ethical challenges. A number of ethical issues would need to be addressed:

- Is there scientific and clinical rationale for such a trial? If many institutions begin to offer ECMO, it may be desirable to study its effectiveness and safety in this setting to help set emergency standards of care even if the evidence supporting its use is weak.
- Will ECMO be offered to patients at trial sites outside the clinical trial?
- Investigators need to plan procedures for surrogate consent, because almost all eligible participants will be unable to consent themselves.
- Investigators need to address conflicts of commitment between carrying out an RCT of ECMO and providing clinical care. During a severe pandemic, it may be difficult to mobilize resources to carry out the trial, since key personnel will likely be needed for clinical duties. Thus, it would be preferable to carry out such a trial when the pandemic is of mild severity and there is no dire shortage of ICU personnel.

Because these challenges would be difficult to address during a severe pandemic, it might be desirable to discuss them now.

Concerns About Emergency Public Health Policies

During a declared public health emergency, public acceptance of and trust in emergency measures will be crucial. As part of public engagement and outreach, it would be prudent for public health officials to anticipate concerns that might be raised and to address them explicitly. Furthermore, officials should recognize that some concerns might not be voiced during formal public engagement activities, just as patients may not voice their underlying concerns to the treating physician during patient care.

Because public health emergency powers are so broad, they may provoke distrust of government and scientists. Many Americans distrust government and seek to limit its power. They may view the federal government as infringing on their God-given and constitutionally protected liberty. Plans for mandatory measures such as isolation, quarantine, and allocation of health care resources may be

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viewed as violating their freedom. Some critics may believe that the government cannot play a constructive role in protecting life; in their perspective, this should be left to individual initiative. Such critics may view government allocation of health resources as an unwarranted intrusion on the doctor-patient relationship, which they have voluntarily chosen, as well as a violation of their privacy. Furthermore, some critics may view the government as incompetent and inefficient and therefore unable to provide effective services during an emergency. The inept response to Hurricane Katrina serves to strengthen this view. Finally, some critics may view the government as corrupt, favoring special interests rather than the common person. Thus, they may suspect emergency powers will serve to benefit only the well-connected and the well-to-do. These objections to emergency preparedness plans may be based not on the merits of particular provisions in the plans but instead on a political and social philosophy that is deeply critical of governmental power.

Another sweeping objection to public health emergency powers may rest on distrust of scientists and scientific expertise. Again, there may be several strains to this objection. One criticism is that scientists are not objective. Scientists may be viewed as serving the interests of drug and vaccine manufacturers with whom they have lucrative consulting arrangements. In this view, guidelines that give priority to healthcare workers for scarce resources may be viewed as self-serving. A more fundamental objection concerns the scientific method. Some critics believe that scientists disregard or play down the risks of interventions that are obvious to a layperson. The scientific method is not viewed as objective and leading to a societal good, but rather as a means of asserting power over the ordinary person and promoting conclusions that defy common sense and the wisdom of the people. Again, these populist objections are manifest with regard to other public health measures. Some people continue to oppose childhood vaccination as causing serious adverse effects such as autism, despite a number of consensus, peer-reviewed panels that have concluded that there is no association. Furthermore, the debacle of swine flu vaccination in 1976 may be viewed as an example of ineptitude and arrogance by both government and scientists. The Internet allows such objections to public health measures to be rapidly and widely disseminated.

What can be done to respond to these objections?

First, these objections need to be acknowledged and addressed directly. In patient care it is helpful for the treating physician to listen to the patient's concerns, acknowledge them, show that he or she understands them, and empathize with the underlying feeling that animates the concerns, even if he or she does not agree with them. Such acknowledgment of concerns legitimizes the underlying feelings and may be a helpful first step in finding common ground.

Second, the highest-level public health officials should articulate to the public a vision of what kind of nation we aspire to be in a dire public health emergency. There should be an appeal to values we hold in common as human beings

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and as Americans—such as helping others in great need, making sacrifices, and generosity. These values, which are widely shared among different faith traditions and cultures, provide the grounding for more formal ethical principles like fairness and maximizing the number of lives saved. Furthermore, leaders need to articulate a vision of the proper role of government during a public health emergency. Acknowledging that people differ in how much power they believe government should have during ordinary times, leaders need to make the case that, during extraordinary times such as public health emergencies, special powers are needed. Leaders should also reassure the public that emergency powers will be cancelled as soon as the emergency passes.

In conclusion, ethical issues will be prominent in setting public health policies during the influenza pandemic. Public health officials will need to articulate the ethical reasoning that supports their policies and to develop a process for setting policy that is regarded as fair and participatory. Officials will need to explain why during a declared public health emergency restrictions on liberty and allocation of scarce health resources is ethically appropriate.

Acknowledgments

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References

Beauchamp, T. L., and J. F. Childress. 2008. *Principles of biomedical Ethics*. New York: Oxford University Press.

Bertozzi, S., A. Kelso, M. Tashiro, V. Savy, J. Farrar, M. Osterholm, S. Jameel, and C. P. Muller. 2009. Pandemic flu: from the front lines. Interviewed by D. Butler. *Nature* 461(7260):20-21.

Childress, J. F., R. R. Faden, R. D. Gaare, L. O. Gostin, J. Kahn, R. J. Bonnie, N. E. Kass, A. C. Mastroianni, J. D. Moreno, and P. Nieburg. 2002. Public health ethics: mapping the terrain. *Journal of Law and Medical Ethics* 30(2):170-178.

Colgrove, J., and R. Bayer. 2005. Manifold restraints: liberty, public health, and the legacy of *Jacobson v Massachusetts*. *American Journal of Public Health* 95(4):571-576.

Daniels, N., and J. Sabin. 2002. *Setting limits fairly—can we learn to shared medical resources?* New York: Oxford University Press.

Emanuel, E. J., and A. Wertheimer. 2006. Who should get influenza vaccine when not all can? *Science* 312(5775):854-855.

Fidler, D. P., L. O. Gostin, and H. Markel. 2007. Through the quarantine looking glass: drug-resistant tuberculosis and public health governance, law, and ethics. *Journal of Law Medicine and Ethics* 35(4):616-628, 512.

Gostin, L. O. 2008. *Public health law: power, duty, restraint,* 2nd edition. Berkeley: University of California Press.

Gostin, L. O., J. W. Sapsin, S. P. Teret, S. Burris, J. S. Mair, J. G. Hodge, Jr., and J. S. Vernick. 2002. The Model State Emergency Health Powers Act: planning for and response to bioterrorism and naturally occurring infectious diseases. *Journal of the American Medical Association* 288(5):622-628.

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Gostin, L. O., R. Bayer, and A. L. Fairchild. 2003. Ethical and legal challenges posed by severe acute respiratory syndrome: implications for the control of severe infectious disease threats. *Journal of the American Medical Association* 290(24):3229-3237.

IOM (Institute of Medicine). 2009. *Guidance for establishing crisis standards of care for use in disaster situations*. Washington, DC: The National Academies Press.

Jennings, B., and J. Arras. In review. Ethical guidance for public health emergency preparedness and response. *Morbidity and Mortality Weekly Report*.

Kinlaw, K., and R. J. Levine. 2007. *Ethical guidelines in pandemic influenza* 2007. Recommendations of the Ethics Subcommittee of the Advisory Committee to the Director, Centers for Disease Control and Prevention, http://www.cdc.gov/od/science/phethics/panFlu_Ethic_Guidelines.pdf (accessed October 14, 2009).

Lo, B. 2009a. Best interests. In *Resolving ethical dilemmas: a guide for clinicians*. Philadelphia: Lippincott Williams & Wilkins.

———. 2009b. IRB review of human participants research. In *Ethical issues in clinical research: a practical guide*. Philadelphia: Lippincott Williams & Wilkins.

Lo, B., and M. H. Katz. 2005. Clinical decision making during public health emergencies: ethical considerations. *Annals of Internal Medicine* 143(7):493-498.

Maunder, R., J. Hunter, L. Vincent, J. Bennett, N. Peladeau, M. Leszcz, J. Sadavoy, L. M. Verhaeghe, R. Steinberg, and T. Mazzulli. 2003. The immediate psychological and occupational impact of the 2003 SARS outbreak in a teaching hospital. *Canadian Medical Association Journal* 168(10):1245-1251.

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A9

RUMORS OF PANDEMIC: MONITORING EMERGING DISEASE OUTBREAKS ON THE INTERNET

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Summary

Unofficial or informal sources (also called "rumors" or "unstructured data") of emerging disease outbreaks such as media reports and firsthand accounts have become an important mechanism for detecting these outbreaks (Brownstein et al., 2009a). These sources are disseminated by a variety of human-based and automated biosurveillance networks that are now routinely monitored by public health authorities at all levels. The 2005 revisions to the International Health Regulations (IHR) recognize that these sources often appear in advance of official notification of disease threats and are important in allowing the timely response to emerging diseases. Early media reports of respiratory illness in Mexico were among the first signs of the 2009-H1N1 influenza A pandemic and unofficial information sources are a critical mechanism for following the pandemic (Brownstein et al., 2009b). Studies to evaluate the sensitivity and specificity of informal sources and to improve the detection of emerging disease outbreaks are under way.

Introduction

The work of ProMED-mail (the International Society for Infectious Diseases Program for Monitoring Emerging Diseases) and that of the Institute of Medicine (IOM) have intersected in several ways since the well-known IOM (1992) publication of *Emerging Infections: Microbial Threats to Health in the United States*. This report ended a period of complacency in medicine where we had seen terms like the "conquest of infectious diseases" or "the end of infectious diseases," and

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we were brought into the present day by the emergence of several important diseases. The IOM has done a great deal in bringing these issues to the forefront.

A Tale of Two Emerging Diseases

Let us consider two emerging diseases, one before the birth of the Internet and one after it became a mature entity. The first was detected in 1981 (CDC, 1981). An article in *Morbidity and Mortality Weekly Report* (*MMWR*) was published recognizing a cluster of *Pneumocystis* pneumonia in gay men in Los Angeles. This outbreak became apparent only because treatment for *Pneumocystis carinii* was only available from the Centers for Disease Control and Prevention (CDC). CDC investigators noted this cluster of an unusual pathogen in an unusual patient population and that was the first recognition of what came to be known as HIV/AIDS.

However, we know well that HIV infection did not start in 1981 and that the epidemic had been going on for many years, largely in Africa, but also in other parts of the world. Certainly, HIV was widespread throughout Africa at the time it became apparent in the United States and yet, although this was not a subtle disease that could easily be missed, it was essentially unknown in the West.

What if we had known earlier? Two trends were visible in the early 1990s. One was the growth and popularization of the Internet, as it was coming out of the exclusive domain of the military and a few academic centers. This was the age, for example, when America Online (AOL) was born. The second was the recognition of the importance of emerging infectious diseases as HIV, Legionnaire's disease, and resurgent rheumatic fever became evident. Many clinicians and scientists soon had access to electronic mail and some began to wonder whether this medium could be used as a way of speeding the transmission of information about emerging diseases.

A group of very prescient individuals, Steve Morse, Jack Woodall, and Barbara Hatch-Rosenberg, met at a UN-sponsored conference on detection of the use of biological weapons and began an email list among the attendees at the meeting. This mailing list became the nidus of the forum, the beginning of what was to become ProMED-mail (for Program for Monitoring Emerging Diseases). They began sending each other reports of emerging diseases, some of which might have involved the accidental or intentional release of biological weapons material. Soon many people wanted to share this information and join this mailing list, and from the initial group of about forty individuals, ProMED-mail was born (Madoff, 2004; Madoff and Woodall, 2005).

The outbreak referred to in this report and reproduced in Box A9-1 on the following page, of course, was the beginning of the pandemic that would become known as severe acute respiratory syndrome (SARS), the second disease in our tale. The report was in many ways typical of a ProMED report: an email from a reader who had overheard a rumor of what was going on in Guanzhou. Comments in an informal online source said that there were hospitals that had been

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BOX A9-1

PNEUMONIA - CHINA (GUANGDONG): RFI
****

Date: 10 Feb 2003
From: Stephen O. Cunnion, MD, PhD, MPH
International Consultants in Health, Inc
Member ASTM&H, ISTM

This morning I received this email and then searched your archives and found nothing that pertained to it. Does anyone know anything about this problem?

"Have you heard of an epidemic in Guangzhou? An acquaintance of mine from a teacher's chat room lives there and reports that the hospitals there have been closed and people are dying."

SOURCE: ProMED (2003).

closed and people who were dying. Since there were H5N1 avian influenza cases in Hong Kong at around this time, there were many questions about whether this could have been avian influenza. All ProMED reports are moderated and the moderator comment questioned whether this outbreak in fact was due to flu. It was not clear at the time.

SARS traveled quickly. The first Canadian death occurred in March 2003, raising the issue of who needs to know what and when (Poutanen et al., 2003). One of the problems with the traditional public health system is that it often presumes to know who needs access to information. But the ethos of ProMED has always been for transparency—that we cannot predict who is going to need to know. Who would have guessed that doctors in an emergency room in Toronto were going to be seeing cases of SARS so quickly after this mysterious illness appeared in Asia?

Hierarchical Surveillance Systems Versus Informal-Source Surveillance Systems

If we look at how traditional public health works, we can see that there is a flow of information from the ground up (Figure A9-1). Laboratories, practitioners, and members of the general public report to local officials, who then report to regional officials, and they to national officials. These, in turn, report to world bodies, who will publicize or convey back information to others as they deem necessary and inform the people who need to be involved in response to an outbreak or who need to be aware of it.

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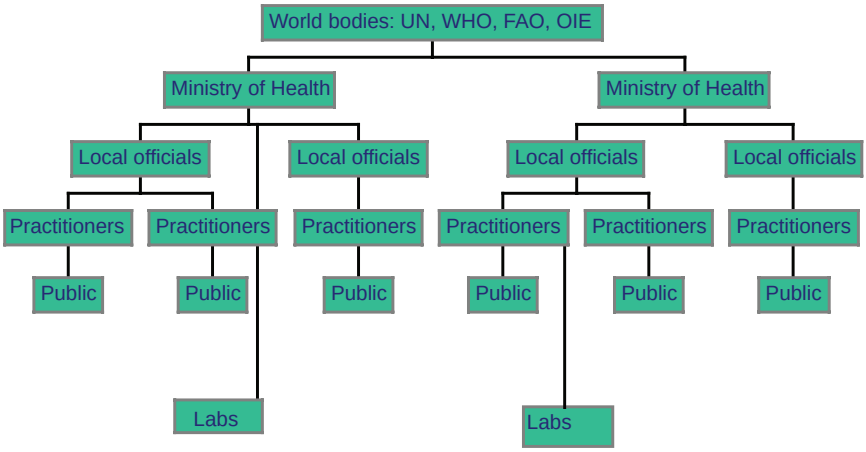

FIGURE A9-1 Hierarchichal nature of traditional public health reporting.

This is a powerful system and one that is very good at capturing much information and funneling it towards people who can collect, digest, and process it. However, it is also a system that takes time and one in which any break in the chain can lead to the loss of information.

In contrast, the idea behind informal biosurveillance systems (Figure A9-2) is that they not only deal with a hierarchical system but also can communicate in both directions with many levels of the system, such as local health officials, laboratories, ministries, and the World Health Organization (WHO), in addition to healthcare workers in the field, the public, and the media. This kind of process can speed the flow of information and can improve our ability to detect outbreaks.

Automated and Manual Biosurveillance Systems

Shortly after ProMED began operating, it became clear that the space on the Internet was becoming larger and larger and that it really was not possible for a person to look at everything and see everything. The idea of web crawling, or using automated search systems to mine the Internet for early warnings of emerging diseases, was born.

One of the first systems in the public health domain was the Global Public Health Information Network (GPHIN), established by the Public Health Agency of Canada and still operated by this entity (Mykhalovskiy and Weir, 2006). GPHIN remains a large and robust system that alerts public health officials and agencies such as CDC and the WHO that use it on a paid subscription basis to find out information about emerging diseases.

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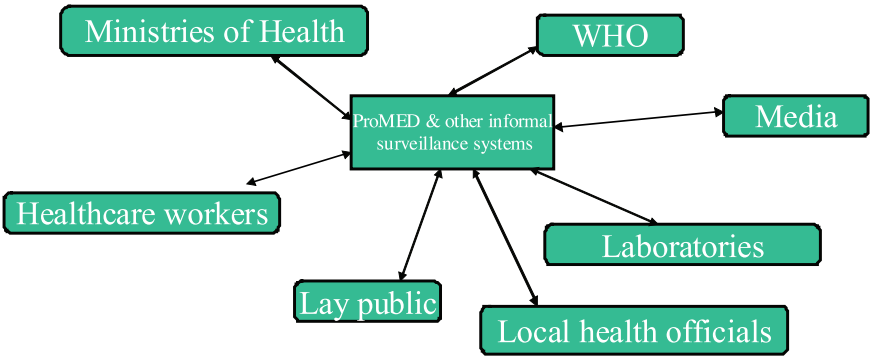

FIGURE A9-2 Informal-source surveillance.

HealthMap, based at Children's Hospital in Boston and with whom ProMED has been recently collaborating, is another type of automated tracking system for mining the Internet for reports infectious diseases (Brownstein and Freifeld, 2007). HealthMap uses automated systems similarly to GPHIN and goes a step further in trying to place reports in a geographical context, that is, on a map. They use multiple sources, including ProMED reports, WHO reports, a variety of news media sources, and other freely available sources. HealthMap places these reports in a geographical context and makes them available to everyone at no cost. Through their collaboration, HealthMap and ProMED are developing innovative ways to look at how emerging disease information is collected and distributed.

There are several automated or partially automated "biosurveillance" systems, terminology used by Reis and others (2003). Veratect is a commercial project that makes use of a variety of automated and human sources that was begun by personnel from the ARGUS system. Other biosurveillance systems include MedIsys, a web crawling tool organized by the European Union and focused on that region, and Biocaster, based in Japan. A number of these systems have been extensively reviewed in a recent publication (Walters et al., 2009).

There are also several human-based or manual biosurveillance systems, including the well-known Epi-X run by CDC, which is a closed and confidential network open only to public health officials. Other systems include an emerging infections network (EIN) run by the Infectious Disease Society of America (IDSA) (Polgreen et al., 2008), the Geo-Sentinel system run by the International Society of Travel Medicine (ISTM) with involvement of CDC (Freedman et al., 1999), and WHO's Global Outbreak Alert and Reporting Network (GOARN). Other systems focus on particular diseases or particular regions, or have a specialized focus.

An important point is that redundancy in this setting is good. These systems do not always pick up exactly the same signals, and having a variety of systems

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in place helps keep checks and balances on the other systems, and helps fill in and recognize gaps.

Automated and Manual Biosurveillance Collaboration

The collaboration between ProMED and HealthMap began with the simple ideas that ProMED reports would feed HealthMap and that HealthMap would automatically parse the text-rich and unstructured ProMED reports, categorize them by disease, and place them on their map of the world with each map point containing a link back to the ProMED report.

Soon it became apparent that there were other areas for collaboration. One of them was that ProMED could exploit HealthMap's automatic systems for finding and reporting on disease outbreaks in the news media and other sources. HealthMap could generate alerts for ProMED staff so that, for example, a ProMED virology moderator could receive reports up to several times a day on a particular set of viral disease search terms.

This would clearly help in the discovery of new content and, we hoped, improve the timeliness of reporting because it would not depend on a reader seeing a report and sending it to ProMED, or on a ProMED rapporteur or staff member finding the report and posting it. The improved timeliness would also improve the capture.

HealthMap uses automated systems to place events geographically (so-called "geotagging"), to categorize events by disease type and by location. These were not always accurate; for example, a news story that talks about a "plague of cheating" on the football field could be detected as a plague outbreak, or a report of a disease outbreak in guinea pigs could be placed in Guinea on the map.

These types of errors can be captured and corrected by what we call "curation" of the HealthMap data, which is done manually by the ProMED staff. This kind of interaction, or community input from the ProMED staff into the HealthMap administration, would help improve the precision of the report. Also, the geotagging of HealthMap reports, which is automated, could place events at the country level, sometimes at the province or state level, but not more precisely than that. ProMED and HealthMap have developed tools so that its staff can virtually take a pin and place it on the precise location or locations of an outbreak.

This is essentially the marriage of an automated system with a human-based system in a way that strengthens both. Figure A9-3 shows a specialized map developed by HealthMap with the locations in ProMED reports. Each point is a clickable link that leads back to a full report of the outbreak.

Other Types of Informal Surveillance: Google Flu Trends

There are some other creative ways for monitoring Internet data for disease outbreak events.

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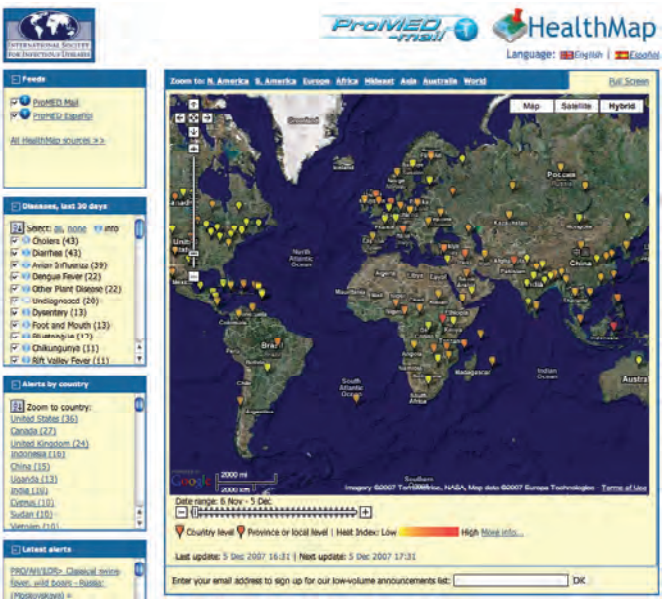

FIGURE A9-3 HealthMap screen shot.
SOURCE: See http://healthmap.org/promed/en.

One can monitor the "searchstream," that is, the terms that people use to search on the Internet with the premise that if an outbreak is going on, people will search using terms related to that outbreak (Polgreen et al., 2008). If there is a flu epidemic, for example, people will search "flu," or "fever," or "Tamiflu," or various similar terms. This approach has been refined and validated by Google Flu Trends (Ginsberg et al., 2009).

Google Flu Trends show that indeed if they monitor this searchstream it would detect influenza peaks at times before influenza-like illness (ILI) was actually detectable by other methods. Figure A9-4 is a screen shot of Google Flu Trends that shows the slow rise in ILI activity at this time of year. Also shown are the previous year's peaks and the spring peak associated with the 2009-H1N1 influenza A outbreak here in the United States. This can be monitored at the national level and then also at the state level.

H1N1 and Informal Source Surveillance

What clues to the ongoing 2009-H1N1 influenza A outbreak could be found in informal sources? A weblog from the journal *Science* (excerpted in Box A9-2) (Cohen, 2009) has recorded the outbreak of swine flu day by day and, according

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FIGURE A9-4 Google Flu Trends screen shot.
SOURCE: See http://www.google.org/flutrends/us/.

to its May 5, 2009, entry, the first documented cases were in Mexico City, later found to be confirmed with swine flu.

Retrospectively, one of the earliest reports appeared on HealthMap on April 1, 2009, from the Veracruz region of Mexico, showing an outbreak of pneumonia in that region.

Other blog entries discuss the role of the traditional public health system, its detection of the swine flu outbreak through laboratory findings, and its response to it. But at the same time informal sources were used, including HealthMap and Veratect, for recording information on this outbreak early on.

The April 11, 2009, entry discusses the revised IHRs, which became effective in 2007. The revised regulations recognize and to some extent codify the use of informal sources as valid sources of information for world public health and allow countries to report on reportable diseases of potential public health and international importance.

This was a key event that took many years to accomplish and WHO and the World Health Assembly deserve great credit for allowing it to happen. ProMED's first report on April 22, 2009, followed the *MMWR* publication of the swine flu cases in California.

Box A9-2 is a brief summary of the use of informal information sources in the context of this current outbreak. Informal surveillance systems played a relatively minor role and the traditional public health system worked quite well in terms of this outbreak. The systems that have been in place for what we all thought would probably be an avian flu outbreak functioned quite effectively.

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BOX A9-2
Swine Flu Day by Day

11 March: First documented symptoms (as of 5 May) in a Mexico City resident who later would be found to have confirmed infection with A(H1N1) swine flu.

30 March: A 10-year-old boy with fever, cold, and vomiting goes to the Naval Medical Center San Diego in California. As part of a clinical study, a nasopharyngeal swab is sent across town to the Naval Health Research Center (NHRC).

1 April: NHRC researchers determine that the boy is likely infected with influenza A, but they cannot subtype the strain. As per protocol, the sample is sent to Marshfield Labs in Wisconsin. HealthMap, a global disease alert system run by academics, flags a news story from Mexico about a strange respiratory outbreak in the state of Veracruz that has claimed two lives.

6 April: Veratect, a Kirkland, Washington-based company that scours news reports for emerging threats, reports in its subscription-only database that local Mexican health officials have declared an alert because of respiratory disease outbreak in La Gloria, Veracruz state, Mexico.

11 April: As per the International Health Regulations (IHR), the World Health Organization (WHO) has a pandemic alert and response network, which relies on designated people or institutions in each member country to report unusual disease patterns. PAHO, a regional office of WHO, asks the Mexican IHR "focal point" to verify the outbreak reported in the news.

12 April: Mexico's director general of epidemiology confirms to PAHO the existence of acute respiratory infections Studies continue. Mexico's focal point considers outbreak to be a "potential public health event of international importance" because it meets IHR criteria: severe public health impact and an unusual event.

21 April: Samples from Mexico arrive at PHAC.

22 April: CDC publishes first dispatch in the Morbidity and Mortality Weekly Report (MMWR) about two cases in California. Mexico reports atypical influenza behavior associated with severe pneumonia in various cities. InDRE [Instituto de Diagnóstico y Referencia Epidemiológicos] ships samples to PHAC s National Microbiology Laboratory in Winnipeg and CDC.
ProMED's first report on human cases citing CDC report.

23 April: Samples from Mexico arrive at CDC. PHAC and CDC confirm Mexico cases are the same A(H1N1) of swine origin.

SOURCE: Excerpted and adapted from Cohen (2009).

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It is important to mention, however, that informal sources have played a role in monitoring the progress of this outbreak and in keeping tabs on what is happening. To date, ProMED has posted more than 230 reports about it, many of them long, multipart reports, since April 2009.

Establishing a Baseline to Evaluate Informal Source Disease Surveillance

How well do informal sources work in detecting and reporting public health events? How can we look at this, evaluate it, and improve it? One of the activities that ProMED has pursued in collaboration with HealthMap is to take the archive of ProMED data, which consists of more than 40,000 free text reports dating back to 1994, and put them into a structured database. This was done by extracting, in a mostly automated way, the information from reports based on disease occurrence, type of disease, location, numbers of cases, dates of onset, dates of detection, dates of lab confirmation, and so forth, and putting them into a structured database and combining these data with external informal sources (such as news media). For the first time ProMED was able to see clearly what it had been doing.

Each circle in Figure A9-5 represents a particular disease. Many of the diseases that ProMED reports on are undiagnosed or unidentified, but there are quite a few others that are; avian flu is again at the forefront.

Through this approach, diseases can be followed over time. An individual disease can be observed and in some ways a bit of the history of emerging infectious diseases over the past 15 years can be seen. The system provides the ability to look at ProMED reports, the numbers of ProMED reports over time, and to track disease occurrence. It also shows that it is important to look not just for what is expected, but for that which is not.

From the structured database, it is possible to visualize the locations of ProMED reports over the period. It was noted that reports tend to occur most frequently in the northern hemisphere, in the information-rich and media-rich regions of the world, the United States and Western Europe in particular. Thus, the Southern Hemisphere, South America, Africa, and Asia are much less well covered by ProMED, a problem that ProMED is aware of and striving to solve.

One of the ways in which ProMED is addressing this issue is through regional programs. One of its oldest and best-established programs is in Latin America, which Eduardo Gotuzzo helped form in collaboration with the Panamerican Infectious Disease Association (API). ProMED has established relationships with the Mekong Basin Disease Surveillance Group in the countries that border the Mekong River in Southeast Asia in collaboration with WHO and the Rockefeller Foundation. With funding provided by Google.org it has established two new networks, in East Africa and in Francophone Africa, particularly West Africa; and the Nuclear Threat Initiative (NTI) provided funding for a Russian-language system based in the former Soviet Union.

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FIGURE A9-5 Quantitation of subjects in ProMED reports from 1996-2008. The size of each circle corresponds to the number of reports on a given topic.

These are all areas where disease surveillance was and continues to be relatively poor, so the regional networks serve two functions: one is to improve regional collaboration to help providers and public health within these regions, and the other is to help inform the broader world about problems within these regions. They serve that function nicely and ProMED expects to see further growth within these networks.

ProMED and HealthMap have studied the structured global baseline of its reports, news reports, and other reports by comparing the dates of detection of a series of outbreaks and establishing a group of distinct outbreaks based on geographic region and time period. We first assessed the sensitivity and scope of these datasets with a descriptive analysis of ProMED reports. Next, analyzing the WHO's Global Alert and Response (GAR) reports between 1996 and 2008, we

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selected human outbreaks of infectious, non-food-borne diseases that were not considered seasonal or endemic to the region, and were not isolated, imported cases, then extracted the corresponding ProMED and HealthMap reports. WHO reports are not necessarily the first report or the first time that WHO becomes aware of or works on an outbreak. However, they are a gold standard, a publicly available record that could be used to look at these data.

We subsequently created timelines of the progression and reporting for each outbreak, compared the timing in reporting by official and informal sources, and attempted to identify factors that may contribute to differences in the timing of reporting. A qualitative analysis of the ProMED data set revealed a sensitive increase in the number of ProMED reports for specific diseases and locations around the time the WHO reported corresponding outbreaks. Figure A9-6 is a timeline showing time differences between official WHO reports, informal reports, and various "outbreak milestones." The line at 0 days represents no lead/lag over the WHO report. The line represents the date of the EPR report and each blue dot represents the date of something else, a date identifiable within a ProMED report. For the earliest ProMED report, the dates of symptom onset, hospitalization, death, or lab confirmation are recorded and the black diamonds represent the median time before the publication, or the official verification of the report. For 355 WHO-confirmed outbreaks, ProMED reported on average 18 days (95 percent C.I.: 12.2-23.8) earlier than WHO's GAR reports, while HealthMap reported 12 days (5.4-18.2) earlier (Figure A9-1). A further analysis revealed country- and disease-dependent differences in reporting. Sensitivity was 0.946 (0.923-0.970) for ProMED (n = 355), and 1.000 (1-1) for HealthMap (n = 39). This preliminary work shows that informal online disease reporting can facilitate both sensitive and timely detection of disease outbreaks. An examination of the finer-grained differences in reporting depending on the disease and location reveals the most informatively valuable areas in which efforts for monitoring the vast amount of informal online reports should be targeted. Early and accurate recognition of outbreaks is crucial for expediting the initiation of appropriate interventions.

It is also possible to look at these data by country and see clear differences between individual countries and regions in the speed of early reporting according to disease type. Some diseases are reported in a much more timely way than others, both by ProMED and by WHO. The structured database can be used to try to identify the gaps in ProMED's and other informal surveillance systems too, by disease type, by geography, and by language; find the most effective signals, both in terms of accuracy and timeliness; and learn ways to reduce noise. Signal-to-noise ratio is a major problem with biosurveillance systems.

It is possible that one of the reasons more alarm bells did not go off when outbreaks of pneumonia were being reported in Mexico is that outbreaks of pneumonia are frequent. How do we know which ones matter and how do we know which ones are worth our attention? Hopefully an analysis of these data will help

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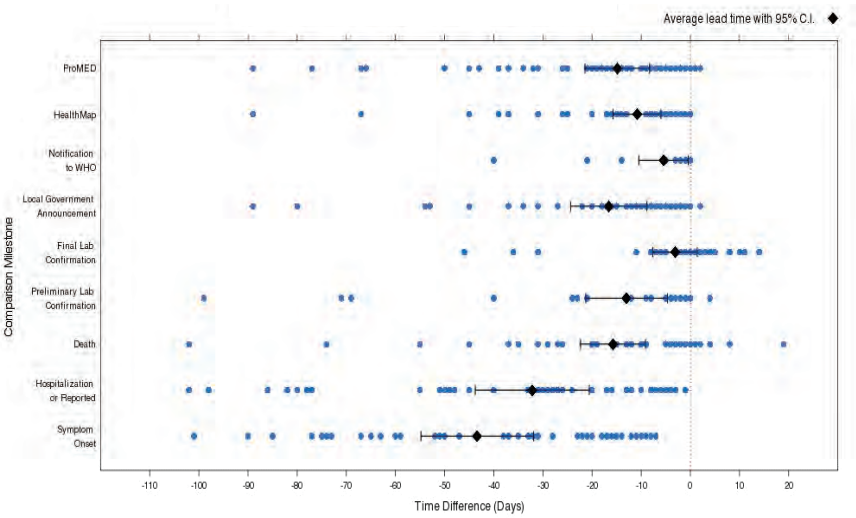

FIGURE A9-6 Timeline showing time differences between official WHO reports, selected informal reports, and various "outbreak milestones."

identify the right signals and make it possible to shorten the interval between outbreak and detection. Using this analysis, we can prospectively evaluate these findings using ProMED and HealthMap as we go forward.

Conclusions

The monitoring of informal sources of information or rumors is an important tool in public health. It is free of political constraints, it is transparent, and it allows for clinicians and other observers to have a role in reporting on emerging diseases.

Informal sources of information can complement and assist the traditional public health systems rather than attempt to replace them. Multiple systems are complementary and enhance the ability to detect outbreaks. Those using informal surveillance systems need to maintain a broad view and not focus on a particular disease, region, or type of disease. They need to keep their eyes on the horizon and need to work to improve the signal-to-noise ratio and to improve geographic coverage.

Acknowledgments

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References

Brownstein, J. S., and C. C. Freifeld. 2007. HealthMap: the development of automated real-time Internet surveillance for epidemic intelligence. *Eurosurveillance* 12(11):E071129.5.

Brownstein, J. S., C. C. Freifeld, and L. C. Madoff. 2009a. Digital disease detection—harnessing the Web for public health surveillance. *New England Journal of Medicine* 360(21):2153-2155, 2157.

———. 2009b. Influenza A (H1N1) virus, 2009—online monitoring. *New England Journal of Medicine* 360(21):2156.

CDC (Centers for Disease Control and Prevention). 1981. Pneumocystis pneumonia—Los Angeles. *Morbidity and Mortality Weekly Report* 30(21):1-3.

Cohen, J. 2009. *Swine flu outbreak, day by day*, http://blogs.sciencemag.org/scienceinsider/special/swine-flu-timeline.html (accessed November 15, 2009).

Freedman, D. O., P. E. Kozarsky, L. H. Weld, and M. S. Cetron. 1999. GeoSentinel: the global emerging infections sentinel network of the International Society of Travel Medicine. *Journal of Travel Medicine* 6(2):94-98.

Ginsberg, J., M. H. Mohebbi, R. S. Patel, L. Brammer, M. S. Smolinski, and L. Brilliant. 2009. Detecting influenza epidemics using search engine query data. *Nature* 457(7232):1012-1014.

IOM (Institute of Medicine). 1992. *Emerging infections: microbial threats to health in the United States*. Washington, DC: National Academy Press.

Madoff, L. C. 2004. ProMED-mail: an early warning system for emerging diseases. *Clinical Infectious Diseases* 39(2):227-232.

Madoff, L. C., and J. P. Woodall. 2005. The Internet and the global monitoring of emerging diseases: lessons from the first 10 years of ProMED-mail. *Archives of Medical Research* 36(6):724-730.

Mykhalovskiy, E., and L. Weir. 2006. The Global Public Health Intelligence Network and early warning outbreak detection: a Canadian contribution to global public health. *Canadian Journal of Public Health* 97(1):42-44.

Polgreen, P. M., Y. Chen, D. M. Pennock, and F. D. Nelson. 2008. Using Internet searches for influenza surveillance. *Clinical Infectious Diseases* 47(11):1443-1448.

Poutanen, S. M., D. E. Low, B. Henry, S. Finkelstein, D. Rose, K. Green, R. Tellier, R. Draker, D. Adachi, M. Ayers, A. K. Chan, D. M. Skowronski, I. Salit, A. E. Simor, A. S. Slutsky, P. W. Doyle, M. Krajden, M. Petric, R. C. Bruham, A. J. McGreer, National Microbiology Laboratory Canada, Canadian Severe Acute Respiratory Syndrome Study Team. 2003. Identification of severe acute respiratory syndrome in Canada. *New England Journal of Medicine* 348(20):1995-2005.

ProMED. 2003. *Pneumonia—China (Guangdong): RFI*, http://www.promedmail.org/pls/pm/pm?an=20030210.0357 (accessed November 20, 2009).

Reis, B. Y., M. Pagano, and K. D. Mandl. 2003. Using temporal context to improve biosurveillance. *Proceedings of the National Academy of Sciences* 100(4):1961-1965.

Walters, R., P. Harlan, N. Nelson, and D. Hartley. 2009. Data sources for biosurveillance. In *Wiley handbook of science and technology for homeland security*, edited by J. Voeller. Hoboken, NJ: John Wiley and Sons, Inc. Pp. 1-17.

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A10

PRELIMINARY OBSERVATION OF THE EPIDEMIOLOGY OF SEASONAL AND PANDEMIC INFLUENZA A (H1N1) IN SOUTH AFRICA, 2009

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Introduction

The 2009-H1N1 influenza A pandemic took many by surprise. Unexpectedly arising in North America and spreading rapidly throughout the northern hemisphere summer, it encircled the globe within a couple of months. This event has again highlighted the crucial need for a more comprehensive global surveillance system for influenza (Lipsitch et al., 2009; Ortiz et al., 2009).

The World Health Organization (WHO) Influenza Programme has provided valuable information on circulating influenza viruses globally through its network of 128 national influenza centers in 99 countries, supported by five WHO collaborative centers (WHO, 2002, 2008, 2009a). Virus isolates from the majority of these laboratories provide the basis for the annual recommendation by WHO of the strains to be incorporated into the influenza vaccines for the Northern and Southern Hemispheres in February and September, respectively, of each year (WHO, 2009b,c).

However, the African continent is poorly capacitated for influenza surveillance (Schoub et al., 2002). Of the 46 countries constituting the WHO AFRO region, only 18 possess national influenza centers and only 10 are able to perform diagnostic PCR (WHO, 2009d,e). As of September 30, 2009, 12,382 cases of 2009-H1N1 influenza A were reported from this region; the great majority (93 percent) were reported from South Africa (WHO, 2009f).

Influenza Surveillance in South Africa

Systematic surveillance for influenza in South Africa dates back to 1984, when the first surveillance network of sentinel medical practitioners, the "Viral

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Watch," was established in Johannesburg (Besselaar et al., 2001; McAnerney et al., 1994; Schoub et al., 1986, 1994). Currently, the Viral Watch network consists of 243 sentinel sites, which provide clinical and epidemiological data on influenza in the community, as well as material for isolation and antigenic and molecular characterization of viruses, for input to WHO for decision making as to annual vaccine composition recommendations. In response to the 2009-H1N1 influenza A pandemic, the Viral Watch program was supplemented with an additional 10 hospital-based sites situated in all 9 provinces. Additional surveillance was provided by a Severe Acute Respiratory Infection (SARI) surveillance program, also established in 2009 in four large hospitals in three provinces. In addition, a large number of diagnostic specimens were received by the laboratory following widespread concern around the pandemic. Finally, active surveillance was introduced to collect information on all laboratory-confirmed cases due to 2009-H1N1 influenza A nationally, from both private and public laboratories.

Up until 2009, the pattern of influenza isolations, as identified through the Viral Watch program, universally showed a typical unimodal distribution, as shown in Figure A10-1, with a median onset at week 23 (range 15-28), a median peak at week 27 (range 20-32) and a median duration of 10 weeks (range 7-17) (Figure A10-2). This pattern is consistent with other temperate Southern Hemisphere countries. The distribution of influenza subtypes is shown in Figure A10-3. Over the past 25 years, H3N2 was the dominant subtype in 13 of the years, H1N1 in 7, and influenza B in 2 of the years, with an equal distribution of all three in 2 years and an equal combination of H3N2 and B in one of the years.

The 2009-H1N1 Influenza A Pandemic in South Africa

The epidemic curve of the 2009-H1N1 influenza A pandemic as determined through active surveillance for all laboratory-confirmed cases nationally in South Africa, as of September 29th, is shown in Figure A10-4. The first case of 2009-H1N1 influenza A was confirmed in South Africa on June 13, some 2 months after that of the United States and a month or more after other Southern Hemisphere countries (Table A10-1). The reason for this inordinate delay in importation into South Africa is probably related to the relatively low volume of air traffic between it and North America (Chen and Wilson, 2008; Khan et al., 2009).

The first confirmed South African case was in a healthy 16-year-old boy who had visited family in Texas and returned to South Africa on June 10th presenting with clinical signs and symptoms of influenza-like-illness (ILI). A positive diagnosis of 2009-H1N1 influenza A infection was made at the National Institute for Communicable Diseases (NICD) using the CDC real-time (RT-) PCR protocol for the detection and characterization of swine influenza. He was treated with oseltamivir on day 3 after onset of symptoms and made an uneventful recovery; no secondary contacts were identified. During the following 2 weeks, NICD continued to detect sporadic (H1N1) among individuals returning from North America,

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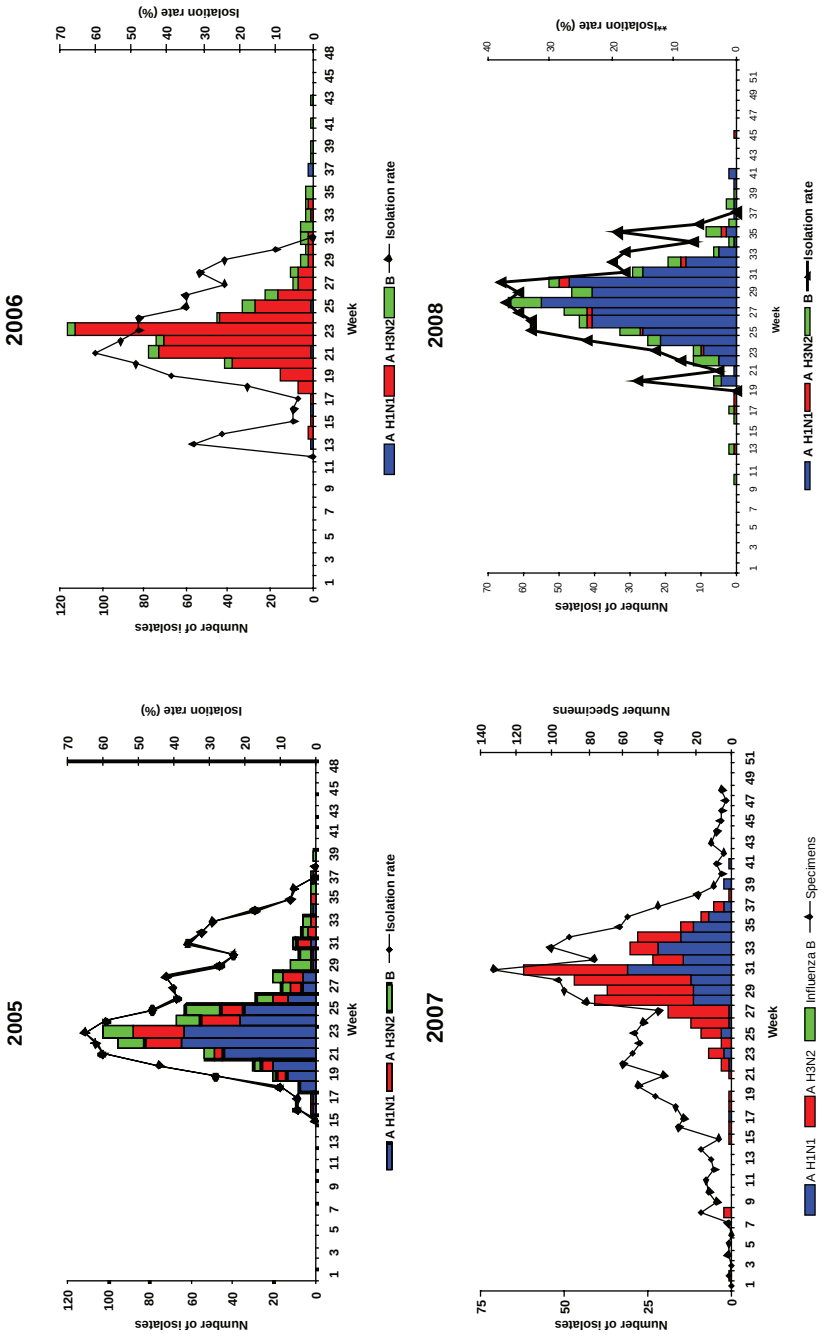

FIGURE A10-1 Influenza results by type and subtype: South Africa 2005-2008.

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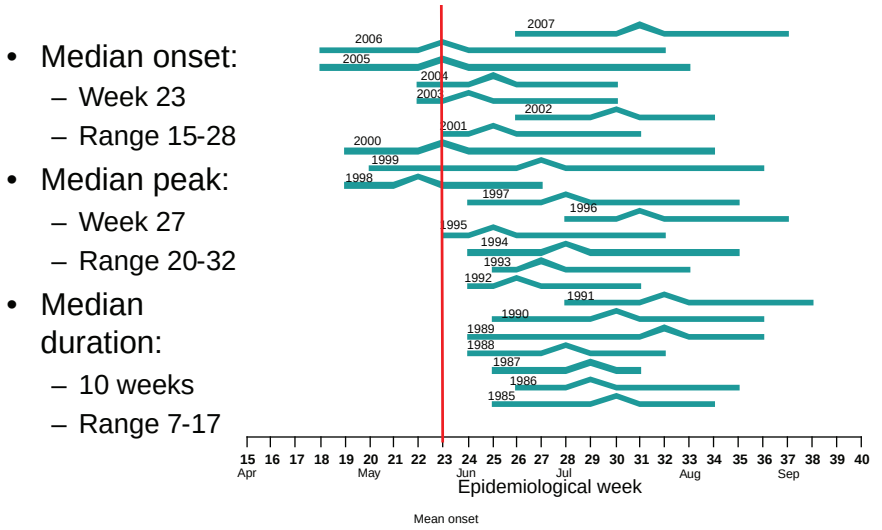

FIGURE A10-2 Onset and duration of influenza season, South Africa, 1985-2007.

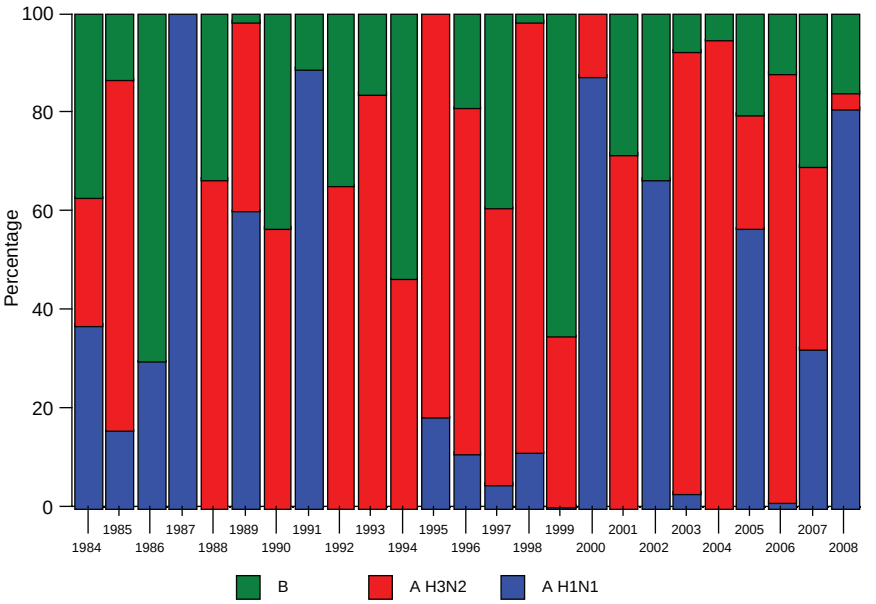

FIGURE A10-3 Influenza strains detected, South Africa, 1984-2008.

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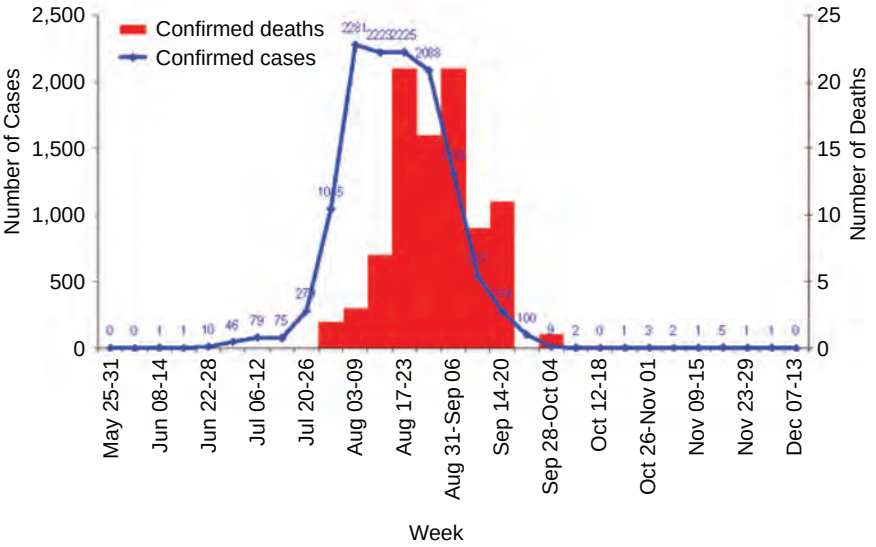

FIGURE A10-4 Epidemic curve of laboratory-confirmed pandemic 2009-H1N1 influenza A cases and deaths by week, South Africa, as of December 15, 2009 (n[cases] = 12,683).

TABLE A10-1 First Confirmed Cases of 2009-H1N1 Influenza A

Argentina	May 16
Australia	May 7
Chile	May 17
New Zealand	April 28
Uruguay	May 27
USA	April 17
South Africa	June 13

South America, and Europe, with documented cases of local transmission resulting to a close household contact. A week later, on June 27th, an outbreak of H1N1 occurred at a sports event in Johannesburg, where 20 young athletes with ILI were confirmed at NICD as pandemic H1N1. The index case of this cluster was probably an 18-year-old male attending from Zimbabwe, believed to have been infected while in transit (possibly through contact with other travellers). Over the next 2 weeks the number of confirmed cases rose steeply and, on July 13th, a month after the first case was diagnosed, over 100 cases had been confirmed in South Africa. At that stage the majority of cases were identified in the Gauteng province, the province with the largest population (incorporating both Johannesburg and Pretoria) and with the highest international exposure through OR Tambo International Airport in Johannesburg. In conformance with the WHO recommendations

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to cease universal laboratory testing of all suspected cases once the 100-case mark had been reached, the NICD and other academic centers reverted to testing only selected cases. Of the first 100 cases, 42 gave a travel history consistent with having acquired the infection abroad (Table A10-2).

Epidemiological Characteristics

As of September 29, 2009, a total of 11,729 cases had been confirmed nationally (Figure A10-4). The first death was confirmed on July 28th; a 22-year-old male student with no apparent comorbid condition. As of September 28th, 83 deaths had been laboratory-confirmed; the details are described below.

The 2009 influenza season, as reflected through the Viral Watch program (community influenza surveillance), showed, for the first time, a bimodal curve (Figure A10-5). A similar bimodal distribution of 2009-H1N1 influenza A cases was also seen from the SARI program (Figure A10-6). Using mid-year population estimates (STATSSA, 2009), incidence data of laboratory-confirmed cases per 100,000 population were calculated for each of the nine provinces of South Africa (Table A10-3). The highest incidence was, not unexpectedly, seen in the Gauteng province, the commercial hub of the country, which is the smallest province geo-

TABLE A10-2 Travel History of 42 Cases Within the First 100 Investigated

North America	**6**	**14%**
USA	6	
South America	**5**	**12%**
Argentina	2	
Brazil	2	
Chile	1	
Europe	**15**	**36%**
Other European Countries	5	
Germany	1	
Greece	1	
Netherlands	1	
Sweden	1	
Turkey	1	
UK	5	
Asia	**8**	**19%**
China	2	
Singapore	4	
Dubai	1	
Bali	1	
Other African Countries	**3**	**7%**
Mauritius	2	
Zimbabwe	1	
Australia	**5**	**12%**

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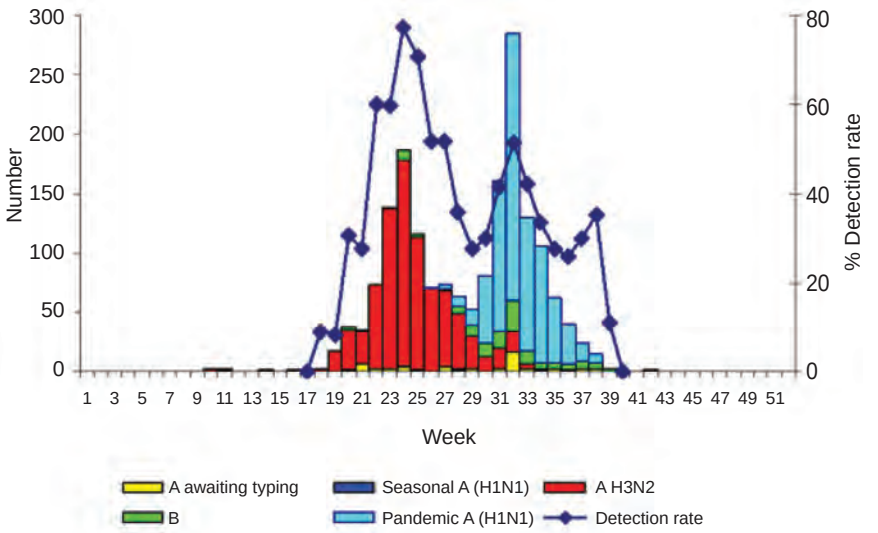

FIGURE A10-5 Positive samples by influenza types and subtype: Viral Watch South Africa 2009.

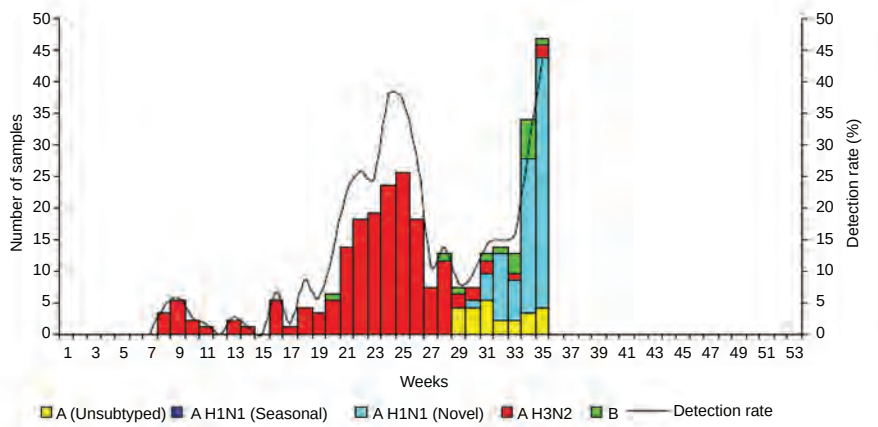

FIGURE A10-6 Severe acute respiratory illness (SARI) surveillance: respiratory virus report.

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TABLE A10-3 Laboratory-Confirmed Pandemic 2009-H1N1 Influenza A Cases by Province, South Africa, as of December 15, 2009

	Laboratory-Confirmed Cases	
Province	Cumulative Total	Incidence Rate (per 100,000 population)
Eastern Cape	682	10.26
Free State	314	10.82
Gauteng	5,579	52.98
KwaZulu-Natal	2,258	21.61
Limpopo	545	10.43
Mpumalanga	500	13.86
Northern Cape	134	11.68
North West	465	13.48
Western Cape	2,113	39.44
Unknown	42	—
South Africa Total	12,632	25.61

graphically but has the largest population, the highest population density, and the greatest contact internationally. This was followed by Western Cape (including Cape Town) and KwaZulu-Natal (including Durban). These provinces are also more urbanized and individuals there would be more likely to seek care and diagnostic testing for influenza than persons in more rural provinces. The age distribution of cases showed a predominance in children and young adults as also seen in countries throughout the world (CDC, 2009; Gilsdorf and Poggensee, 2009; Levy-Bruhl and Vaux, 2009; Lytras et al., 2009; Munayco et al., 2009; WHO, 2009g)—Figure A10-7, Table A10-4. The ages ranged from newborn to 90 years with a median age of 16 years. The age distribution curves for the different influenza subtypes as they presented in the Viral Watch program were compared. The pandemic 2009-H1N1 influenza A pattern was distinct from both the H3N2 of 2009 and the seasonal H1N1 of 2008 (Figures A10-8 and A10-9) and more closely resembled that of influenza B in 2009 (Figure A10-10).

Preliminary Investigation of the First 100 Cases

A more detailed follow-up investigation was carried out on the first 100 cases in South Africa. These cases, however, represented a more affluent, upper socio-economic section of the population and were also not representative of the racial composition of the South African population (Table A10-5). International travel within 7 days of onset of symptoms was reported in 42 cases and no travel or any contact with international travelers in the remainder. Only a minority of cases had recognized comorbid conditions—asthma (7), heart disease (5), preg-

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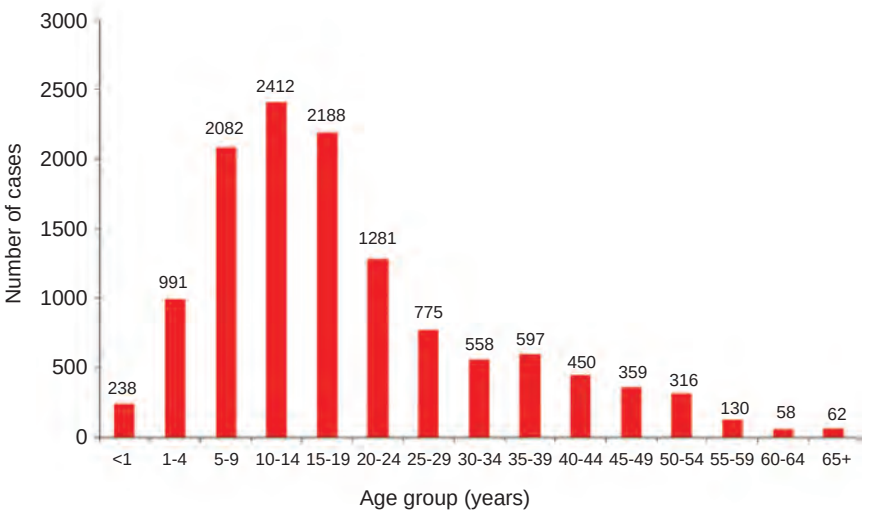

FIGURE A10-7 Number of laboratory confirmed pandemic 2009-H1N1 influenza A cases by age group, as of December 15, 2009 (n = 11,729).

TABLE A10-4 Pandemic 2009-H1N1 Influenza A Cases by Age Group, South Africa, as of December 15, 2009

Age (years)	Number	Incidence per 100,000[a]	Percentage of total
1-4	1,229	243	10
5-9	2,082	402	18
10-14	2,412	460	21
15-19	2,188	420	19
20-24	1,281	260	11
25-29	775	175	7
30-34	558	144	5
35-39	597	182	5
40-44	450	184	4
45-49	359	159	3
50-54	316	155	3
55-59	130	79	1
60-64	58	45	0.5
>65	62	26	0.5

[a]Population figures based on mid-year population estimates 2009 (STATSSA, 2009).

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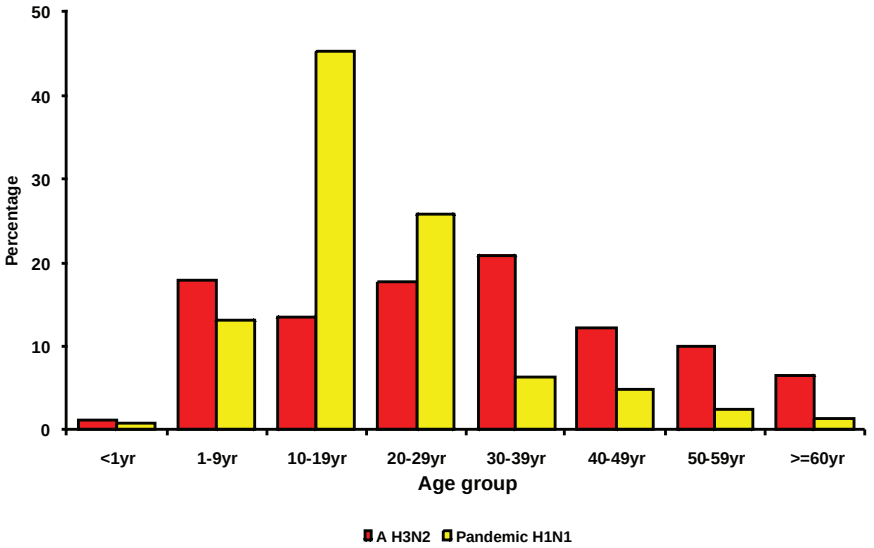

FIGURE A10-8 Age distribution of patients with seasonal A H3N2 and pandemic 2009-H1N1 influenza A.

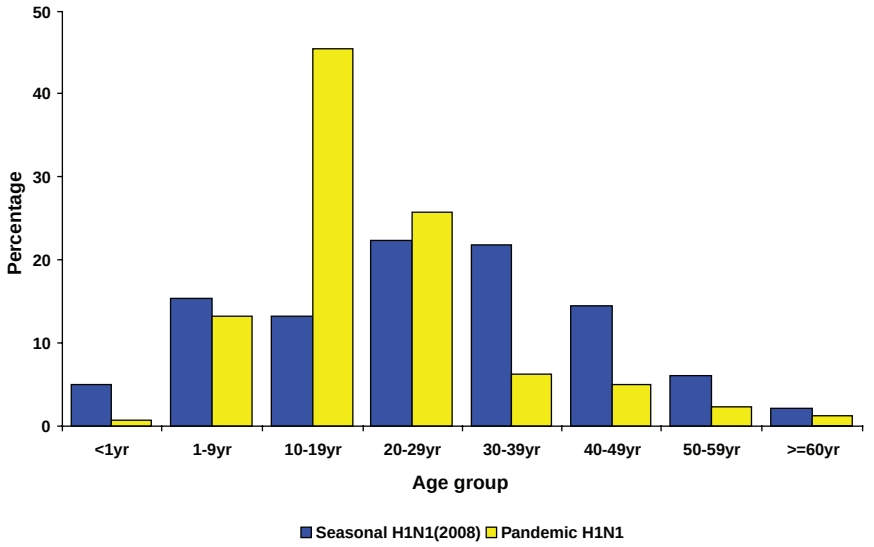

FIGURE A10-9 Age distribution of patients with seasonal A H1N1 (2008) and pandemic 2009-H1N1 influenza A.

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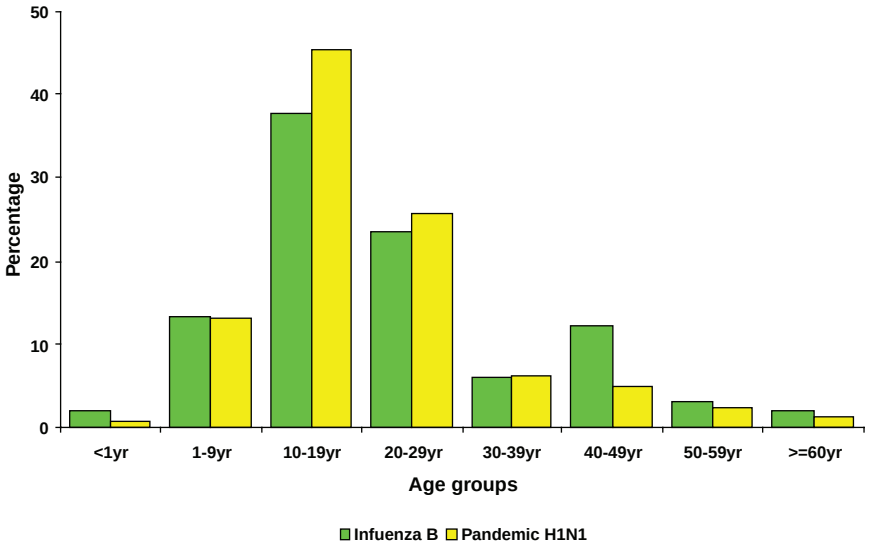

FIGURE A10-10 Age distribution of patients with influenza B and pandemic 2009-H1N1 influenza A.

TABLE A10-5 Breakdown of First 100 Cases by Race

Race	H1N1 Cases N / Percentage	Total South African Population[a] N / Percentage
Asian	12	2.6
African	6	79.3
Mixed race	5	9.0
White	74	9.1
Unknown	3	—
Total	100	100.0

[a]Based on 2009 mid-year population estimates (STATSSA, 2009).

nancy (3), and obesity (2) (BMI > 30). The distribution of reported symptoms in these cases followed that seen generally throughout the world (Eurosurveillance, 2009b-e)—Figure A10-11.

The mean time from onset of symptoms to presentation at a health facility was 2.0 days (SD 1.5 days, range 0-7 days) and symptom onset to recovery was 7.9 days (SD 1.5 days, range 0-7 days). Eleven cases were hospitalized, some as a precaution to isolate the patient and 6 developed complications including pneumonia (3), otitis media (1), myocarditis (1), and other (1).

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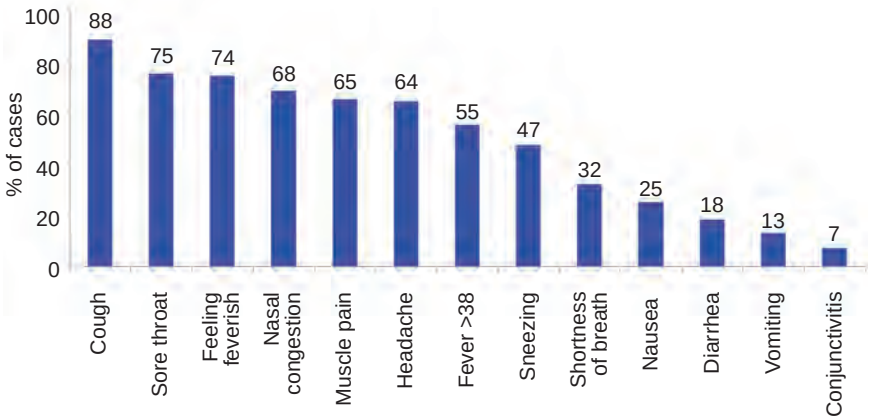

FIGURE A10-11 Reported symptoms in first 100 confirmed cases, South Africa.

Preliminary Investigation of Deaths

As of December 17, 2009, 92 laboratory-confirmed deaths were recorded in South Africa. The ages range from 3 days to 70 years, with a median age of 33 years—significantly higher than the overall median age of 15 years. Deaths were more common in females (60 percent) whereas the gender ratio was approximately equal in nonfatal cases. This was due, to a large extent, to the unusually large proportion of deaths in pregnant woman: 26 of the 91 cases (28 percent) with known clinical history. All but three of the deaths in pregnancy occurred in the third trimester (one in the second trimester and two in the puerperium). Of the 14 pregnancy-related fatal cases with known HIV status, 10 (71 percent) were HIV-positive; the national HIV seroprevalence in women attending public-sector antenatal clinics is 29 percent (Department of Health, 2009). Other comorbid conditions in this group were tuberculosis (TB) in 9 (11 percent) and preeclampsia in 2 (8 percent).

Of the 66 nonpregnant deaths, most (61 percent) were male. HIV was recorded in 6 of 17 patients (35 percent) as compared to the overall HIV prevalence of 17 to 19 percent for South Africa (Department of Health, 2009). Active TB was found in 2 of 46 cases (4 percent) and other comorbid conditions included obesity (12 of 46; 26 percent), diabetes (11 of 45; 24 percent), and cardiac disease (8 of 44; 18 percent).

Conclusion

In many respects the 2009-H1N1 influenza A pandemic has behaved similarly to both developed and developing countries throughout the world. These

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include age distribution, epidemiology, clinical features and overall relative mildness. The late introduction into South Africa appeared, to some extent, to be due to relatively lower air traffic levels and provided a window to observe any further genetic movement in the virus. Phenotypic changes in the virus were certainly not apparent from the clinical and epidemiological observations. Virological characterization is presently under way to determine antigenic drift, resistance, and presence of any virulence markers. Two particular risk groups in South Africa do perhaps need to be highlighted—those involving pregnancy and HIV. Although pregnancy is a well-recognized risk factor in H1N1 (Jamieson et al., 2009; Mangtani et al., 2009), South Africa experienced an unusually high number of women in late pregnancy who succumbed to H1N1. Second, the high rate of HIV positivity in both pregnant and nonpregnant individuals who died (considerably higher than the background HIV positivity in these two groups) needs special attention. In both groups the HIV prevalence was nearly double that of the respective national prevalence rates (Department of Health, 2009). These are, however, preliminary observations and are subject to potentially significant bias. For example, pregnancy may well be a factor that could increase the likelihood of a death being reported because of relatively greater access to a health facility. Also HIV may be artificially high as patients with more advanced disease and the stigma of HIV infection may be more likely to be treated and also more likely to succumb to H1N1. Whether persons living with HIV constitute a risk group for more severe influenza infection in the absence of secondary infection remains to be established (Kunisaki and Janoff, 2009). A study in an HIV-infected pediatric population in South Africa, also failed to demonstrate differences in outcome of influenza infection (Madhi et al., 2002). An understanding of these risk factors is of urgent importance, particularly in countries with a high prevalence of HIV and limited vaccine resources.

References

Besselaar, T. G., B. D. Schoub, and J. M. McAnerney. 2001. Phylogenetic studies of South African influenza A viruses: 1997-1999. In *Options for the Control of Influenza IV*, edited by A. D. M. E. Osterhaus, N. Cox, and A. W. Hampson. Proceedings of the Fourth International Conference on the Control of Influenza IV, Crete, Greece, September 23-28, 2000. *Excerpta Medica* 1219:139-145.

CDC (Centers for Disease Control and Prevention). 2009. Update: Novel influenza A (H1N1) virus infections—worldwide, May 6, 2009. *Morbidity and Mortality Weekly Report* 58(RR17):453-457.

Chen, L. H., and M. E. Wilson. 2008. The role of the traveler in emerging infections and magnitude of travel. *Medical Clinics of North America* 92(6):1409-1432.

Department of Health. 2009. 2008 National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa.

ECDC Working Group on Influenza A(H1N1)v. 2009. Preliminary analysis of influenza A(H1N1)v individual and aggregated case reports from EU and EFTA countries. *Eurosurveillance* 14(23), http://www.eurosurveillance.org/images/dynamic/EE/V14N23/art19238.pdf (accessed October 22, 2009).

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Gilsdorf, A., and G. Poggensee. 2009. Influenza A(H1N1)v in Germany: the first 10,000 cases. *Eurosurveillance* 14(34), http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19318 (accessed October 22, 2009).

Jamieson, D. J., M. A. Honein, S. A. Rasmussen, J. L. Williams, D. L. Swerdlow, M. S. Biggerstaff, S. Lindstrom, J. K. Louie, C. M. Christ, S. R. Bohm, V. P. Fonseca, K. A. Ritger, D. J. Kuhles, P. Eggers, H. Bruce, H. A. Davidson, E. Lutterloh, M. L. Harris, C. Burke, N. Cocoros, L. Finelli, K. F. MacFarlane, B. Shu, S. J. Olsen. 2009. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 374(9688):451-458.

Khan, K, J. Arino, W. Hu, P. Raposo, J. Sears, F. Calderon, C. Heidebrecht, M. Macdonald, J. Liauw, A. Chan, and M. Gardam. 2009. Spread of a novel influenza A (H1N1) virus via global airline transportation. *New England Journal of Medicine* 361(2):212-214.

Kunisaki, K. M., and E. N. Janoff. 2009. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infectious Disease* 9(8):493-504.

Levy-Bruhl, D., and S. Vaux. 2009. Influenza A(H1N1)v investigation teams. Modified surveillance of influenza A(H1N1)v virus infections in France. *Eurosurveillanc*e 14(29), http://www.eurosurveillance.org/images/dynamic/EE/V14N29/art19276.pdf (accessed October 22, 2009).

Lipsitch, M., S. Riley, S. Cauchemez, A. C. Ghani, and N. M. Ferguson. 2009. Managing and reducing uncertainty in an emerging influenza pandemic. *New England Journal of Medicine* 361(2):112-115.

Lytras, T., G. Theocharopoulos, S. Tsiodras, A. Mentis, T. Panagiotopoulos, and S. Bonovas. 2009. Enhanced surveillance of influenza A(H1N1)v in Greece during the containment phase. *Eurosurveillance* 14(29), http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19275 (accessed October 22, 2009).

Madhi, S. A., N. Ramasamy, T. G. Bessellar, H. Saloojee, and K. P. Klugman. 2002. Lower respiratory tract infections associated with influenza A and B viruses in an area with a high prevalence of pediatric human immunodeficiency type 1 infection. *Pediatric Infectious Disease Journal* 21(4):291-297.

Mangtani, P., T. K. Mak, and D. Pfeifer. 2009. Pandemic H1N1 infection in pregnant women in the USA. *Lancet* 374(9688):429-430.

McAnerney, J. M., S. Johnson, and B. D. Schoub. 1994. Surveillance of respiratory viruses—a 10 year laboratory based study. *South African Medical Journal* 84(8 Pt. 1):473-477.

Munayco, C. V., J. Gomez, V. A. Laguna-Torres, J. Arrasco, T. J. Kochel, V. Fiestas, J. Garcia, J. Perez, I. Torres, F. Condori, H. Nishiura, and H. Chowell. 2009. Epidemiological and transmissibility analysis of influenza A(H1N1)v in a southern hemisphere setting: Peru. *Eurosurveillance* 14(32), http://www.eurosurveillance.org/images/dynamic/EE/V14N32/art19299.pdf (accessed October 22, 2009).

Ortiz, J. R., V. Sotomayor, O. C. Uez, O. Oliva, D. Bettels, M. McCarron, J. S. Bresee, and A. W. Mounts. 2009. Strategy to enhance influenza surveillance worldwide. *Emerging Infectious Diseases* 15(8):1271-1278.

Schoub, B. D., S. Johnson, J. M. McAnerney, E. Martin, and I. L. Dos Santos. 1986. Laboratory studies of the 1984 influenza epidemic on the Witwatersrand. *South African Medical Journal* 70(13):815-818.

Schoub, B. D., S. Johnson, and J. M. McAnerney. 1994. Benefits and limitations of the Witwatersrand influenza and acute respiratory infections surveillance programme. *South African Medical Journal* 84(10):674-678.

Schoub, B. D., J. M. McAnerney, and T. G. Besselaar. 2002. Regional perspectives on influenza surveillance in Africa. *Vaccine* 20(2):S45-S46.

STATSSA (Statistics South Africa). 2009. *Mid-year population estimates 2009*, www.statssa.gov.za (accessed November 17, 2009).

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

WHO (World Health Organization). 2002. WHO Global Influenza Programme: survey on capacities of national influenza centres, January-June 2002. *Weekly Epidemiological Record* 77(42):350-358.
———. 2008. Brief summary of analyses of the 2007 survey on the capacity of National Influenza Centres. *Weekly Epidemiological Record* 83(16):133-144.
———. 2009a. Global influenza surveillance network: laboratory surveillance and response to pandemic H1N1 2009. *Weekly Epidemiological Record* 84(36):361-365.
———.2009b. Recommended composition of influenza virus vaccines for use in the 2009-2010 influenza season (northern hemisphere winter). *Weekly Epidemiological Record* 84(9):65-72.
———.2009c. Recommended composition of influenza virus vaccines for use in the 2010 influenza season (southern hemisphere winter). *Weekly Epidemiological Record* 84(41):421-436.
———. 2009d. *National influenza centres*, http://www.who.int/csr/disease/influenza/centres/en/index.html (accessed September 30, 2009).
———. 2009e. *Countries able to perform PCR to diagnose influenza A (H1N1) virus infection in humans*, http://www.who.int/csr/resources/publications/swineflu/country_pcr_capacity/en/index.html (accessed October 12, 2009).
———. 2009f. *Pandemic inlfuenza (H1N1)*, http://www.afro.who.int/ddc/influenzaa/index.html (accessed October 5, 2009).
———. 2009g. New influenza A (H1N1) virus: global epidemiological situation, June 2009. *Weekly Epidemiological Record* 84(25):249-257.

A11

REFLECTIONS ON THE 1976 SWINE FLU VACCINATION PROGRAM[76]

David J. Sencer[77] and J. Donald Millar[78]

In 1976, 2 recruits at Fort Dix, New Jersey, had an influenza like illness. Isolates of virus taken from them included A/New Jersey/76 (Hsw1n1), a strain similar to the virus believed at the time to be the cause of the 1918 pandemic, commonly known as swine flu. Serologic studies at Fort Dix suggested that >200 soldiers had been infected and that person-to-person transmission had occurred. We review the process by which these events led to the public health decision to mass-vaccinate the American public against the virus and the subsequent events that led to the program's cancellation. Observations of policy and implementation success and failures are presented that could help guide decisions regarding avian influenza.

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Kilbourne in 1976 (Kilbourne, 1976) noted that pandemics of influenza occur every 11 years. Since the latest prediction in the New York Times (Editorial, 2005) suggests that after 39 years we may be overdue for a pandemic, and since 2 US senators have recently headlined the possibility (Obama and Lugar, 2005), that observation may become a political fact. Whether it becomes a scientific fact and a policy fact is yet to be seen. Some reflections on 1976 from 2 insiders' viewpoints may identify some of the pitfalls that public health policymakers will face in addressing potential influenza pandemics.

Swine Flu at Fort Dix

On February 3, 1976, the New Jersey State Health Department sent the Center for Disease Control (CDC) in Atlanta isolates of virus from recruits at Fort Dix, New Jersey, who had influenzalike illnesses. Most of the isolates were identified as A/Victoria/75 (H3N2), the contemporary epidemic strain. Two of the isolates, however, were not typeable in that laboratory. On February 10, additional isolates were sent and identified in CDC laboratories as A/New Jersey/76 (Hsw1N1), similar to the virus of the 1918 pandemic and better known as "swine flu."

A meeting of representatives of the military, the National Institute of Health, the Food and Drug Administration (FDA), and the State of New Jersey Department of Health was quickly convened on Saturday, February 14, 1976. Plans of action included heightened surveillance in and around Fort Dix, investigation of the ill recruits to determine if contact with pigs had occurred, and serologic testing of recruits to determine if spread had occurred at Fort Dix.

Surveillance activities at Fort Dix gave no indication that recruits had contact with pigs. Surveillance in the surrounding communities found influenza caused by the current strain of influenza, A/Victoria, but no additional cases of swine flu. Serologic testing at Fort Dix indicated that person-to-person transmission had occurred in >200 recruits (Hodder et al., 1977).

In 1974 and 1975, 2 instances of humans infected with swine influenza viruses had been documented in the United States. Both persons involved had close contact with pigs, and no evidence for spread of the virus beyond family members with pig contact could be found (Dowdle and Hattwick, 1977).

The National Influenza Immunization Program

On March 10, 1976, the Advisory Committee on Immunization Practices of the United States Public Health Service (ACIP) reviewed the findings. The committee concluded that with a new strain (the H1N1 New Jersey strain) that could be transmitted from person to person, a pandemic was a possibility. Specifically, the following facts were of concern: 1) persons <50 years of age had

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no antibodies to this new strain; 2) a current interpandemic strain (A/Victoria) of influenza was widely circulating; 3) this early detection of an outbreak caused by A/New Jersey/76/Hsw1N1 (H1N1) provided an opportunity to produce a vaccine since there was sufficient time between the initial isolates and the advent of an expected influenza season to produce vaccine. In the past when a new pandemic strain had been identified, there had not been enough time to manufacture vaccine on any large scale; 4) influenza vaccines had been used for years with demonstrated safety and efficacy when the currently circulating vaccine strain was incorporated; 5) the military vaccine formulation for years had included H1N1, an indication that production was possible, and no documented adverse effects had been described.

ACIP recommended that an immunization program be launched to prevent the effects of a possible pandemic. One ACIP member summarized the consensus by stating "If we believe in prevention, we have no alternative but to offer and urge the immunization of the population." One ACIP member expressed the view that the vaccine should be stockpiled, not given.

Making this decision carried an unusual urgency. The pharmaceutical industry had just finished manufacture of the vaccine to be used in the 1976–1977 influenza season. At that time, influenza vaccine was produced in fertilized hen's eggs from special flocks of hens. Roosters used for fertilizing the hens were still available; if they were slaughtered, as was customary, the industry could not resume production for several months.

On March 13, an action memo was presented to the Secretary of the Department of Health Education and Welfare (DHEW). It outlined the problem and presented 4 alternative courses of action. First was "business as usual," with the marketplace prevailing and the assumption that a pandemic might not occur. The second was a recommendation that the federal government embark on a major program to immunize a highly susceptible population. As a reason to adopt this plan of action, the memo stated that "the Administration can tolerate unnecessary health expenditures better than unnecessary death and illness if a pandemic should occur." The third proposed course of action was a minimal response, in which the federal government would contract for sufficient vaccine to provide for traditional federal beneficiaries—military personnel, Native Americans, and Medicare-eligible persons. The fourth alternative was a program that would represent an exclusively federal response without involvement of the states.

The proposal recommended by the director of CDC was the second course, namely, for the federal government to contract with private pharmaceutical companies to produce sufficient vaccine to permit the entire population to be immunized against H1N1. The federal government would make grants to state health departments to organize and conduct immunization programs. The federal government would provide vaccine to state health departments and private medical

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practices. Since influenza caused by A/Victoria was active worldwide, industry was asked to incorporate the swine flu into an A/Victoria product to be used for populations at high risk.

Before the discussions with the secretary of DHEW had been completed, a member of his staff sent a memo to a health policy advisor in the White House, raising the specter of the 1918 pandemic, which had been specifically underemphasized in the CDC presentation. CDC's presentation highlighted the pandemic potential, comparing it with the 1968–69 Hong Kong and 1957–58 Asian pandemics. President Gerald Ford's staff recommended that the president convene a large group of well-known and respected scientists (Albert Sabin and Jonas Salk had to be included) and public representatives to hear the government's proposal and make recommendations to the president about it. After the meeting, the president had a press conference, highlighted by the unique simultaneous appearance of Salk and Sabin. President Ford announced that he accepted the recommendations that CDC had originally made to the secretary of DHEW. The National Influenza Immunization Program (NIIP) was initiated.

The proposal was presented to 4 committees of the Congress, House and Senate authorization committees and House and Senate appropriation committees. All 4 committees reported out favorable legislation, and an appropriation bill was passed and signed.

The estimated budgeted cost of the program was $137 million. When Congress passed the appropriation, newspapers mischaracterized the cost as "$1.9 billion" because the $137 million was included as part of a $1.9 billion supplemental appropriation for the Department of Labor. In the minds of the public, this misconception prevailed.

Immediately after the congressional hearing, a meeting of all directors of state health departments and medical societies was held at CDC. The program was presented by CDC, and attendees were asked for comments. A representative from the New Jersey state health department opposed the plan; the Wisconsin state medical society opposed any federal involvement. Otherwise, state and local health departments approved the plan.

Within CDC, a unit charged with implementing the pro- gram, which reported to the director, was established. This unit, NIIP, had complete authority to draw upon any resources at CDC needed. NIIP was responsible for relations with state and local health departments (including administration of the grant program for state operations, technical advice to the procurement staff for vaccine, and warehousing and distribution of the vaccine to state health departments) and established a proactive system of surveillance for possible adverse effects of the influenza vaccines, the NIIP Surveillance Assessment Center (NIIP-SAC). (This innovative surveillance system would prove to be NIIP's Trojan horse.) In spite of the obstacles discussed below, NIIP administered a program that immunized 45 million in 10 weeks, which resulted in doubling the level of immunization for persons deemed to be at high risk, rapidly identifying

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adverse effects, and developing and administering an informed consent form for use in a community-based program.

Obstacles to the Vaccination Plan

The principal obstacle was the lack of vaccines. As test batches were prepared, the largest ever field trials of influenza vaccines ensued. The vaccines appeared efficacious and safe (although in the initial trials, children did not respond immunologically to a single dose of vaccine, and a second trial with a revised schedule was needed) (Denny et al., 1976). Hopes were heightened for a late summer/early fall kickoff of mass immunization operations.

In January 1976, before the New Jersey outbreak, CDC had proposed legislation that would have compensated persons damaged as a result of immunization when it was licensed by FDA and administered in the manner recommended by ACIP. The rationale given was that immunization protects the community as well as the individual (a societal benefit) and that when a person participating in that societal benefit is damaged, society had a responsibility to that person. The proposal was sent back from a staff member in the Surgeon General's office with a handwritten note, "This is not a problem."

Soon, however, NIIP received the first of 2 crippling blows to hopes to immunize "every man, woman, and child." The first was later in 1976, when instead of boxes of bottled vaccine, the vaccine manufacturers delivered an ultimatum—that the federal government indemnify them against claims of adverse reactions as a requirement for release of the vaccines. The government quickly capitulated to industry's demand for indemnification. While the manufacturers' ultimatum reflected the trend of increased litigiousness in American society, its unintended, unmistakable subliminal message blared "There's something wrong with this vaccine." This public misperception, warranted or not, ensured that every coincidental health event that occurred in the wake of the swine flu shot would be scrutinized and attributed to the vaccine.

On August 2, 1976, deaths apparently due to an influenzalike illness were reported from Pennsylvania in older men who had attended the convention of the American Legion in Philadelphia. A combined team of CDC and state and local health workers immediately investigated. By the next day, epidemiologic evidence indicated that the disease was not influenza (no secondary cases occurred in the households of the patients). By August 4, laboratory evidence conclusively ruled out influenza. However, this series of events was interpreted by the media and others as an attempt by the government to "stimulate" NIIP.

Shortly after the national campaign began, 3 elderly persons died after receiving the vaccine in the same clinic. Although investigations found no evidence that the vaccine and deaths were causally related, press frenzy was so intense it drew a televised rebuke from Walter Cronkite for sensationalizing coincidental happenings.

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Guillain-Barré Syndrome

What NIIP did not and could not survive, however, was the second blow, finding cases of Guillain-Barré syndrome (GBS) among persons receiving swine flu immunizations. As of 1976, >50 "antecedent events" had been identified in temporal relationship to GBS, events that were considered as possible factors in its cause. The list included viral infections, injections, and "being struck by lightning." Whether or not any of the antecedents had a causal relationship to GBS was, and remains, unclear. When cases of GBS were identified among recipients of the swine flu vaccines, they were, of course, well covered by the press. Because GBS cases are always present in the population, the necessary public health questions concerning the cases among vaccine recipients were "Is the number of cases of GBS among vaccine recipients higher than would be expected? And if so, are the increased cases the result of increased surveillance or a true increase?" Leading epidemiologists debated these points, but the consensus, based on the intensified surveillance for GBS (and other conditions) in recipients of the vaccines, was that the number of cases of GBS appeared to be an excess.

Had H1N1 influenza been transmitted at that time, the small apparent risk of GBS from immunization would have been eclipsed by the obvious immediate benefit of vaccine-induced protection against swine flu. However, in December 1976, with >40 million persons immunized and no evidence of H1N1 transmission, federal health officials decided that the possibility of an association of GBS with the vaccine, however small, necessitated stopping immunization, at least until the issue could be explored. A moratorium on the use of the influenza vaccines was announced on December 16; it effectively ended NIIP of 1976. Four days later the New York Times published an op-ed article that began by asserting, "Misunderstandings and misconceptions . . . have marked Government . . . during the last eight years," attributing NIIP and its consequences to "political expediency" and "the self interest of government health bureaucracy" (Schwartz, 1976). These simple and sinister innuendos had traction, as did 2 epithets used in the article to describe the program, "debacle" in the text and "Swine Flu Fiasco" in the title.

On February 7, the new secretary of DHEW, Joseph A. Califano, announced the resumption of immunization of high-risk populations with monovalent A/Victoria vaccine that had been prepared as part of the federal contracts, and he dismissed the director of CDC.

Lessons Learned

NIIP may offer lessons for today's policymakers, who are faced with a potential pandemic of avian influenza and struggling with decisions about preventing it (Box A11-1). Two of these lessons bear further scrutiny here.

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BOX A11-1
Lessons Learned from the 1976 National Influenza Immunization Program (NIIP)

1. Expect the unexpected: it will always happen.
   Some examples:

   - Children did not respond to the initial formulation of vaccine.
   - Liability for untoward events after immunization became a major issue.
   - Deaths occurred in Pittsburgh that were coincidental with but unrelated to the vaccines (Schmeck, 1976).
   - Cases of a new and unrelated disease, Legionnaires disease, appeared (Fraser et al., 1977).
   - "Excess" cases of Guillain-Barré syndrome appeared among recipients of vaccines (Schonberger et al., 1981).
   - Erroneous laboratory reports of viral isolates or serologic conversions occurred in Washington, DC, Boston, Virginia, and Taiwan.
   - The pandemic failed to appear.

2. Surveillance for influenza disease worked well. This was plain, "old-fashioned" surveillance without computers. A new strain of influenza was identified within weeks of the first recognized outbreak of illness.
3. Interagency cooperation works without formal agreements. The state health departments, military, National Institutes of Health, US Food and Drug Administration, and Center for Disease Control all worked together in a cooperative and mutually beneficial manner.
4. Surveillance for untoward events demonstrated that only when large numbers of people are exposed to a vaccine or drug are adverse reactions identified (Guillain-Barré syndrome with influenza vaccines; paralysis with the Cutter poliovirus vaccine in 1955).
5. Health legislation can and should be developed on the basis of the epidemiologic picture.
6. Media and public awareness can be a major obstacle to implementing a large, innovative program responding to risks that are difficult, if not impossible, to quantitate.

   - Creating a program as a presidential initiative makes modifying or stopping the program more difficult.
   - Explanations should be communicated by those who can give authoritative scientific information.
   - Periodic press briefings work better than responding to press queries.

7. The advisability of the decision to begin immunization on the strength of the Fort Dix episode is worthy of serious question and debate (see text).
8. The risk of potentially unnecessary costs in a mass vaccination campaign is minimal. (The direct cost of the 1976 program was $137 million. In today's dollars, this is <$500 million.) The potential cost of a pandemic is inestimable but astronomical.

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Media and Presidential Attention

While all decisions related to NIIP had been reached in public sessions (publishing of the initial virus findings in CDC's weekly newsletter, the Morbidity and Mortality Weekly Report (MMWR); New York Times reporter Harold Schmeck's coverage of the ACIP sessions, the president's press conference, and 4 congressional hearings), effective communication from scientifically qualified persons was lacking, and the perception prevailed that the program was motivated by politics rather than science. In retrospect (and to some observers at the time), the president's highly visible convened meeting and subsequent press conference, which included pictures of his being immunized, were mistakes. These instances seemed to underline the suspicion that the program was politically motivated, rather than a public health response to a possible catastrophe.

Annex 11 of the draft DHEW pandemic preparedness plan states, "For policy decisions and in communication, making clear what is not known is as important as stating what is known. When assumptions are made, the basis for the assumptions and the uncertainties surrounding them should be communicated" (Department of Health and Human Services, 2003). This goal is much better accomplished if the explanations are communicated by those closest to the problem, who can give authoritative scientific information. Scientific information coming from a nonscientific political figure is likely to encourage skepticism, not enthusiasm.

Neither CDC nor the health agencies of the federal government had been in the habit of holding regular press conferences. CDC considered that its appropriate main line of communication was to states and local health departments, believing that they were best placed to communicate with the public. MMWR served both a professional and public audience and accounted for much of CDC's press coverage. In 1976, no all-news stations existed, only the nightly news. The decision to stop the NIIP on December 16, 1976, was announced by a press release from the office of the assistant secretary for health. The decision to reinstitute the immunization of those at high risk was announced by a press release from the office of the secretary, DHEW. In retrospect, periodic press briefings would have served better than responding to press queries. The public must understand that decisions are based on public health, not politics. To this end, health communication should be by health personnel through a regular schedule of media briefings.

Decision to Begin Immunization

This decision is worthy of serious question and debate. As Walter Dowdle (2006) points out in this issue of Emerging Infectious Diseases, the prevailing wisdom was that a pandemic could be expected at any time. Public health officials were concerned that if immunization was delayed until H1N1 was documented

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to have spread to other groups, the disease would spread faster than any ability to mobilize preventive vaccination efforts. Three cases of swine influenza had recently occurred in persons who had contact with pigs. In 1918, after the initial outbreak of influenza at Fort Riley in April, widespread outbreaks of influenza did not occur until late summer (Schoenbaum et al., 1976).

The Delphi exercise of Schoenbaum in early fall of 1976 (Schoenbaum et al., 1976) was the most serious scientific undertaking to poll scientists to decide whether or not to continue the program. Its main finding was that the cost benefit would be best if immunization were limited to those >25 years of age (and now young children are believed to be a potent source of spread of influenza virus!). Unfortunately, no biblical Joseph was there to rise from prison and interpret the future.

As Dowdle further states (2006), risk assessment and risk management are separate functions. But they must come together with policymakers, who must understand both. These discussions should not take place in large groups in the president's cabinet room but in an environment that can establish an educated understanding of the situation. Once the policy decisions are made, implementation should be left to a single designated agency. Advisory groups should be small but representative. CDC had the lead responsibility for operation of the program. Implementation by committee does not work. Within CDC, a unit was established for program execution, including surveillance, outbreak investigation, vaccine procurement and distribution, assignment of personnel to states, and awarding and monitoring grants to the states. Communications up the chain of command to the policymakers and laterally to other directly involved federal agencies were the responsibility of the CDC director, not the director of NIIP, who was responsible for communications to the states and local health departments, those ultimately implementing operations of the program. This organizational mode functioned well, a tribute to the lack of interagency jealousies.

Decision-Making Risks

When lives are at stake, it is better to err on the side of overreaction than underreaction. Because of the unpredictability of influenza, responsible public health leaders must be willing to take risks on behalf of the public. This requires personal courage and a reasonable level of understanding by the politicians to whom these public health leaders are accountable. All policy decisions entail risks and benefits: risks or benefits to the decision maker; risks or benefits to those affected by the decision. In 1976, the federal government wisely opted to put protection of the public first.

Dr Sencer was director of CDC from 1966 to 1977.

Dr Millar was director of NIIP in 1976.

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References

Denny FW, Glezen WP, Karzon DT, Katz SL, Krugman S, McIntosh K, Parrott RH. Commentary. J Pediatr. 1976;88:1057.

Department of Health and Human services [*sic*]. Annex 11: Pandemic influenza response and preparedness plan. Washington: The Department; 2003 Aug 26.

Dowdle WR. Influenza pandemic periodicity, virus recycling, and the art of risk assessment. Emerg Infect Dis. 2006;12:34–9.

Dowdle WR, Hattwick MAW. Swine influenza virus infections in humans. J Infect Dis. 1977;136: S386–9.

Fraser DW, Tsai TR, Orenstein W, Parkin WE, Beecham HJ, Sharrar RG, et al. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med. 1977;297:1189–97.

Hodder RA, Gaydos JC, Allen RG, Top FH Jr, Nowosiwsky T, Russell PK. Swine influenza A at Fort Dix, New Jersey (January–February 1976). III. Extent of spread and duration of the outbreak. J Infect Dis. 1977;136:S369–75.

Kilbourne ED. Flu to the starboard! Man the harpoons! Fill with vaccine! Get the captain! Hurry! New York Times. 1976 Feb 13. p. 32, col. 4.

Obama B, Lugar R. Grounding a pandemic. Op-ed section. New York Times. 2005 Jun 6. [cited 1 Nov 2005]. Available from http://www.nytimes.com/2005/06/06/opinion/06obama.html?ex=1130994000&en=1b199f715505a19c&ei=5070.

Schmeck HM Jr. More deaths reported after shots but no link to flu vaccine is found. New York Times. 1976 Oct 14; Sect. A:1+.

Schoenbaum SC, McNeil BJ, Kavat J. The swine-influenza decision. N Engl J Med. 1976;295:759–65.

Schonberger LB, Hurwitz ES, Katona P, Holman RC, Bregman DJ. Guillain-Barré syndrome: its epidemiology and associations with influenza vaccination. Ann Neurol. 1981;9(Suppl):31–8.

Schwartz H. Swine flu fiasco. New York Times. 21 Dec 1976:33.

Unprepared for a flu pandemic [editorial]. New York Times. 2005 Jul 17; Sect. 4:11 (col. 1).

A12

SOUTHERN HEMISPHERE, NORTHERN HEMISPHERE: A GLOBAL INFLUENZA WORLD

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Comment

The global response to the 2009-H1N1 influenza A pandemic has been heartening, drawing in no small measure from experience gained from the 1997 influenza H5N1 "Bird Flu" and 2002/2003 severe acute respiratory syndrome (SARS) outbreaks. In each case, recognition of the virus's principal source, chicken in

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the case of the H5N1/HK/97 virus (Shortridge, 1999a) and civet cat[80] for the SARS coronavirus (Guan et al., 2003), prevented further zoonotic spread. The Bird Flu incident provided the foundation for dealing with SARS. There is still much to be learned about influenza toward improving pandemic preparedness. This will require renewed vigor across a range of influenza studies and public health measures. It cannot be denied that our goal must be to the vision of *no more pandemics*. The 2009-H1N1 influenza A pandemic has rekindled this vision and is seen, in part, against a background of 30 years in Hong Kong, a place that in effect functioned as an influenza sentinel post. This informal designation followed the hypothesis that southern China is an epicenter for the emergence of pandemic influenza viruses (Shortridge and Stuart-Harris, 1982), a hypothesis that was the anchor for subsequent thinking and goals considered here.

Another H1N1 Virus

Should we have been surprised?

Simple epidemiological information based on the ages of those initially infected by the pandemic H1N1 virus in 1918 in Canton (now Guangzhou) in southeastern China suggests that an H1N1-like virus had been active in the area for about 11 years prior to 1918 (Shortridge, 1999b). Molecular evolutionary studies indicate that such a virus had circulated from as early as 1911 (Smith et al., 2009a). These data, seroarcheological studies, and virus isolation suggest that H1N1 or H1-like viruses circulated in humans four times over the last 120 or so years. Indeed, the H1N1 lineage may have extended back to the 1830s (Gammelin et al., 1990), a dating in accord with the emergence of a pandemic in China, possibly southern China, in 1830-1831 (Patterson, 1985). Thus, it is clear that this subtype of virus has an affinity for the human host. This includes the 1950-like H1N1 virus that reappeared in 1977 (Kendal et al., 1978; Nakajima et al., 1978) whether or not it is a rogue virus. And now, in 2009 another H1N1 virus has been able to establish a niche in humans—and doing so with pandemic gusto—in the face of a global population seemingly well protected with H1 antibodies. Whereas the pandemic viruses of the last century arose in southern China (see below about the 1918 virus) and were of Eurasian genetic extraction, the H1N1 2009 virus arose in North America and was of mixed geographical and host extractions.

The answer to the question posed is both “no” and “yes.” There is much to learn about the epidemiology, ecology, and science of H1N1 viruses.

China H1N1—Then and Now

While the 1918 pandemic seemingly manifested in Western Europe and the United States in late winter and early spring, it did not apparently do so in China

[80]Civet cat appeared to be the immediate source for human infection but the primary animal reservoir is probably bat.

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until June in Canton (Table A12-1; Cadbury, 1920; Chun, 1919; Shortridge, 1983). Infection there was mild, and no influenza deaths were recorded at the Canton Hospital. Consonant with the time of the Canton outbreak, more solid data come from Hong Kong 110km to the southeast, where influenza deaths abruptly started in June, continuing thereafter throughout the year (Table A12-2; Shortridge, 1983). The effects of the outbreak were most severe from 1918 to

TABLE A12-1 China H1N1—Then and Now

1918	H1N1-like virus[a]		
South	Virus smoldering ~11 years pre-1918?		
South	June, outbreaks in pigs following northward human spread		
North-east	October, pigs infected at same time as humans		
South	Hong Kong, June, human deaths		
2009-H1N1 influenza A human cases virologically confirmed (publicly available data)[b]			
Mainland	5,592	September 9	
Hong Kong	15,357	September 9	1st case May 1
Taiwan	94	September 9	
Macao	1,435	September 9	
Porcine infection not known to this time.			

[a]Adapted from Cadbury (1920), Chun (1919), and Shortridge (1983).
[b]CHP (2009).

TABLE A12-2 Deaths Due to Influenza in Hong Kong for Each Month from 1918-1928

	Year											Monthly
Month	1918	1919	1920	1921	1922	1923	1924	1925	1926	1927	1928	totals
January	0	21	39	20	13	5	2	3	2	0	7	112
February	0	16	118	19	13	6	1	3	3	0	9	188
March	0	25	75	20	13	4	2	2	0	1	8	150
April	0	41	38	22	18	5	10	3	2	1	6	146
May	1	75	32	27	13	7	5	4	4	0	7	175
June	108	137	61	26	44	13	5	4	4	3	8	413
July	53	77	22	54	40	14	9	11	4	4	12	300
August	10	30	14	30	30	5	4	3	6	7	11	150
September	1	8	30	28	40	11	5	6	3	3	27	162
October	70	8	44	13	64	7	5	0	4	3	10	228
November	95	9	35	27	76	2	2	5	1	4	10	266
December	67	2	34	17	58	4	2	1	0	3	6	194
Totals	405	449	542	303	422	83	52	45	33	29	121	2,484

NOTE: These figures may not be accurate for the whole population since influenza was not notifiable, and were derived from those provided by the same hospital and practitioners.
SOURCE: Shortridge (1983).

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1922, exacting a heavy toll on a territory already coping with other infectious disease problems including malaria, tuberculosis, plague, smallpox, cholera, and measles (e.g., Starling, 2007) (Box A12-1).

The 2009-H1N1 influenza A virus was recognized in the United States and Mexico in mid-April. Airplane travel could quickly seed the virus worldwide, more so than in previous pandemics, catching the Southern Hemisphere winter and summer in the Asian tropics at the usual time of peak influenza activity there (see below). Hong Kong, with its experience of dealing with influenza, was able to react with sound public health measures and diagnostic services. The first case was recognized on May 1st and 4 months later there were around 15,000 cases, a figure that is probably an underestimate. The vast majority of cases were mild. At the time of the Institute of Medicine (IOM) workshop (mid-September 2009), the numbers of cases in mainland China, Taiwan, and Macao were trickling in. Elsewhere in tropical Asia, reported numbers were also low (SEARO/WHO 2009).

BOX A12-1
Brief Overview of the Origin of the 1918 Pandemic H1N1 Virus and the Classical H1N1 Swine Flu Virus

Origin of the 1918 Pandemic Virus

Differing times of yearly influenza occurrence in temperate and tropical zones may be a key factor, something not appreciated until the late 1980s (see later discussion). Economic migrants from the southestern part of the influenza epicenter would have carried the H1N1 virus to Western Europe and the United States prior to 1918. Outbreaks there occurred in late winter and early spring 1918 before later doing so that year in the Canton area and in Hong Kong in summer, the usual time of peak occurrence (Shortridge, 1999b).

Origin of Classical Swine Flu Virus

Outbreaks of influenza in pigs followed the spread of the virus northward of Canton and were recorded at the time of human infection in the far northeast (Chun, 1919), suggesting initial human-to-pig transmission. Could there have been a similar occurrence in pigs in the United States around 1918 resulting in endemicity? Infection of piglets experimentally with the reconstructed 1918 pandemic virus is of interest (Weingartl et al., 2009). Phylogenetic studies on the hemagglutinins (HAs) from a range of H1N1 viruses suggest that the classical swine/Iowa/15/30 virus was not a direct descendant of the 1918 pandemic virus, rather from a common ancestral virus around 1905 (Kanegae et al., 1994). It seems that much activity was taking place in southern China involving an H1 or H1-like virus from around the turn of the century until 1918. While much must be conjectured, we may overlook it to our peril.

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Temporal Occurrence

Attention has been drawn to the influence of season on times of influenza occurrence. Influenza had been thought to be a winter infection. It clearly occurs in temperate zones with a recognizable disease burden, but in the tropics and subtropics? A meeting was convened in Singapore in late 1988 with influenza colleagues from around the Pacific Basin with an emphasis on those from Asia. Although much of the data were rudimentary or incomplete, generalized patterns of occurrence were discernible and are shown in Figure A12-1 (Reichelderfer et al., 1989). The winter occurrence in northern Asia was consistent with winter elsewhere, but in tropical and subtropical zones the influenza virus was present for much of the year or year-round, often with a peak at the hottest, weather-

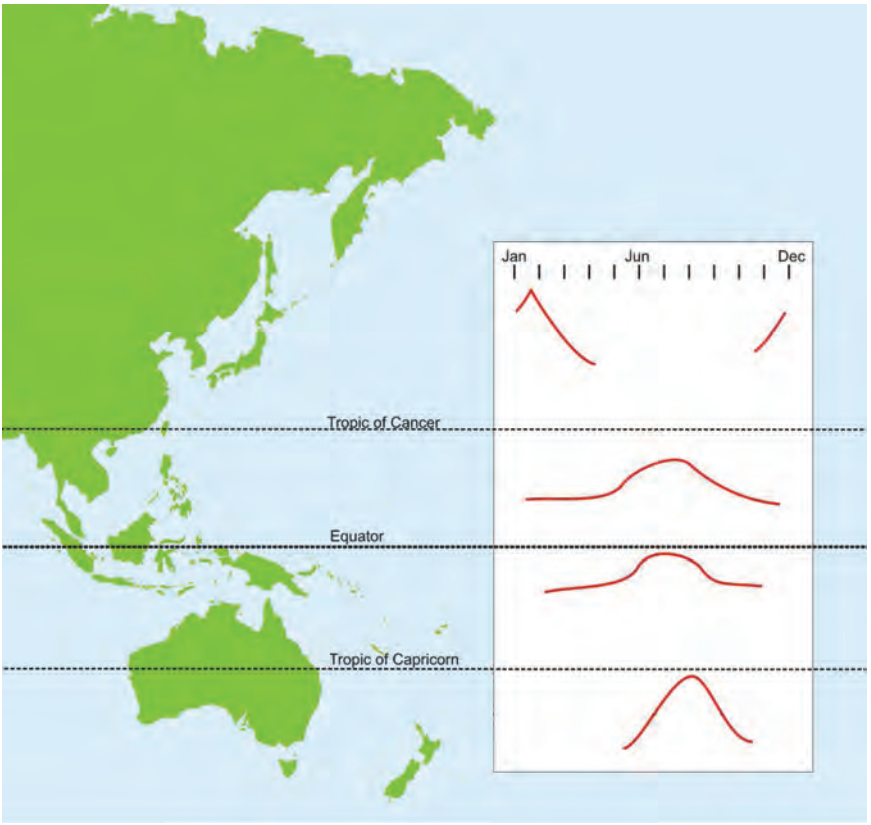

FIGURE A12-1 General patterns of temporal occurrence of influenza A and B viruses in eastern Asia and Australasia.
SOURCE: Adapted from Reichelderfer et al. (1989).

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affected times usually midyear. An important fallout from this was the recognition that the disease burden in the Asian tropics and subtropics is just as significant as that in temperate zones, warranting *inter alia* recommendation for influenza vaccination (Chiu et al., 2002, 2009; Wong et al., 2004, 2006).

The ability of seemingly the same influenza viruses to manifest in a cold, dry, or damp winter and year-round in a hot, humid climate is more than a little curious. Experimental guinea pig studies suggest that aerosol transmission predominates during winter in temperate regions and through contact in the tropics (Lowen and Palese, 2009). No doubt, a variety of factors are involved, for example, host susceptibility, virus transmissibility including quantity and quality of virus spread, and, perhaps, hand hygiene in different zones given that it seemingly contributes to preventing household infections in subtropical Hong Kong (Cowling et al., 2009). The writer takes the view that stress is also probably a factor. He considers that the most stressful time in a temperate zone is winter, whereas the tropics are stressful year-round, particularly so with seasonal climatic changes (Chan et al., 2009). In either case, the lining of the upper respiratory tract may be compromised, facilitating influenza infection and infections by other respiratory viruses. It is noteworthy that epidemics of respiratory syncytial virus pneumonia in children in equatorial Indonesia are associated with weather changes (Omer et al., 2008).

Patterns of Occurrence of 2009-H1N1 Influenza A in Australasia and Hong Kong

The time of appearance of the 2009-H1N1 influenza A virus provided the opportunity to see how the Southern Hemisphere would behave as a guide to dealing with the forthcoming outbreak in the Northern Hemisphere winter. As a bonus, the virus would be expected to be present in tropical East Asia in the Northern Hemisphere around the same time (Figure A12-1).

In New Zealand, the outbreak followed the usual seasonal pattern starting in May and declining from mid-July onward (Baker et al., 2009). The situation was generally similar in Australia, with a little interstate variation (Australian Influenza Surveillance Summary Report, 2009). In both countries, the 2009-H1N1 influenza A virus soon predominated the seasonal virus. Its morbidity was probably lower than might have been expected. While health services coped well, those most affected usually had underlying conditions. Meanwhile, in Hong Kong a similar situation prevailed: 2009-H1N1 influenza A started to rise in mid-June, peaking in July and beginning to fall in August. The resumption of school in September saw a big rise in cases, and then falling off by early October (CHP, 2009). By contrast with Australia and New Zealand, the seasonal H3N2 was less easily displaced and comprised as much as about 50 percent in the peak period falling to less than 5 percent by early October (Table A12-3). Other respiratory viruses were isolated during midsummer including medically important paramyxoviruses,

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which occur variably throughout the year, and respiratory syncytial virus in the summer (Sung et al., 1987, 1992).

Thus, the experience in Australasia and Hong Kong in the first round indicates that the pandemic is mild. Experimental ferret infection studies by Perez et al. (2009) showed that the 2009-H1N1 influenza A virus "is more transmissible than, and has a biological advantage over, prototypical seasonal H1 or H3 strains." The authors also point out the possibility of dual infections by H1N1 2009 and H3N2 viruses and clinical implications. In this sense, the isolation of a high percentage of H3N2 viruses at the time of the summer peak in Hong Kong (Table A12-3) is of relevance. Ideally, as many isolates of the three categories of variants as practicable from the Northern Hemisphere winter should be sequenced for evidence of reassortment, as should those obtained from tropical East Asia throughout the year.

Recycling of H Subtypes

The appearance of the 2009-H1N1 influenza A virus has rekindled the notion that there is a limited range of H subtypes that can cause pandemics, namely H1, H2, and H3. This does not exclude the possibility that other H subtypes have expressed this trait in earlier centuries or that we are in a period of transition of human susceptibility in which other H subtypes, say H5, H7, and H9, are possible pandemic candidates.

With the caveat of the reliability of seroarcheology and interpretation of the historical record, H1N1 or H1N1-like viruses have occurred singly or have coexisted with H2 or H3 viruses (Shortridge, 1992, 1999b). This raises concern that a similar situation could arise with the 2009-H1N1 influenza A virus.

Immediate concerns are that (1) it usurps one, the other, or both prevailing H1N1 and H3N2 variants and (2) it coexists with one, the other, or both of the variants. A medium- to long-term concern is that an H2-like virus will emerge, usurp, or coexist with prevailing variants.

Based on the evidence that H1 and H3 viruses cocirculated before the 1918 pandemic, it seems a reasonable possibility that the prevailing variants will be usurped. Preliminary ferret infection experiments suggest that H1N1 2009 viruses will do this (Perez et al., 2009). A range of such experiments must be pursued.

And what might the future hold for the influenza type B virus in the face of the new H1N1 2009 competitor or a triad of type A variants?

H5N1 Virus

While the 2009-H1N1 influenza A virus may have overtaken the H5N1 virus in pandemicity, occasionally reported human cases and continued virus presence in avians are cause for concern (WHO, 2009). The virus has spread

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TABLE A12-3 Respiratory Pathogens Isolated in Hong Kong at Selected Times During the 2009-H1N1 Influenza A Outbreak[a]

	July 13-19, 2009		August 10-16, 2009		September 27 to October 3, 2009[b]	
Agent	Number	Type/ Subtype	Number	Type/ Subtype	Number	Type/ Subtype
Adenovirus	16	Untyped: 3 Type 1: 3 Type 2: 2 Type 3: 1 Type 4: 1 Type 5: 2 Type 6: 1 Type 8: 2 Type 14: 1	15	Untyped: 8 Type 1: 2 Type 2: 5		
Influenza A	1022	Untyped: 4 H1: 65 H1 2009: 549 H3: 404	1691	Untyped: 1 H1: 88 H1 2009: 846 H3: 756	1001	Untyped: H1: 21 H1 2009: 910 H3: 54
Influenza B	13		30		14	
Parainfluenza	38	Type 1: 22 Type 2: 3 Type 3: 12 Type 4: 1	17	Type 1: 4 Type 2: 1 Type 3: 12		
Respiratory syncytial virus	10		37			
Rhinovirus	6		22			
Mycoplasma pneumoniae	7		3			

[a]Data abstracted from reports from Virology Division, Centre for Health Protection, Department of Health, Hong Kong SAR (CHP, 2009).

[b]Blank spaces in this timeframe denote no isolation reported.

from eastern Asia across the Eurasian land mass to northern Africa. The pattern of human infection in Egypt is different from that recorded elsewhere (Dudley, 2009), and asymptomatic infection is increasingly appreciated (Dudley, 2008). The virus appears to be endemic in poultry in southern China (Chen et al., 2006) and recent studies have shown its presence in wild birds in 10 provinces (Kou

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et al., 2009) and in mammals, namely raccoon dogs (Qi et al., 2009) and pikas (Zhou et al., 2009). Continued virus surveillance and responsible reporting are necessary. International human and animal health authorities now face exceedingly complex influenza issues.

Food, Flu, and the Future

With the big increase in global population in the past 60 or so years has come the need to supply dietary meat protein on an unprecedented scale, bringing with it infectious agents arising from intensified animal production (Greger, 2006). The 2009-H1N1 influenza A virus most likely arose in the United States and Mexico region through intensive pig production (Greger, 2009), distant from the epicenter of southern China. This suggests the prospect of new influenza pandemic epicenters elsewhere in the future.

A similar situation applies to poultry meat and egg production in Asia generally and China in particular, where chicken has become a "near-daily staple." This was facilitated by the control of Newcastle disease, the major poultry disease of the region, through vaccine improvements and distribution (Shortridge, 1982; Copland, 1987; Higgins and Shortridge, 1988), benefits that have extended to minor poultry. The industrialization of poultry production probably played a major role in the genesis and spread of the H5N1 virus as pig production seemingly has done for the 2009-H1N1 influenza A virus. A more serious problem could arise through lapses in biosecurity, resulting in an avian or porcine reassortant capable of great human devastation.

In a land noted for consumption of wildlife and where nothing is wasted (Parham, 2006), wildlife farming in China poses new threats. The H5N1 virus was isolated from farmed Bar-headed Geese at Qinghai Lake, western China (Butler, 2006), a location from which migratory birds may have started the virus's westward spread across Eurasia. (Commercially raised civet cats were the source of the SARS virus; see Guan et al., 2003.)

Industrial avian and animal production have wider implications for human health (Nierenberg and Garces, 2005). At this point it is hard to see how a projected human population of 9 billion in 2050 will have adequate food security (Adams, 2009). The time is now ripe to put microbes, biotechnology and reconstituted ribosomes to good use for the large-scale production of dietary protein.

Some Areas for Investigation

The appearance of the 2009-H1N1 influenza A virus and its ability to give rise to a pandemic prompt a number of areas for follow-up investigation. Some of these intersect. The areas are listed in Table A12-4 and briefly discussed.

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TABLE A12-4 Some Areas for Investigation

Category 1: 2009-H1N1 influenza A virus
- Basis of novel H1 HA appearance (recycling)
- Pig "mixing-vessel" hypothesis
- A third-party or facilitating virus
- Potential "hot spots" (e.g., high concentrations of animals - increased virus surveillance)

Category 2A: Recycling of HA antigens
- H2 to return?
- Systematic global serological study of those born after 1968

Category 2B: Clinical
- 2009-H1N1 influenza A virus post-infection sequelae (e.g., lethargy [von Economo])?

Category 3: The HA
- HA antigenic epitope analysis, all H subtypes
- Escape mutants
- Antigenic hierarchic capabilities
- Pathogenesis
- Secondary factors (e.g., HA torsion, side chain flexibility)

Category 4: A rock and a hard place
- Evaluate potential prophylactic value of immunomodulatory agents (e.g., statins, agonists)

2009-H1N1 Influenza A Virus

The role of the pig as a "mixing vessel" is central, a hypothesis set rolling by the isolation of early human H3N2 variants in pigs from China (Shortridge et al., 1977; Scholtissek et al., 1985). Events surrounding the genesis of the 2009-H1N1 influenza A virus need not be reiterated. Suffice it to ask whether the acquisition of Eurasian "avian-like" swine genes through reassortment in the pig could have facilitated the transition of a virus of North American geographical lineage into a pandemic virus? The Eurasian genetic composition of the pandemic viruses of the past century prompts this question. While there does not seem to be a common genetic template for a pandemic virus (save for a change of HA), the recognition of likely progenitors of a pandemic virus some years earlier in the case of the 2009-H1N1 influenza A virus puts a new spin on the concept of pre-pandemic "bridging strains" (Shortridge et al., 1979). Moreover, the virus had seemingly transmitted to humans several months before the recognition of the outbreak (Smith et al., 2009b). Maybe George Orwell in his satire on farm animals got it right—pigs rule (Orwell, 1945).

That the 2009-H1N1 influenza A virus was able to squeeze through a human "firewall" of H1 antibodies signals that its HA antigen intrinsically has an unrecognized propensity for antigenic change or that an adaptation process has taken

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place over a number of years in the massive high-density pig populations of North America. While it is not possible to predict the number of antigenic variants that the virus is capable of producing, current information suggests that its life expectancy may be relatively short, akin, say, to the 11-year reign of the H2N2 Asian virus. In addition, the 2009-H1N1 influenza A virus may behave as a short-term third-party or facilitating virus undergoing further reassortment in a pig or human with a novel HA leading to a new round of pandemicity.

In addition to ramping up virus surveillance of pigs, it is essential that recommendations on industrial pig production be pursued (Greger, 2009). This is now an inescapable global issue.

Recycling of HA Antigens

The reappearance of an H1N1 pandemic virus in 2009 revives the concept of recycling of H subtypes. Furthermore, its presence in humans along with prevailing H3N2 variants may pave the way for an H2 virus, perhaps sooner rather than later, either as a totally "new" virus (as was the case in 1957) or as a reassortant of the H1N1 or H3N2 virus or both. If it were a totally "new" H2N2 virus, matching its gene constellation with that of the 1957 pandemic virus would be illuminating toward understanding the genetic factors that engender pandemicity. The apparent cocirculation of H1- and H2-like viruses at least in southern China from 1888 to 1898 (Cantlie, 1891; Shortridge, 1999b) raises the possibility of a repeat of this in the early part of this century. H2 or H2-like viruses do not appear to have cocirculated with H3-like viruses. Evidence of H2 virus infection of humans must be sought.

That being said, it is important that all unidentified human and porcine isolates be checked for H2 gene sequence or HA antigen and for, say, H5, H7, and H9 viruses (CHP, 2009). Recent estimates suggest that the pandemic H2N2 1957 virus entered the human population two to six years before the pandemic (Smith et al., 2009a). The isolation of avian/swine reassortant H2N3 viruses from diseased pigs in the United States is of concern (Ma et al., 2007). While the isolation of H2 viruses from pigs or humans may prove elusive, it would be wise to set about the detection of H2 antibody in humans born after 1968, particularly in children. The interpretation of serological studies for the detection of presumptive antibody to avian influenza viruses in mammalian sera by widely used hemagglutination inhibition is more complex than the simple test belies. Whatever the diagnostic approach, it is suggested that investigation be carried out through an international collaborative effort using standardized reagents and techniques. Furthermore, there should be an international group to set about this task as a matter of urgency.

Clinical

An epidemic of encephalitis lethargica (EL) followed the 1918 pandemic, claiming the lives of an estimated half-million people. The appearance of an

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H1N1 pandemic virus partly of swine origin nine decades later raises the possibility of EL in this one.

It is not known whether the 1918 H1N1 virus was the cause of the EL epidemic. von Economo, who initially described it, apparently thought not. Recent investigation of EL and other disorders suggests that EL may be the outcome of an autoimmune response to streptococcal infection (Dale et al., 2004; Vincent, 2004; Vilensky and Gilman, 2006). The extent of post-H1N1 influenza streptococcal pneumonia in survivors of the 1918 pandemic is not known. Nonetheless, it would seem reasonable to keep the possibility of EL-like illness in clinical purview now, even though the 2009-H1N1 influenza A pandemic is generally mild and with limited antibiotic cover.

The HA

Although there is accumulating evidence indicative of recycling of H subtypes H1, H2, and H3, the possibility that the other 13 H subtypes have pandemic capabilities cannot be excluded irrespective of their avian hosts and ecological backgrounds. There is no simple answer, but it might initially be approached in two parts.

1. HA structure and function through determination of three dimensional structure, antigenic epitope mapping, and receptor binding site.
2. Biologically through the detection of virus escape mutants in culture under pressure of using extensive panels of monoclonal antibodies as a gauge of a virus H subtype's ability to escape the host's immune response (e.g., Kaverin et al., 2004).

It could be reasoned that, unless an HA has intrinsic hierarchic antigenic capabilities to produce a succession of antigenic variants in humans, it is unlikely to progress beyond initial infection. The detection of presumptive antibody to all avian H subtypes examined in rural southern China contributes to this view (Shortridge, 1992). The ability of H3N2 viruses to have a 41-year presence thus far in humans might be inferred from the coexistence of many antigenic variants in the domestic duck population of southern China (Shortridge et al., 1990). In this sense, H1 and H2 viruses are an enigma. With so few H1 and H2 viruses in domestic ducks and wild waterfowl, it will be as illuminating as it is critical to measure the extent of the H1N1 2009 virus's ability to produce escape mutants—even more so for the H2 subtype because of the increasing possibility of its being recycled.

Intrinsic to understanding the outcome of infection is understanding the earliest stages of pathogenesis in the upper respiratory tract. Might it be possible to distinguish among events that take place in, say, the nasal turbinates following infection by a seasonal flu virus, a precursor pandemic virus, and the earliest detected pandemic virus? Whatever the situation, it would be beneficial to know

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much more about the overall process of pathogenesis given that human defenses have been breached since 1997 by H5, H9, H7, and H1 viruses.

While the role of cell receptor type in determining the outcome of virus infection now seems less clear (Nicholls et al., 2008), the strength of cell-virus binding may be influenced by secondary factors such a torsion in the HA molecule and flexibility of the subterminal carbohydrate side chain. This is a complex area that will take a long time to resolve.

A Rock and a Hard Place

A universal influenza vaccine is a long way off and, even with the best of intentions, it is unrealistic to expect sufficient vaccine to be available for yearly needs, a pandemic such as that of 2009-H1N1 influenza A let alone confront a full-blooded pandemic. Factors here include vaccine manufacturing problems, cost, distribution, and administration of the vaccine. Nor will there be sufficient antiviral agents available of an order of magnitude. Many of the world's population will be affected, particularly the poor. Improved understanding of the outcome of severe influenza infection indicates that the response of the host is more important than the amount of virus generated (La Gruta et al., 2007). Dysregulation of the cytokine response is the basis of much of this; its control through immunomodulatory agents offers an indirect approach to dealing with infection. Cheap generic agents such as statins, and fibrate and glitazone PPAR agonists used to treat a variety of medical conditions are attractive propositions (Fedson, 2009a,b). Statins, for example, which are used to treat high cholesterol levels can reduce the levels of pro-inflammatory cytokines and chemokines in influenza infection. The prophylaxis/therapy envisaged for severe influenza is simple, logical and imaginative (Clark and Alleva, 2009); rigorously explored experimentation beckons.

No More Pandemics

Having observed the changing tide of progress in influenza over the years from the Hong Kong influenza sentinel post, I feel the time is appropriate in the early phase of the 2009-H1N1 influenza A pandemic to rethink our view of pandemics. There is now better understanding of influenza virus ecology, the zoonotic dimension of pandemics, reaction to threats and outbreaks in incipient and pandemic phases, and special features of the virus and its disease to allow transition from a reactive or defensive position to a more positive one, namely, *no more pandemics* (Figure A12-2). This transition derives largely from almost four decades of consolidation of the hypothesis that pandemic influenza is a zoonosis that is consequent upon studies on the origin of the 1968 H3N2 (Hong Kong) pandemic virus (Webster and Laver, 1972). This signifies the nonhuman virus's

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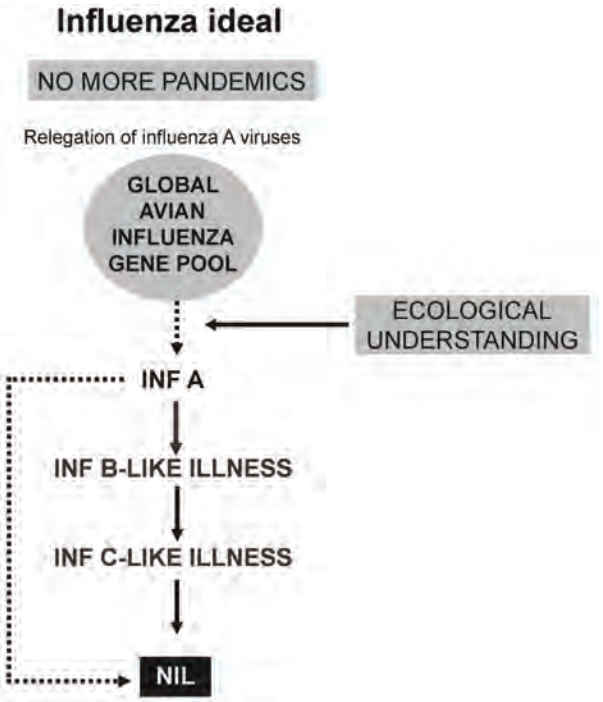

FIGURE A12-2 Long-term steps for the prevention of influenza pandemics.

ability to cross the species barrier to humans and the most likely H subtype of the time to do so. A recognition of these properties provides the type and level of preventative action appropriate for birds and mammals to break the chain of zoonotic transmission. There is still a long way to go; it will require *inter alia* global mapping of avian influenza viruses and the influenza viruses of other hosts bearing in mind that pandemic influenza by its very nature is a zoonosis that is noneradicable.

If pandemics can be stopped, it might be reasoned that over time, without renewal of genetic vigor through cycles of pandemicity, prevailing type A variants may be of declining pathogenicity, doing so to the level of the type B virus. Ideally, they disappear or, more likely, reduce to the level of type C virus pathogenicity. After all, as pointed out by Gammelin et al. (1990), influenza B and C viruses have a common root with A viruses and may have developed their own type under selection pressures specific for humans. These views represent a mindset that is really an influenza vision well into the future.

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Virus Surveillance

Virus surveillance is the cornerstone of influenza ecology, epidemiology, disease occurrence, and public health measures through to pandemic preparedness. Yet surprisingly little is done; when it is, it is often in response to a disease outbreak. It is not often appreciated that dangerous or potentially dangerous influenza viruses can be carried by subclinically infected birds and mammals and be spread from population to population and across different populations. One might reasonably ask if, in hindsight, long-term systematic virus surveillance of pig populations, on the one hand, and concerted action on the part of farm operators and civil authorities, on the other, would have averted the 2009-H1N1 influenza A pandemic. Whatever the case, 2009-H1N1 influenza A is another wake-up call indicating the need for long-term surveillance, especially of domestic birds and mammals. This requires long-term scientific will, political will, and financial commitment. With the increasing movement toward industrial agribusiness operations for meat protein production, surveillance for influenza viruses (and other recognized and unrecognized agents) is imperative. Surveillance must be increased globally (Figure A12-3). The time is nigh for international and other agencies to formulate policies and recommendations to this end.

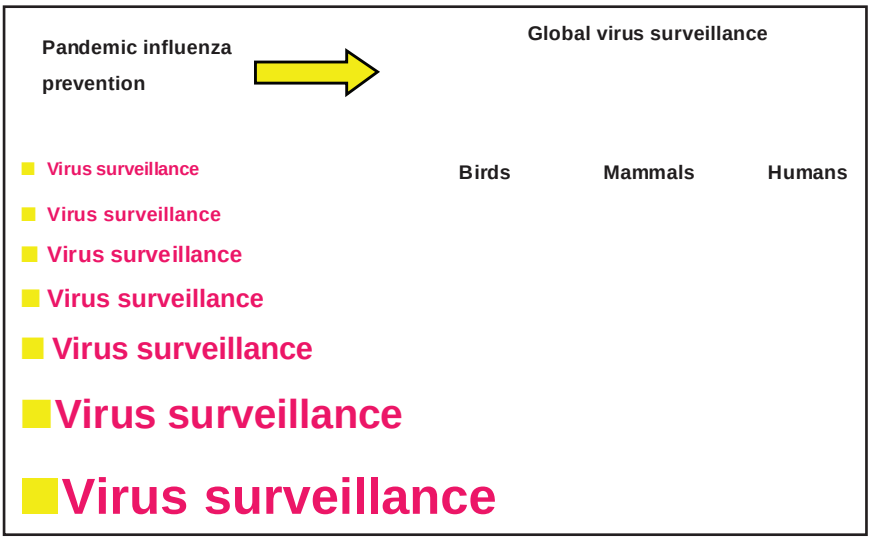

FIGURE A12-3 Emphasizing the need for increasing influenza virus surveillance for the prevention of pandemic influenza.

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Global Need

Understanding the origin of influenza pandemics has moved from superstition to science (Anonymous, 1920). The scientific advances in influenza and their potential for global benefit must be clearly enunciated to national and international decision makers. This approach will particularly require international collaboration, cooperation and collective action for the common good. Nations must work as one global community (Figure A12-4). This approach is definitely possible and not without precedent. All nations worked together in the wake of World War II in spite of the difficulties of the Cold War for the eradication of smallpox. It is anticipated that poliomyelitis will be eradicated within a decade, in no small measure due to substantial funding and effort from Rotary International.

A pandemic requires panglobal effort and is best dealt with through the decision-making process of the United Nations. This may well bring with it the need for structural and organizational changes to deal effectively with the many complexities of influenza and its pandemic viruses. Similar principles should apply to all emerging infectious diseases (Morse, 2009).

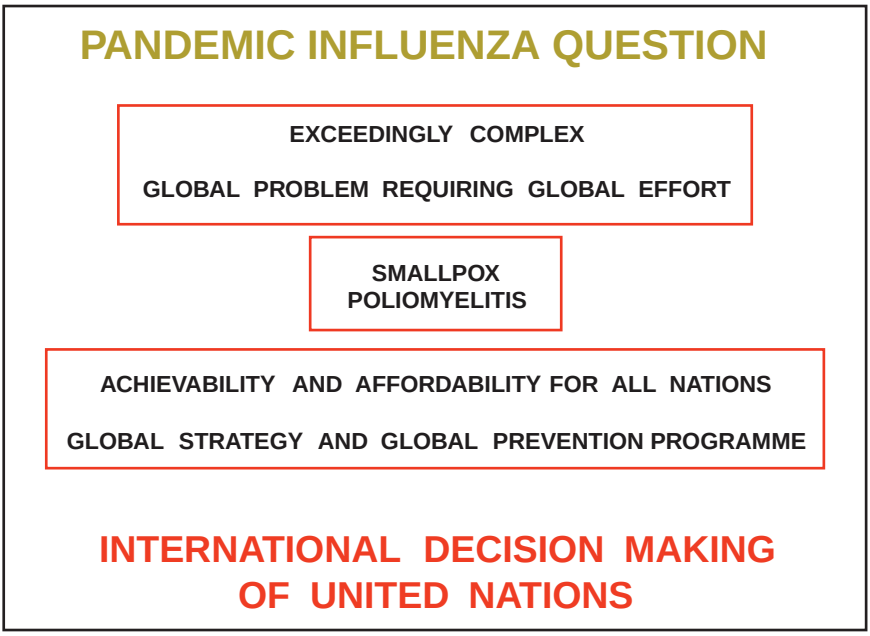

FIGURE A12-4 Toward a unified, global effort for the prevention of pandemic influenza.

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Guiding Principle

The basic principle that emerges through this report is the prevention of influenza pandemics, taking prevention further to a vision: *no more pandemics.* The foundation for such a vision, especially in the case of influenza pandemics and their historical association with China, is not new. It goes back about 2,500 years to what Joseph Needham called the Chinese Hippocratic Corpus—*The best medicine is preventive medicine*—later consolidated to—*A skillful doctor cures illness when there is no sign of disease, and thus the disease never comes* (Figure A12-5; Needham, 1980; Needham and Lu, 2000).

Appreciation

Appreciation for core support to the writer and others is due to the World Health Organization, Geneva, in the 1970s for promoting and fostering studies on the ecology of influenza viruses through its Veterinary Public Health Unit; the National Institutes of Health, Bethesda, Maryland, for supporting such studies through St. Jude Children's Research Hospital, Memphis; the Centers for Disease Control and Prevention, Atlanta, for studies in moving the animal-human influenza link forward and, later The Wellcome Trust, London and the Li Ka Shing

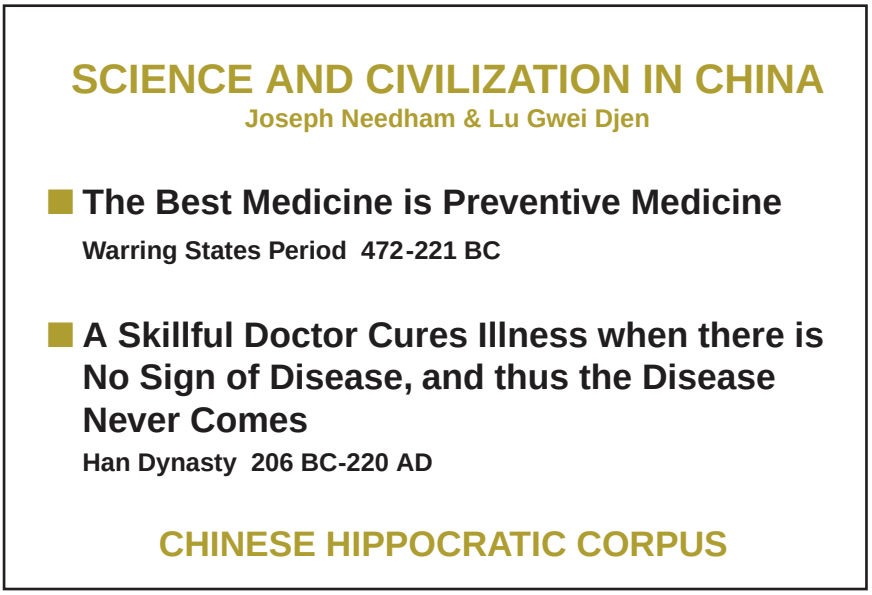

FIGURE A12-5 Fundamental principles still apply.
SOURCE: Adapted from Needham (1980) and Needham and Lu (2000).

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Foundation, Hong Kong, for supporting further studies in these areas. It would be fair to say that the generous support from these and other organizations to so many across the field has contributed much to the global pool of understanding about influenza virus ecology and epidemiology that provided the foundation for dealing with the H5N1 virus in 1997, SARS in 2003, and now the 2009-H1N1 influenza A pandemic. These experiences will be stepping stones to future influenza and other infectious disease issues that lie ahead in a changing world.

References

Adams, D. 2009 (October 21). GM research is needed urgently to avoid food crisis, says Royal Society. *The Guardian*, http://www.guardian.co.uk/environment/2009/oct/21/gm-research-food/print (accessed November 17, 2009).

Anonymous. 1920 (March). How influenza started in China! *The Far East Review* March:170.

Australian Influenza Surveillance Summary Report. 2009. No. 13. Reporting period: 7 August 2009-14 August 2009. Department of Health and Aging, Australian Government.

Baker, M. G., N. Wilson, Q. S. Huang, S. Parine, L. Lopez, D. Bandaranayake, M. Tobias, K. Mason, G. F. Mackereth, M. Jacobs, C. Thornley, S. Roberts, and C. McArthur. 2009. Pandemic influenza A (H1N1)v in New Zealand: the experience from April to August 2009. *Eurosurveillance* 14(34):1-5.

Butler, D. 2006. Blogger reveals China's migratory goose farms near the site of the flu outbreak. *Nature* 441(7091):263.

Cadbury, W. W. 1920. The 1918 pandemic of influenza in Canton. *China Medical Journal* 34:1-17.

Cantlie, J. 1891 (August 29). The first recorded appearance of the modern influenza epidemic. *British Medical Journal*:491.

Chan, P. K. S., H. Y. Mok, T. C. Lee, I. M. T. Chiu, W. Y. Lam, and J. L.Y. Sung. 2009. Seasonal influenza activity in Hong Kong and its association with meteorological variations. *Journal of Medical Virology* 81(10):1797-1806.

Chen, H., G. J. D. Smith, K. S. Li, J. Wang, X. H. Fan, J. M. Rayner, D. Vijaykrishna, J. X. Zhang, L. J. Zhang, C. T. Guo, C. L. Cheung, K. M. Xu, L. Duan, K. Huang, K. Qin, Y. H. C.. Leung, W. L. Wu, H. R. Lu, Y. Chen, N. S. Xia, T. S. P. Naipospos, K. Yuen, S. S. Hassan, S. Bahri, T. D. Nguyen, R. G. Webster, J. S. M. Peiris, and Y. Guan. 2006. Establishment of multiple sublineages of H5N1 influenza viruses in Asia: implications for pandemic control. *Proceedings of the National Academy of Sciences* 103(8):2845-2850.

Chiu, S. S., Y. L. Lau, K. H. Chan, W. H. Wong, and J. S. Peiris. 2002. Influenza-related hospitalizations among children in Hong Kong. *New England Journal of Medicine* 347(26):2097-2103.

Chiu, S. S., K. H. Chan, H. Chen, B. W. Young, W. Lim, W. H. S. Wong, Y. L. Lau, and J. S. M. Peiris. 2009. Virologically confirmed population-based burden of hospitalization caused by influenza A and B among children in Hong Kong. *Clinical Infectious Diseases* 49(7):1016-1021.

CHP (Centre for Health Protection). 2009. *Flu express/notifiable infectious diseases/swine and seasonal flu monitor/update on human swine influenza/virus isolation and serology testing (respiratory pathogens)*. Centre for Health Protection, Department of Health, The Government of the Hong Kong Special Administrative Region.

Chun, J. W. H. 1919. Influenza including its infection among pigs. *National Medical Journal, China* 5:34-44.

Clark, I., and L. Alleva. 2009. Invited commentary on David Fedson's article *Influenza and Other Respiratory Viruses* 3(5):199-201.

Copland, J. W., editor. 1987. Newcastle disease in poultry: a new food pellet vaccine. *ACIR Monograph* No.5. Canberra, Australia: Australian Centre for International Agricultural Research.

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Cowling, B. J., K. H. Chan, V. J. Fang, C. K. Y. Cheng, R.O.P. Fung, W. Wai, J. Sin, W. H. Seto, R. Yung, D. W. S. Chu, B. C. F. Chui, P. W. Y. Lee, M. C. Chiu, H. C. Lee, T. M. Uyeki, P. M. Houck, J. S. M. Peiris, and G. M. Leung. 2009. Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial. *Annals of Internal Medicine* 151(7):437-446.

Dale, R. C., A. J. Church, R. A. H. Surtes, A. J. Lees, J. E. Adcock, B. Harding, B. G. R. Neville, and G. Giovannoni. 2004. Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. *Brain* 127(Pt. 1):21-33.

Dudley, J. P. 2008. Public health and epidemiological considerations for avian influenza risk mapping and risk assessment. *Ecology and Society* 13(2):21.

———. 2009. Age-specific infection and death rates for human A (H5N1) avian influenza in Egypt. *Eurosurveillance* 14(18):19198.

Fedson, D. S. 2009a. Confronting the next influenza pandemic with anti-inflammatory and immunomodulatory agents: why they are needed and how they might work. *Influenza and Other Respiratory Viruses* 3(4):129-142.

———. 2009b. Meeting the challenge of influenza pandemic preparedness in developing countries. *Emerging Infectious Diseases* 15(3):365-371.

Gammelin, M., A. Altmuller, U. Reinhardt, J. Mandler, V. R. Harley, J. P. Hudson, W. M. Fitch, and C. Scholtissek. 1990. Phylogenetic analysis of nucleoprotein suggests that the human influenza A viruses emerged from a 19th century avian ancestor. *Molecular Biology and Evolution* 7(2):194-200.

Greger, M. 2006. *Bird flu. A virus of our own hatching.* New York: Lantern Books.

———. 2009. *CDC confirms ties to virus first discovered in U.S. pig factories*, http://www.humanesociety.org/news/news/2009/04/swine_flu_virus_origin_1998_042909.html (accessed November 17, 2009).

Guan, Y., B. J. Zheng, Y. Q. He, X. L. Liu, Z. X. Zhuang, C .L. Cheung, S. W. Luo, P. H. Li, L. J. Zhang, Y. J. Guan, K. M. Butt, K. L. Wong, K. W. Chan, W. Lim, K. F. Shortridge, K. Y. Yuen, J .S. M. Peiris, and L. L. M. Poon. 2003. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 302(5643):276-278.

Higgins, D. A., and K. F. Shortridge. 1988. Newcastle disease in tropical and developing countries. In *Newcastle Disease*, edited by D. J. Alexander. Boston: Kluwer Academic Publications. Pp. 273-302.

Kanegae, Y., S. Sugita, K. F. Shortridge, Y. Yoshioka, and K. Nerome. 1994. Origin and evolutionary pathways of the H1 hemagglutinin gene of avian, swine and human influenza viruses. *Archives of Virology* 134(1-2):17-28.

Kaverin, N. V., I. A. Rudneva, N. A. Ilyushina, A. S. Lipatov, S. Krauss, and R. G. Webster. 2004. Structural differences among hemagglutinins of influenza A virus subtypes are reflected in their antigenic architecture: analysis of H9 escape mutants. *Journal of Virology* 78(1):240-249.

Kendal, A. P., G. R. Noble, J. J. Skehel, and R. G. Webster. 1978. Antigenic similarity of influenza A (H1N1) viruses from epidemics in 1977-1978 to "Scandinavian" strains isolated in epidemics of 1950-1951. *Virology* 89(2):632-636.

Kou, Z., Y. D. Li, Z. H.Yin, S.Guo, M. L.Wang, X. B. Gao, P. Li, L. J.Tang, P. Jiang, Z. Luo, Z. Xin, C. Q. Ding, Y. B. He, Z. Y. Ren, P. Cui, H. F. Zhao, Z. Zhang, S. Tang, B. P. Yan, F. M. Lei, and T. X . Li. 2009. The survey of H5N1 flu viruses in wild birds in 14 provinces of China from 2004-2007. *PLoS ONE* 4(9):e6926.

La Gruta, N. L., K. Kedzierska, J. Stambas, and P. C. Doherty. 2007. A question of self-preservation: immunopathology in influenza virus infection. *Immunology and Cell Biology* 85(2):85-92.

Lowen, A., and P. Palese. 2009 (August 18). Transmission of influenza viruses in temperate zones is predominantly by aerosol, in the tropics by contact. *PLoS Currents: Influenza*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2762697/ (accessed January 4, 2010).

Copyright National Academy of Sciences. All rights reserved.

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Ma, W. J., A. L. Vincent, M. R. Gramer, C. B. Brockwelll, K. M. Lager, B. H. Janke, P. C. Gauger, D. P. Patnayak, R. J. Webby, and J. A. Richt. 2007. Identification of H2N3 Influenza A viruses from swine in the United States. *Proceedings of the National Academy of Sciences* 104(52):20949-20954.

Morse, S. S. 2009. Emerging infections: condemned to repeat? In *Microbial evolution and co-adaptation.* Washington, DC: The National Academies Press. Pp. 191-208.

Nakajima, K., U. Dresselberger, and P. Palese. 1978. Recent human influenza A (H1N1) viruses are closely related genetically to strains isolated in 1950. *Nature* 274(5669):334-339.

Needham, J. 1980. *China and the origins of immunology*. Centre of Asian Studies occasional papers and monographs, No.41. University of Hong Kong, Hong Kong.

Needham, J., and G. D. Lu. 2000. The origins of immunology. In *Science and civilization in China. Biology and biological technology, Part VI: Medicine*. Vol.6, edited by N. Sivan. Cambridge: Cambridge University Press. Pp. 114-174.

Nicholls, J. M., R. W. Y. Chan, R. J. Russell, G. M. Air, and J. S. M. Peiris. 2008. Evolving complexities of influenza virus and its receptors. *Trends in Microbiology* 16(4):149-157.

Nierenberg, D., and L. Garces. 2005. *Industrial animal agriculture. The next global health crisis?* London: World Society for the Protection of Animals.

Omer, S. B., A. Sutanto, H. Sarwo, M. Linehan, I. G. G. Djelantik, D. Mercer, V. Moniaga, L. H. Moulton, A.Widjaya, P. Muljati, B. D. Gessner, and M. C. Steinhoff. 2008. Climatic, temporal and geographic characteristics of respiratory syncytial virus disease in a tropical island population. *Epidemiology and Infection* 136(10):1319-1327.

Orwell, G. 1945. *Animal farm.* Harmondsworth, England: Penguin Books.

Parham, W. 2006. *South China's taste for wildlife*, http://fas.org/blog/china/reports-and-data/south_chinas_taste_for_wildlife (accessed November 17, 2009).

Patterson, K. D. 1985. Pandemic and epidemic influenza, 1830-1848. *Social Science and Medicine* 21(5):571-580.

Perez, D., E. Sorrell, M. Angel, J. Q. Yi, D. Hickman, L. Pena, G. Ramirez-Nieto, B. Kimble, and Y. Araya. 2009. Fitness of pandemic H1N1 and seasonal influenza A viruses during co-infection: evidence of competitive advantage of pandemic H1N1 influenza versus seasonal influenza. *PLoS Currents: Influenza*, http://knol.google.com/k/daniel-perez/fitness-of-pandemic (accessed November 17, 2009).

Qi, X., X. H. Li, P. Rider, W. X. Fan, H. W. Gu, L. T. Xu, Y. H. Yang, S. W. Lu, H. Wang, and F.Y. Lui. 2009. Molecular avian influenza A viruses isolated from raccoon dogs in China. *PLoS ONE* 4(3):e4682.

Reichelderfer, P., A. P. Kendal, K. F. Shortridge, A. Hampson, et al. 1989. Influenza surveillance in the Pacific Basin. Seasonality of virus occurrence: a preliminary report. In *Proceedings: First Asia Pacific Congress of Medical Virology*, Singapore, 1988, edited by Y. C. Chan, S. Doraisingham, and A. E. Ling. Singapore: World Scientific. Pp. 412-444.

Scholtissek, C., H. Burger, O. Kistner, and K. F. Shortridge. 1985. The nucleoprotein as a possible major factor in determining host specificity of influenza H3N2 viruses. *Virology* 147(2):278-294.

SEARO/WHO (World Health Organization Regional Office for Southeast Asia). 2009. *Pandemic H1N1-2009 influenza situation in SEA region*, http://www.searo.who.int/en/section10/Section2562.htm (accessed November 17, 2009).

Shortridge, K. F., editor. 1982. *Newcastle disease and its control in Southeast Asia.* Hong Kong: Hong Kong University Press.

———. 1983. Pandemic influenza: application of epidemiology and ecology in the region of southern China to prospective studies. In *The origin of pandemic influenza viruses*, edited by W. G. Laver. New York: Elsevier Science Publishing Company, Inc. Pp. 191-200.

———. 1992. Pandemic influenza: a zoonosis? *Seminars in Respiratory Infections* 7(1):11-25.

———. 1999a. Poultry and the H5N1 outbreak in Hong Kong, 1997: abridged chronology and virus isolation. *Vaccine* 17(Suppl 1):S26-S29.

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

———. 1999b. The 1918 "Spanish flu:" pearls from swine? *Nature Medicine* 5(4):384-385.

Shortridge, K. F., and C. H. Stuart-Harris. 1982. An influenza epicentre? *Lancet* 2(8302):812-813.

Shortridge, K. F., A. Cherry, and A. P. Kendal. 1979. Further studies of the antigenic properties of H3N2 strains of influenza A viruses isolated from swine in southeast Asia. *Journal of General Virology* 44(1):251-254.

Shortridge, K. F., P. A. Underwood, and P. A. King. 1990. Antigenic stability of H3 influenza viruses in the domestic duck population of southern China. *Archives of Virology* 114(1-2):121-136.

Shortridge, K. F., R. G. Webster, W. K. Butterfield, and C. H. Campbell. 1977. Persistence of Hong Kong influenza virus variants in pigs. *Science* 196(4297):1454-1455.

Smith, G. J. D., J. Bahl, D. Vijaykrishna, J. X. Zhang, L. L. M. Poon, H. L.Chen, R. G. Webster, J. S. M. Peiris, and Y. Guan. 2009a. Dating the emergence of pandemic influenza viruses. *Proceedings of the National Academy of Sciences* 106(28):11709-11712.

Smith, G. J. D., D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghwani, S. Bhatt, J. S. M. Peiris, Y.Guan, and A. Rambaut. 2009b. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* 459(7250):1122-1125.

Starling, A. E. 2007. *Plague, SARS and the story of medicine in Hong Kong*. Hong Kong Museum of Medical Sciences Society 2006. Hong Kong: Hong Kong University Press.

Sung, R. Y. T., H. G. S. Murray, R. C. K. Chan, D. P. Davies, and G. L. French. 1987. Seasonal patterns of respiratory syncytial virus infection in Hong Kong. *Journal of Infectious Diseases* 156(3):527-528.

Sung, R. Y. T., R. C. K. Chan, J. S. Tam, A. B. F. Cheng, and H. G. S. Murray. 1992. Epidemiology and aetiology of acute bronchiolitis in Hong Kong infants. *Epidemiology and Infection* 108(1):147-154.

Vilensky, J. A., and S. Gilman. 2006. Encephalitis lethargica: could this disease be recognized if the epidemic recurred? *Practical Neurology* 6(6):360-367.

Vincent, A. 2004. Encephalitis lethargica: part of a spectrum of post-streptococcal autoimmune disease? *Brain* 127(1):2-3.

Webster, R. G., and W. G. Laver. 1972. The origin of pandemic influenza. *Bulletin of the World Health Organization* 47(4):449-452.

Weingartl, H. M., R. A. Albrecht, K. M. Larger, S. Babiuk, P. Marszal, J. Neufeld, C. Embury-Hyatt, P. Lekcharoensuk, T. M. Tumpey, A. Garcia-Sastre, and J. A. Richt. 2009. Experimental infection of pigs with the human 1918 pandemic influenza virus. *Journal of Virology* 83(9):4287-4296.

WHO (World Health Organization). 2009. *Situation update avian influenza*, http://www.who.int/csr/disease/avian_influenza/updates/en.index.html (accessed November 17, 2009).

Wong, C. M., K. P. Chan, A. J. Hedley, and J. S. M. Peiris. 2004. Influenza-associated mortality in Hong Kong. *Clinical Infectious Diseases* 39(11):1611-1617.

Wong, C. M., L. Yang, K. P. Chan, G. M. Leung, K. H. Chan, Y. Guan, T. H. Lam, A. J. Hedley, and J. S. M. Peiris. 2006. Influenza-associated hospitalization in a subtropical city. *PLOS Medicine* 3(4):e121.

Zhou, J. Y., W. B. Sun, J. H. Wang, J. Q. Guo, W. Yin, N. P. Wu, L. J. Li, Y. Yan, M. Liao, Y. Huang, K. J. Luo, X. T. Jiang, and H. L. Chen. 2009. Characterization of the H5N1 highly pathogenic avian influenza virus derived from wild pikas in China. *Journal of Virology* 83(17):8957-8964.

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A13

INFLUENZA (H1N1) PANDEMIC 2009

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Ministry of Health, Republic of Argentina

Surveillance of Mortality and Morbidity of Respiratory Disease

The influenza surveillance system in Argentina is composed of Sentinel Units that report influenza-like illness (ILI) by case definition and confirm a representative sample by laboratory; the National Laboratory of respiratory viruses; the disease notification system of influenza type by case definition; and typing and subtyping of influenza strains circulating each year in relation to the vaccine formula, which takes place in the three National Influenza Centers of the World Health Organization (WHO). All systems report to the National Surveillance System and National Health Laboratory Surveillance. As shown in Figure A13-1, surveillance had been in place before the new virus alert was declared.

The first case of 2009-H1N1 influenza A was detected in Puerto Madryn, Argentina in a citizen who had returned from Mexico and developed symptoms on April 25, 2009. Because at that time the primers recommended by the Centers for Disease Control and Prevention (CDC) were not available in Argentina for specific diagnosis, culture isolation and partial sequencing of the virus was done at the Instituto Carlos G. Malbrán. The diagnosis took 10 days with the consequences of the expected spread.

In the first week of May, the director of Epidemiology of Chubut was investigating contacts and their chemoprophylaxis. Argentina's Ministry of Health sent a rapid response team to conduct an intervention and provide chemoprophylaxis for the schoolmates of the index case's daughter, who was also symptomatic. After the investigation, it was serologically determined that the virus was circulating in the area and that the treatment and chemoprophylaxis that were completed managed to stop the circulation.

Starting on May 16th, 2009, the first indigenous cases detected in Argentina, which were associated with a school outbreak, originating from a class trip to the United States (Figure A13-1). As shown in Figure A13-2, the virus spread freely from the index case until May 23rd when an intervention was performed with treatment of cases, chemoprophylaxis of contacts, and school closings on May 25th, all of which helped to contain the outbreak (Figure A13-3).

Figure A13-3 illustrates that in a study of close contacts (green columns) of the students, only a few became ill (blue columns). With this relationship, it was

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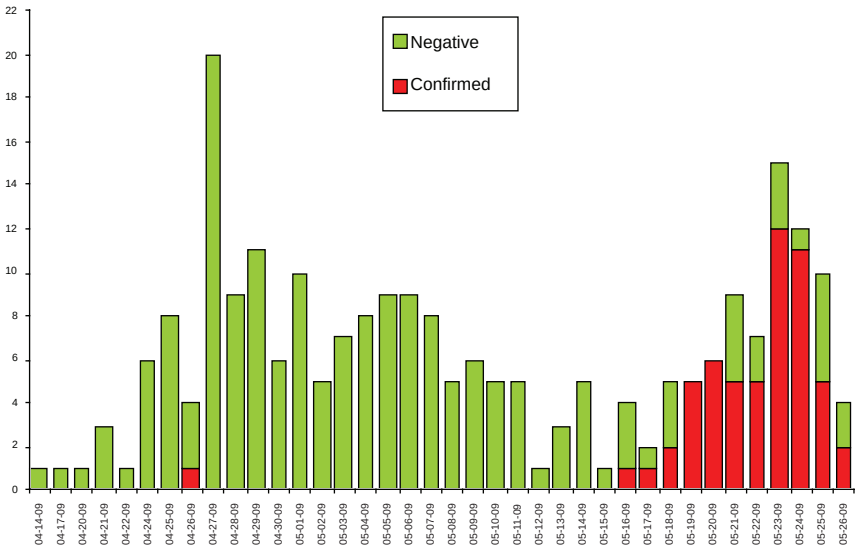

FIGURE A13-1 Cases of 2009-H1N1 influenza A by date of onset of symptoms, April-May 2009, Argentina (n = 250).
SOURCE: Ministry of Health National Surveillance System.

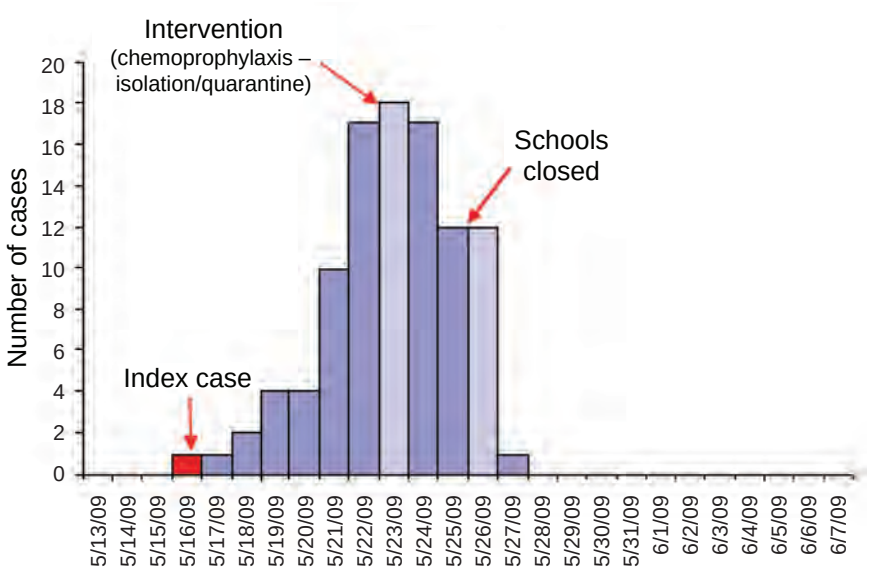

FIGURE A13-2 Distribution of confirmed cases by date of onset of symptoms (n = 99).
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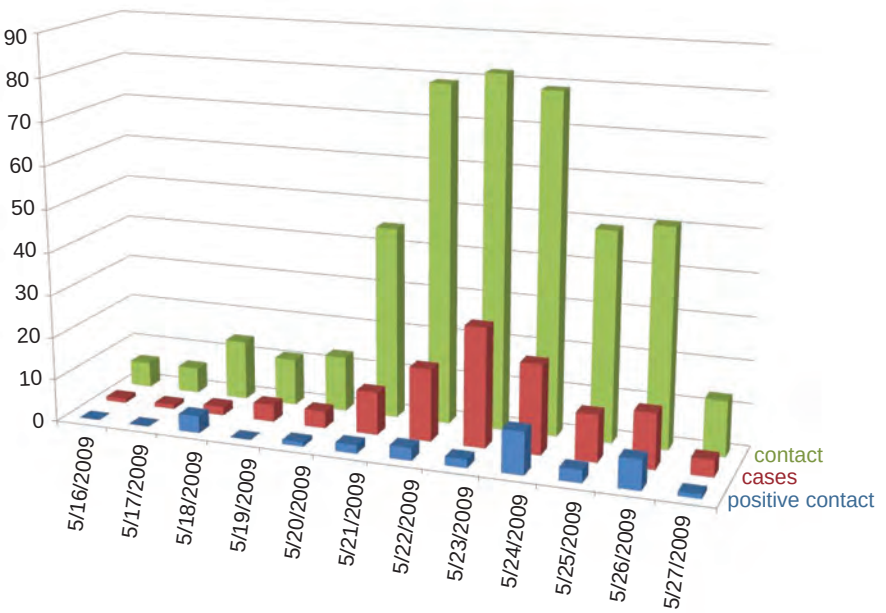

FIGURE A13-3 Temporal presentation of cases and contacts in the school population under study, May 16-31, 2009 (n = 102).
SOURCE: Ministry of Health National Surveillance System.

estimated that the transmission to close contacts at home was 1.1 percent versus 8.7 percent in school. It was also found that the incubation period at school was 48 hours and that dissemination rate was $R_0 = 2.4$.

By that time a large number of schools that had been affected or were highly suspected to be affected were identified, given the high interaction of students in extracurricular programs ranging from academics to sports and social activities (Figure A13-4).

Based on the school data and the estimated population of schools north of Greater Buenos Aires, Ciudad Autónoma de Buenos Aires (CABA), a mathematical model estimated that of 100,000 people, 8,000 cases would appear in 13 days, which would be sufficient for spread through the general population. For this reason, the national health authorities recommended closing schools from June 8th to 19th in the indicated area. Unfortunately, this did not happen because health and education authorities in these jurisdictions did not believe the measure was appropriate.

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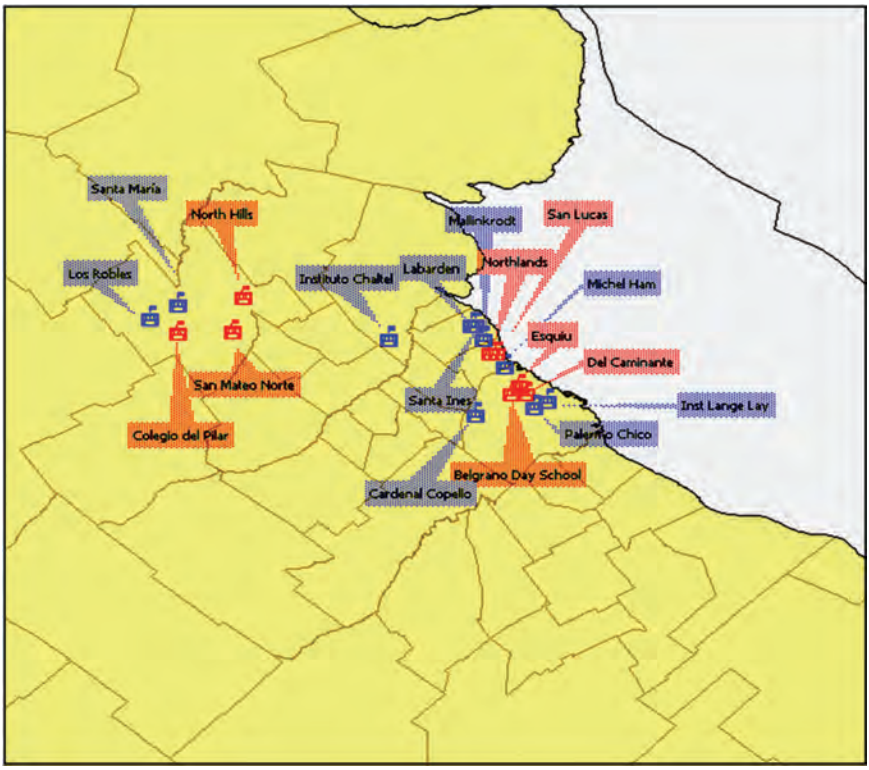

FIGURE A13-4 Affected schools, May 2009 (Red: confirmed case. Blue: clinical case). SOURCE: Ministry of Health National Surveillance System.

Soon, viral spread in the metropolitan area and CABA became sustained, with serious and fatal cases. Between April and July in the Province of Buenos Aires and CABA (Figure A13-5), the majority of cases at the beginning of the outbreak belonged to the group of schoolchildren 5-15 years old. The recommendation to close schools from June 8th to19th may have helped to reduce transmission to other age groups, since it would have limited the transmission among the primary spreaders. This measure could also have avoided the high spread to other parts of Argentina. As shown in Figure A13-6, the outbreak in the interior showed the same start for all age groups, with the majority of cases in the 15-44 years old age cohort (Figure A13-6).

The first fatality occurred on June 15th and, 10 days later, 17 more fatalities were reported in the Province of Buenos Aires and 5 in CABA.

The lack of epidemic containment in CABA and the metropolitan area of theProvince of Buenos Aires led to the spread in major cities within the Province of Buenos Aires as well as several provincial capitals, starting with Santa Fe.

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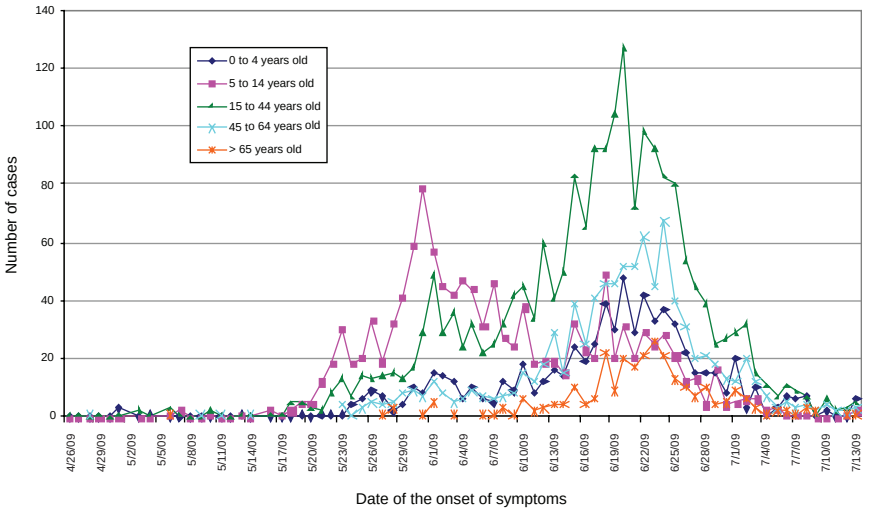

FIGURE A13-5 Distribution of confirmed cases and cases under study by age and date of onset of symptoms, city of Buenos Aires and Province of Buenos Aires, April-July 2009 (n = 5,145).
SOURCE: Ministry of Health National Surveillance System.

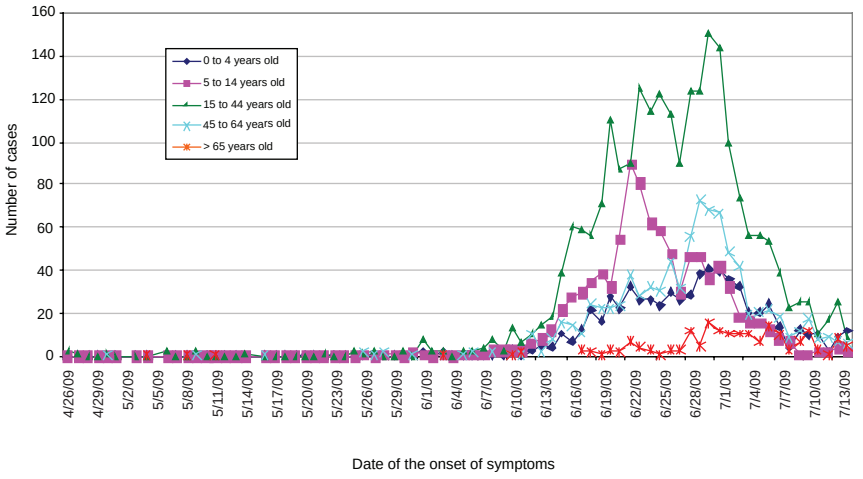

FIGURE A13-6 Distribution of confirmed cases and cases under study by age and date of onset of symptoms, rest of country (except Buenos Aires and Province of Buenos Aires), April-July 2009 (n = 5,030).
SOURCE: Ministry of Health National Surveillance System.

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In the last week of June, the virus had spread throughout most of the country (Figure A13-7).

By July 11, 2009, Argentina had 100 fatalities (mostly in patients 20-40 years old) and 3,000 confirmed cases. It was estimated that 2009-H1N1 influenza A cases would be 100,000 by that date. Most cases occured in children and young adults, with fewer cases in adults over 65 years of age, probably because of prior immunity to H1N1 strains that circulated in the 1950s.

The estimated cases up to week 37 were 1,100,000 and an accumulated rate of 275.2 per 10,000; however, at week 37 the rate was 6.1 per 10,000, and

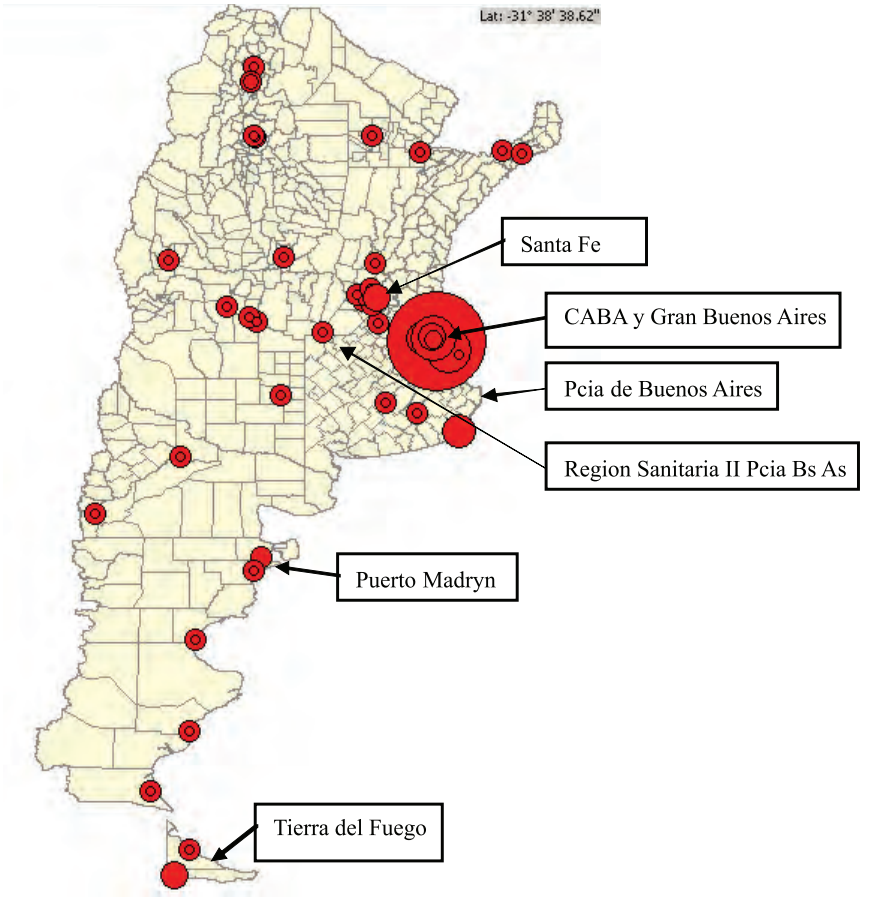

FIGURE A13-7 Distribution of confirmed cases in the country by jurisdiction, Argentina, April-July 2009.
SOURCE: Ministry of Health National Surveillance System.

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the maximum rate at week 27 was 36.6 per 10,000. From the epidemic curve in Figure A13-8, we can observe the different actions taken during the epidemic, the curve of confirmed deaths is superimposed to gauge the effect of the measures. At first, treatment was performed in all cases and prophylaxis in all contacts, as was held in Puerto Madryn in the first case by stopping the chain of transmission. The same was done in the school outbreaks, which is the first peak shown in the curve. Had schools been closed as recommended between June 8th to 19th, the virus probably would not have spread as far and there may have been fewer deaths. An increase in deaths resulted because of the lack of early treatment by shifting to mitigation and only treating cases of severe acute respiratory infection (SARI), as discussed below in the description of the deceased. By recommending treatment for pregnant women, risk groups, and those who are ill, the number of deaths seems to have declined. In addition, school closures and vacations in some jurisdictions appears to have diminished number of cases and deaths.

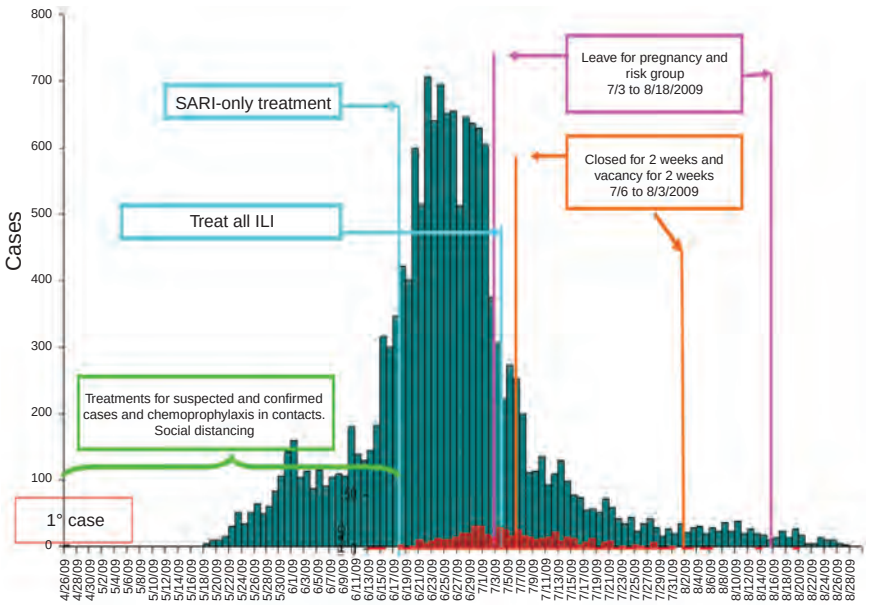

FIGURE A13-8 Confirmed and under study cases of influenza and pandemic influenza (H1N1) 2009 by date of onset of symptoms (n = 15,455), Argentina, April-September 2009.
SOURCE: Ministry of Health National Surveillance System.

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Virological Surveillance

The virological diagnosis performed well with the surveillance methods more specific to the 2009-H1N1 influenza A virus. It should be noted that diagnosis was first performed at the Institute Malbran, after which another 18 laboratories were enabled to perform real-time (RT)-PCR, three of which are the National Influenza Center of the WHO, which also performed culture and serology for this virus. The percentage of positivity for the new virus was 43.3 percent (8,851/20,409). In the weekly distribution, the circulation of respiratory syncytial virus (RSV) is seen during the whole period but the peak of diagnosis occurred in weeks 25 and 26 for the new virus (Figure A13-9).

Figure A13-10 illustrates that RSV is dominant for children up to age one; however, the 2009-H1N1 influenza A virus was dominant for all other age groups.

Analysis of Severe Acute Respiratory Infections and Death

The age distribution of cases of SARI showed that the largest group affected were the 0- to 4-year-olds, but we must consider that some of these correspond to cases of RSV observed in the laboratory diagnosis. The hospitalization rate was 23.4 per 100,000 inhabitants (Figure A13-11).

The time distribution for hospitalized patients shows a peak in late June, about a week after the peak of the ILI epidemic curve, and the beginning of severe cases shifted by 15 days for ILI during the period in which cases were given treatment and prophylaxis was given to their contacts. As of early July, the intensity

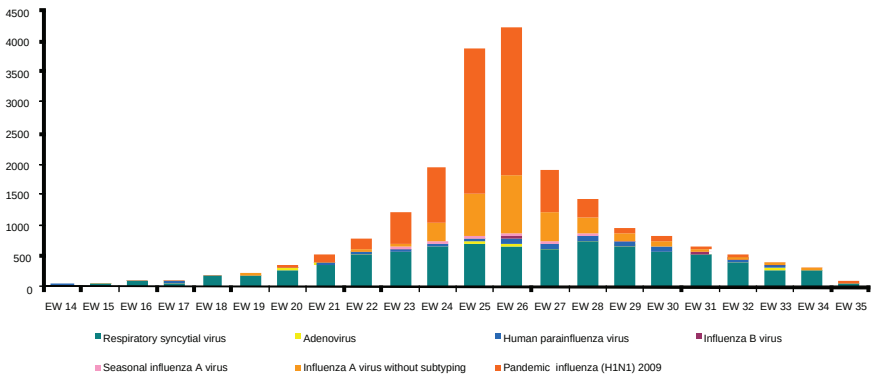

FIGURE A13-9 Distribution of respiratory viruses by epidemiological week, Argentina 2009.
SOURCE: Ministry of Health National Surveillance System.

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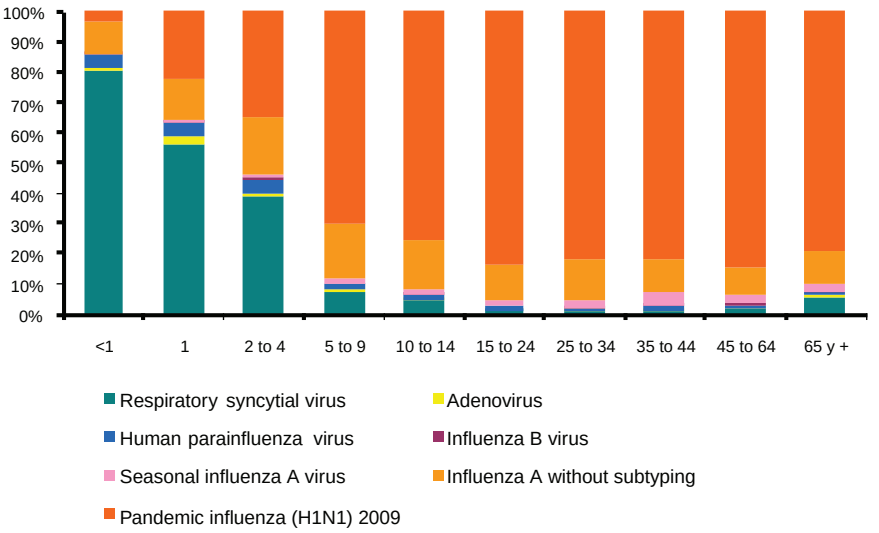

FIGURE A13-10 Distribution of respiratory viruses by age group, Argentina 2009.
SOURCE: Ministry of Health National Surveillance System.

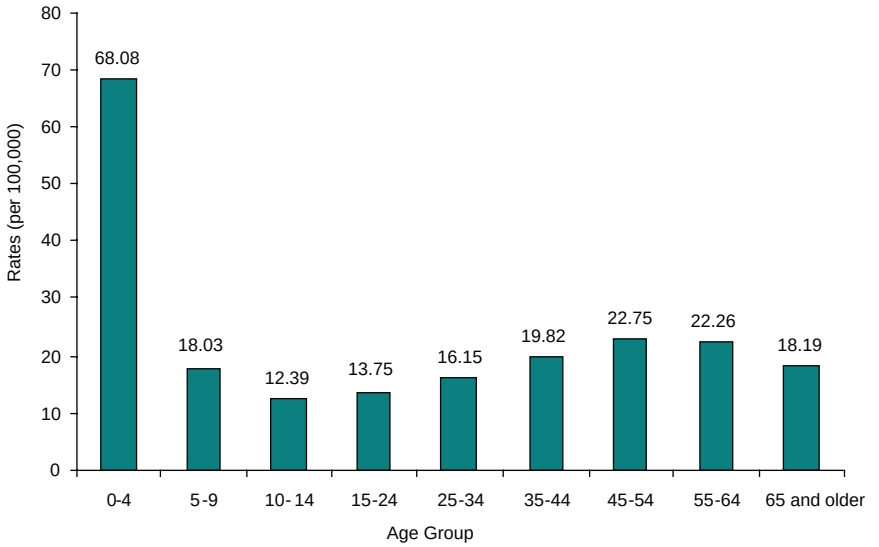

FIGURE A13-11 Distribution of SARI by age group, rates per hundred thousand inhabitants, Argentina 2009 (n = 8,872).
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began to decrease, often coinciding with the new implementation of treatment to all cases of ILI (Figure A13-12).

At week 37 there were 538 confirmed deaths. The age distribution shows that most cases occurred in 40- to 59-year-old adults, but with importance given to the 0- to 9-year-olds for the years of life prematurely lost. However, it is emphasized that only the 20- to 39-year-old group shows female predominance due to the deaths of pregnant women (Figure A13-13). In the distribution of cases and deaths of pregnant women, it is observed that the number of deaths increased when treatment is only for disease mitigation; however, if treatment is implemented for all ILI cases, the number of deaths decreased (Figure A13-14).

Enhanced surveillance was implemented for cases and mortality from infection of the 2009-H1N1 influenza A virus in pregnant women through epidemiological clinical records. A "confirmed case" was defined as a case of acute respiratory illness or positive viral culture via real-time RT-PCR. From May 16, 2009, to July 31, 2009, 15 provinces reported 300 cases of 2009-H1N1 influenza A in pregnant women, 121 of which were confirmed and 85 (70.2 percent) of which were admitted to the hospital.

The incidence rate for 2009-H1N1 influenza A in pregnant women in the study period was 1.72 per 10,000, 1.28 per 10,000 versus the general population at risk (p 0.003). Pregnant women were twice as likely to be hospitalized

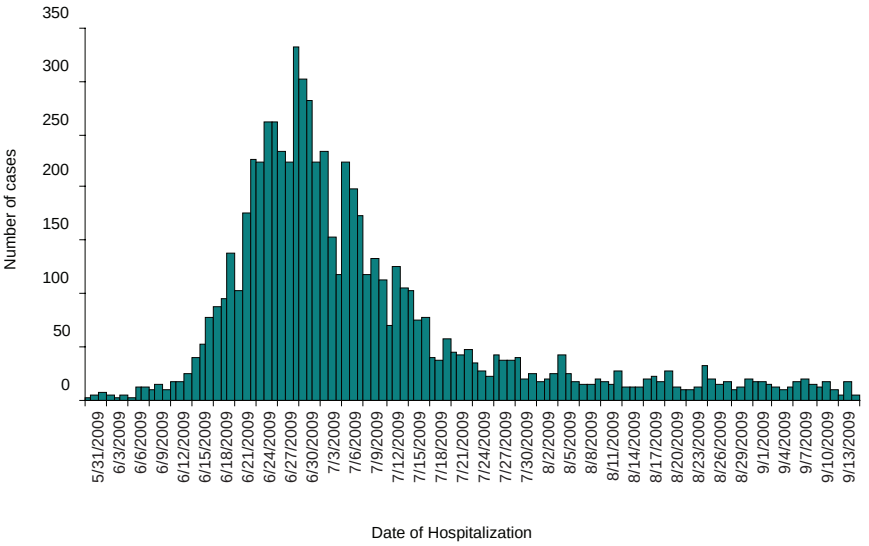

FIGURE A13-12 Distribution of SARI by epidemiological week of onset of symptoms, Argentina 2009 (n = 10,397 EW37).
SOURCE: Ministry of Health National Surveillance System.

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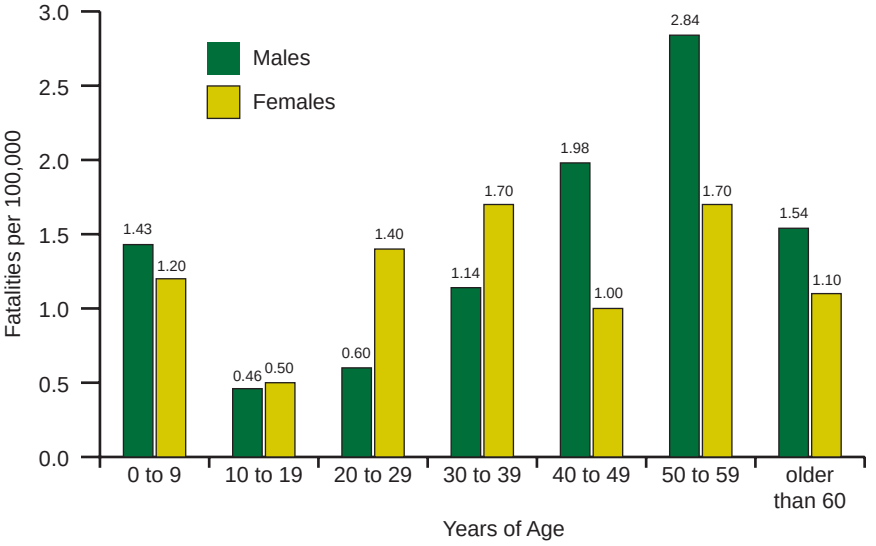

FIGURE A13-13 Distribution of confirmed fatalities by age group and sex, rates per hundred thousand inhabitants, Argentina 2009 (n = 505).
SOURCE: Ministry of Health National Surveillance System.

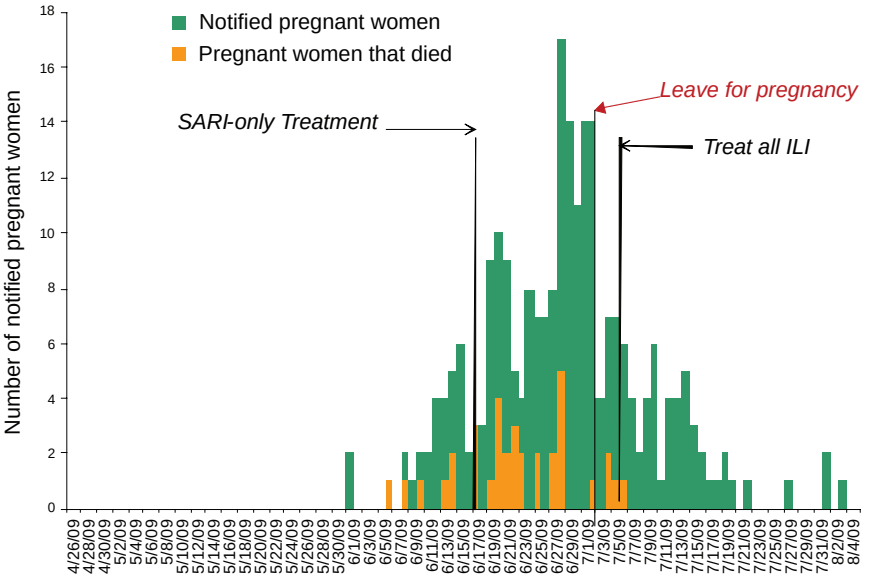

FIGURE A13-14 Number of H1N1 cases among pregnant women, 2009 by day according to date of symptom onset, Argentina 2009 (n = 243).
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than the general population (RR = 1.70, 95 percent CI 1.51-192 p 0.0000). Of the 85 pregnant women hospitalized, 30 deaths were confirmed cases of 2009-H1N1 influenza A, of which 19 developed pneumonia and acute respiratory distress, and 9 required mechanical ventilation in the intensive care unit. The rest of the fatalities were studied by examining medical records following the instrument suggested by WHO and with modifications by PAHO consultants used in Chile. It was applied to 246 deaths in various localities. The underlying conditions predominated in all age groups, ranging from 62 to 93 percent (Figure A13-15).

Figure A13-16 shows the time elapsed between the onset of disease and death, which stands between the date of onset of symptoms and the start of antiviral treatment, which was 6.1 days on average; despite query, the health system treatment implementation was delayed 3.5 days (Figures A13-16 and A13-17). Only 23 percent of deaths showed no underlying conditions. For the age groups and underlying conditions presented, it is shown that the group under 15 years of age predominated neonatal pathology, oncology, immune deficiency, neurological, and congenital conditions. In the 15- to 44-year-old group, obesity, oncology, immune deficiency, and pregnancy predominated. In the 45-year old and over group, metabolic, immune deficiency, and oncology were the most frequent underlying conditions (Table A13-1).

In order to determine the secondary attack rate, a telephone survey was performed, collecting information from1 in 10 confirmed cases (subjects who

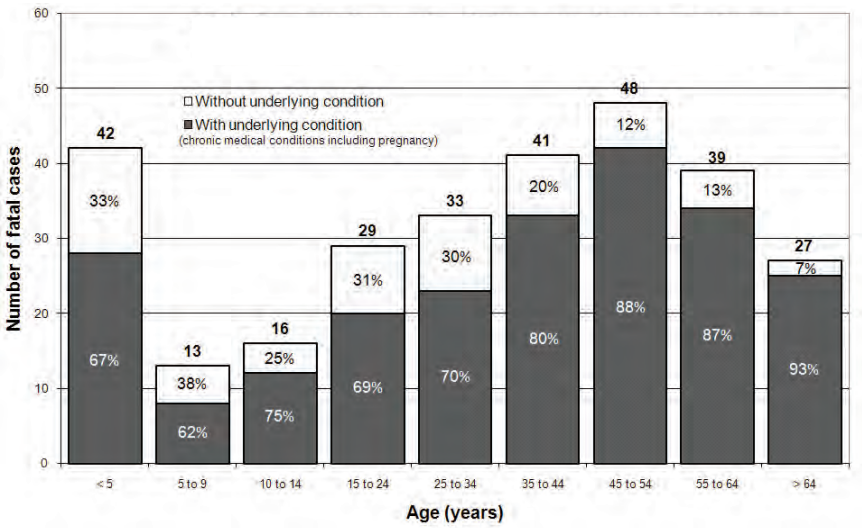

FIGURE A13-15 Fatal cases by underlying conditions and age.
SOURCE: Ministry of Health National Surveillance System.

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Indicator	Average	n	Min	Max
Time from Infection to 1st Consultation	2.4	132	0	9
Time from Infection to Hospitalization	4.7	132	0	14
Hospitalization to ICU	2.7	73	0	7
ICU Permanence	7.0	81	0	26
Mechanical Ventilation Permanence	6.8	98	0	26
Time from Infection to Death	12.2	130	1	30
1st Consultation to Hospitalization	2.3	132	0	12
Hospitalization to Death	7.7	131	0	26
Time from Infection to Start of Antivirals	6.1	102	0	17
1st Consultation to Antivirals	3.5	102	0	15
Hospitalization to Antivirals	1.2	102	–3	11

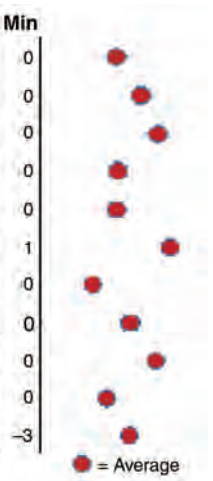

FIGURE A13-16 Time between events.
SOURCE: Ministry of Health National Surveillance System.

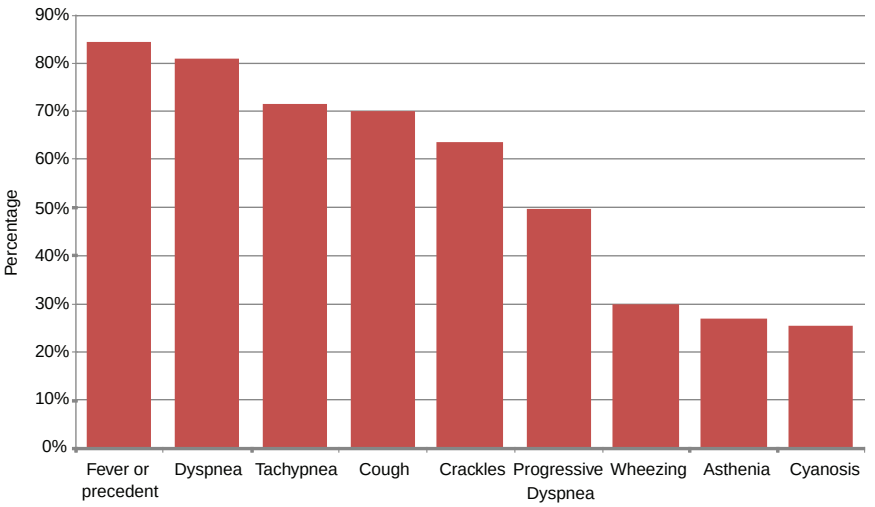

FIGURE A13-17 Signs and symptoms identified in medical records.
SOURCE: Ministry of Health National Surveillance System.

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TABLE A13-1 Underlying Conditions Present by Age Group

Underlying Condition	<15 years n = 62	15-44 years n = 85	>45 n = 88
Drug addiction	0	8	16
Cardiovascular	6	5	19
Diabetes	0	6	19
Pregnancy	0	12	0
Hematologic	8	9	9
Hepatic	1	4	2
Arterial hypertension	2	7	45
Congenital malformation	10	0	0
Neurological	12	2	5
Obesity	3	21	31
Oncology and immunodeficiencies	16	17	24
Neonatal pathology	22	0	0
Kidney	5	6	18
Respiratory	8	8	35
Genetic syndromes	12	2	1
HIV	0	8	1

SOURCE: Ministry of Health National Surveillance System.

had access to a telephone), giving 81 cases for the survey. We collected information from 270 of these contacts and found that 32 had symptoms, giving a high rate of 14 percent (32 of 232). We also found that in these households there were 37 clinical cases taken prior to the survey and the prevalence of disease in these households was confirmed at 43 percent (150 of 351). This sampling was conducted when chemoprophylaxis was given partially; the effectiveness of it was determined. Symptoms were found in 17 out of 71 persons with no chemoprophylaxis and in 8 out of 93 that had received chemoprophylaxis. Therefore, the risk of illness is higher in those who did not have chemoprophylaxis (RR = 2.78, 95 percent CI 1.2-6.8; p = 0.006). During the epidemic there were jurisdictions for which the supply of drugs was low for the period when chemoprophylaxis and treatment were performed for severe cases or for all ILI treatment, as in the Health Region II of the Province Buenos Aires. Also, in other jurisdictions, like the Province of Tierra del Fuego, there was not a mitigation step introducing a transition phase in which treatment of all cases continued, but chemoprophylaxis was not given. This strategy showed a considerable difference in the rate of hospitalization and in mortality, as seen in the pyramids of each region (Figures A13-18 and A13-19).

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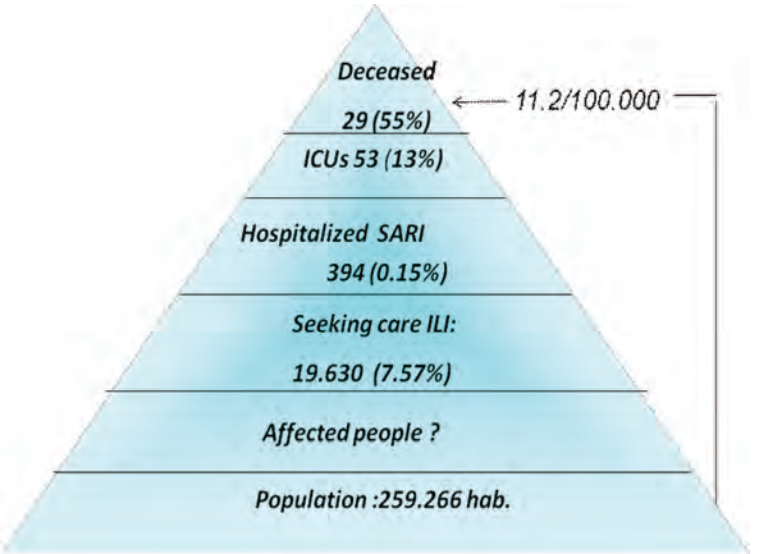

FIGURE A13-18 Descriptive analysis of epidemiological data 2009-H1N1 influenza A pandemic, Health Region II, Province of Buenos Aires, Argentina, May 21 through August 30, 2009 (minimum interventions).
SOURCE: Ministry of Health National Surveillance System.

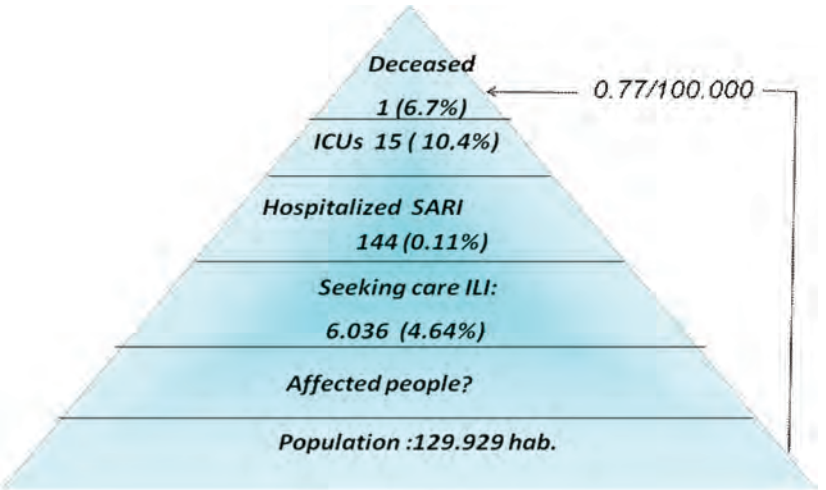

FIGURE A13-19 Descriptive analysis of epidemiological data 2009-H1N1 influenza A pandemic, Tierra del Fuego, Argentina, May 21 through August 30, 2009 (intensive health care and treatment of ILI).
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A14

ORIGINS AND EVOLUTIONARY GENOMICS OF THE 2009 SWINE-ORIGIN H1N1 INFLUENZA A EPIDEMIC[81]

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In March and early April 2009, a new swine-origin influenza A (H1N1) virus (S-OIV) emerged in Mexico and the United States (CDC, 2009a). During the first few weeks of surveillance, the virus spread worldwide to 30 countries (as of May 11) by human-to-human transmission, causing the World Health Organization to raise its pandemic alert to level 5 of 6. This virus has the potential to develop into the first influenza pandemic of the twenty-first century. Here we use evolutionary analysis to estimate the timescale of the origins and the early development of the S-OIV epidemic. We show that it was derived from several viruses circulating in swine, and that the initial transmission to humans occurred several months before recognition of the outbreak. A phylogenetic estimate of the gaps in genetic surveillance indicates a long period of unsampled ancestry before the S-OIV outbreak, suggesting that the reassortment of swine lineages may have occurred years before emergence in humans, and that the multiple genetic ancestry of S-OIV is not indicative of an artificial origin. Furthermore, the unsampled history of the epidemic means that the nature and location of the genetically closest swine viruses reveal little about the immediate origin of the epidemic, despite the fact that we included a panel of closely related and previously unpublished swine influenza isolates. Our results highlight the need for systematic surveillance of influenza in swine, and provide evidence that the mixing of new genetic elements in swine can result in the emergence of viruses with pandemic potential in humans (CDC, 2009a).

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Initial genetic characterization of the S-OIV outbreak by the United States Centers for Disease Control suggested swine as its probable source, on the basis of sequence similarity to previously reported swine influenza isolates (CDC, 2009a). Classical swine H1N1 viruses have circulated in pigs in North America and other regions for at least 80 years (CDC, 2009a**)**. In 1998, a new triple-reassortant H3N2 virus—comprising genes from classical swine H1N1, North American avian, and human H3N2 (A/Sydney/5/97-like) influenza—was reported as the cause of outbreaks in North American swine, with subsequent establishment in pig populations (CDC, 2009a; Shortridge et al., 1977). Co-circulation and mixing of the triple-reassortant H3N2 with established swine lineages subsequently generated further H1N1 and H1N2 reassortant swine viruses (CDC, 2009a; Shortridge et al., 1977; Shope and Lewis, 1931) which have caused sporadic human infections in the United States since 2005 (Newman et al., 2008; Shinde et al., in press). Consequently, human infection with H1N1 swine influenza has been a nationally notifiable disease in the United States since 2007 (CDC, 2009a,b). In Europe, an avian H1N1 virus was introduced to pigs ('avian-like' swine H1N1) and first detected in Belgium in 1979 (Pensaert et al., 1981; CDC, 2009a). This lineage became established and gradually replaced classical swine H1N1 viruses, and also reassorted in pigs with human H3N2 viruses (A/PortChalmers/1/1973-like) (CDC, 2009a). It is noteworthy that, until now, there has been no evidence of Eurasian avian-like swine H1N1 circulating in North American pigs. In Asia, the classical swine influenza lineage circulates, in addition to other identified viruses, including human H3N2, Eurasian avian-like H1N1, and North American triple-reassortant H3N2 (Peiris et al., 2001; Jung and Song, 2007; CDC, 2009a; Shortridge, 1977).

Using comprehensive phylogenetic analyses, we have estimated a temporal reconstruction of the complex reassortment history of the S-OIV outbreak, summarized in Fig. A14-1 (Methods). Our analyses showed that each segment of the S-OIV genome was nested within a well-established swine influenza lineage (that is, a lineage circulating primarily in swine for >10 years before the current outbreak). The most parsimonious interpretation of these results is therefore that the progenitor of the S-OIV epidemic originated in pigs. Some transmission of swine influenza has, however, been observed in secondary hosts in North America, for example, in turkeys (CDC, 2009a). Although the precise evolutionary pathway of the genesis of S-OIV is greatly hindered by the lack of surveillance data (see later), we can conclude that the polymerase genes, plus HA, NP and NS, emerged from a triple-reassortant virus circulating in North American swine. The source triple-reassortant itself comprised genes derived from avian (PB2 and PA), human H3N2 (PB1) and classical swine (HA, NP and NS) lineages. In contrast, the NA and M gene segments have their origin in the Eurasian avian-like swine H1N1 lineage. Phylogenetic analyses from the early days of the outbreak, on the basis of the first publicly available sequences, quickly established this multiple genetic origin (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, in

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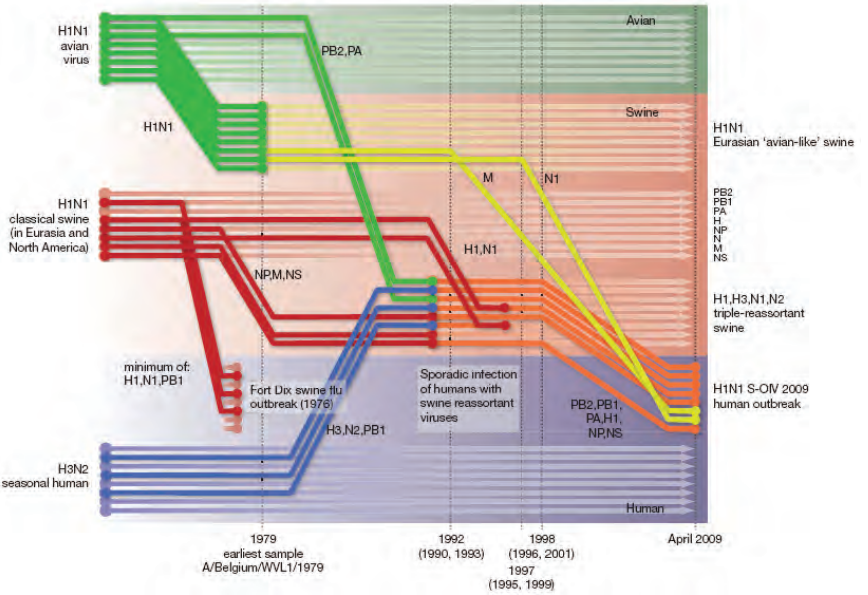

FIGURE A14-1 Reconstruction of the sequence of reassortment events leading up to the emergence of S-OIV. Shaded boxes represent host species; avian (green), swine (red) and human (grey). Coloured lines represent interspecies-transmission pathways of influenza genes. The eight genomic segments are represented as parallel lines in descending order of size. Dates marked with dashed vertical lines on 'elbows' indicate the mean time of divergence of the S-OIV genes from corresponding virus lineages. Reassortment events not involved with the emergence of human disease are omitted. Fort Dix refers to the last major outbreak of S-OIV in humans. The first triple-reassortant swine viruses were detected in 1998, but to improve clarity the origin of this lineage is placed earlier.

press; Trifonov et al., 2009; Garten et al., in press and http://influenza.bio.ed.ac.uk; CDC, 2009a; Shortridge et al., 1977).

Given that S-OIV contains genes of Eurasian origin, we included in our phylogenetic analyses 15 newly sequenced swine influenza viruses from Hong Kong, sampled in the course of a surveillance program conducted since the early 1990s. The viruses were a mixture of seven H1N1 and eight H1N2 subtypes, and viruses belonging to the classical, Eurasian avian-like, and triple-reassortant swine lineages were all present. Both Eurasian and triple-reassortant strains were isolated in Hong Kong in 2009. Extensive reassortment among these three virus lineages was also observed from the Hong Kong surveillance data (Supplementary Table A14-3), with reassortment between Eurasian avian-like and triple-reassortant swine lineages occurring as early as 2003 (for example, Sw/HK/78/2003).

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Notably, for the PB1,HA and M genes, some of these newly generated sequences are more similar to the S-OIV epidemic than any previously reported isolates (Supplementary Fig. A14-3). Notably, seven out of eight genomic segments found in a single 2004 isolate (Sw/HK/915/04 (H1N2)) were located in a sister lineage to the current outbreak. Not only does this suggest that the precursors of S-OIV were swine viruses, but also that they were geographically widely distributed. Crucially, however, the observation of a sister relationship between the current outbreak virus and Sw/HK/915/04 cannot be interpreted as evidence for a Eurasian origin of the outbreak, owing to the long branch of the phylogeny leading to the 2009 human strains (Fig. A14-2 and Table A14-1). This

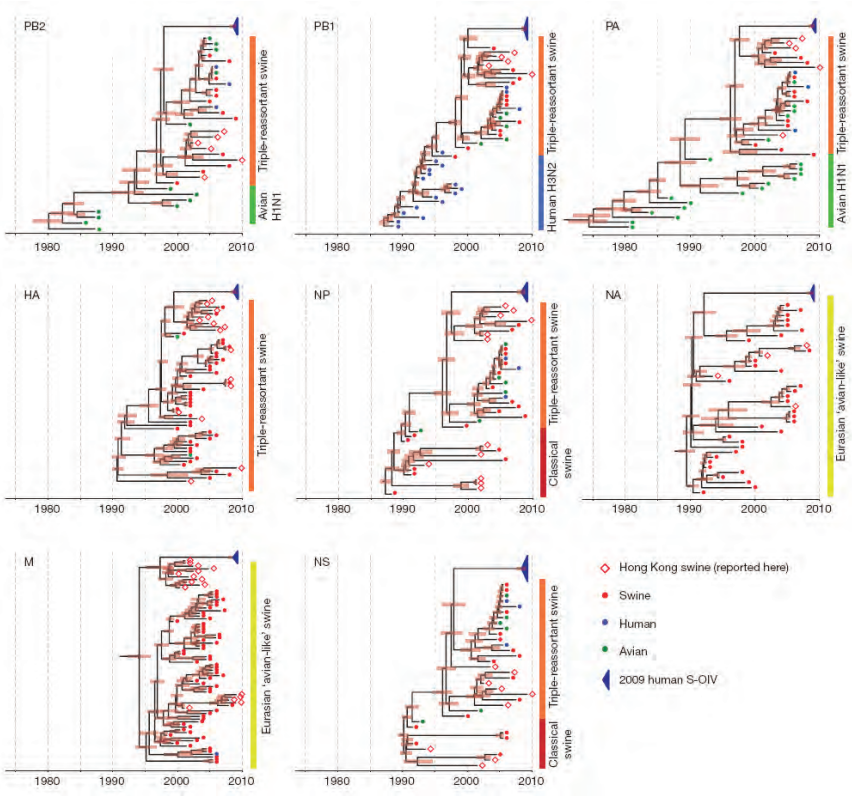

FIGURE A14-2 Genetic relationships and timing of S-OIV for each genomic segment. Symbols represent sampled viruses on a timescale of when they were sampled and coloured by host species (pigs, red; humans, blue; birds, green). Internal nodes are reconstructed common ancestors with 95% credible intervals on their date given by the red bars. The S-OIV outbreak strains are represented by a blue triangle, with the apex representing the common ancestor of these.

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TABLE A14-1 Time of Most Recent Common Ancestors for the S-OIV Outbreak

Gene	TMRCA of outbreak samples	Duration of unsampled diversity (years)	Mean evolutionary rate $\times 10^{-3}$ (subst. per site per year)
HA	28 Aug 2008 (1 Apr 2008, 2 Jan 2009)	9.80 (8.41, 11.02)	3.67 (3.41, 3.92)
MP	3 Aug 2008 (8 Dec 207, 5 Feb 2009)	11.82 (10.17, 13.74)	2.55 (2.19, 2.93)
NA	8 Aug 2008 (23 Feb 2008, 26 Dec 2008)	17.15 (15.40, 18.88)	3.65 (3.22, 4.12)
NP	27 Mar 2008 (15 Sep 2007, 19 Sep 2008)	11.83 (10.53, 13.23)	2.59 (2.34, 2.84)
NS	21 May 2008 (30 Sep 2007, 27 Nov 2008)	11.47 (9.75, 13.21)	2.62 (2.32, 2.92)
PA	7 Oct 2008 (1 Jun 2008, 1 Feb 2009)	11.70 (10.25, 13.10)	2.45 (2.20, 2.69)
PB1	24 Oct 2008 (8 Jul 2008, 27 Jan 2009)	9.24 (7.59, 10.48)	2.34 (2.13, 2.53)
PB2	9 Sep 2008 (12 Apr 2008, 9 Jan 2009)	11.26 (9.93, 12.69)	2.60 (2.29, 2.92)
Genome*	21 Jan 2009 (3 Aug 2008, 13 Mar 2009)	N/A	3.66 (0.61, 6.58)

The values in parentheses represent the 95% credible intervals

*This data set comprises complete or partial genomes of swine-origin influenza A (H1N1) virus outbreak isolates sampled predominantly in the United States between March and May 2009.

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branch must represent either an increased rate of evolution leading to the outbreak, or a long period during which the ancestors of the current epidemic went unsampled. To test these hypotheses, we regressed genetic divergence against sampling date for each gene, and found in favour of the latter: the evolutionary rate preceding the S-OIV epidemic is entirely typical for swine influenza (Supplementary Figs A14-4 and A14-5).

Therefore, to quantify the period of unsampled diversity, and to estimate the date of origin for the S-OIV outbreak, we performed a Bayesian molecular clock analysis for each gene (Methods). We also estimated the rate of evolution and time of the most recent common ancestor (TMRCA) of a set of genome sequences sampled from the S-OIV epidemic (between March and May 2009; isolates listed in Supplementary Table A14-5). We found that the common ancestor of the S-OIV outbreak and the closest related swine viruses existed between 9.2 and 17.2 years ago, depending on the genomic segment, hence the ancestors of the epidemic have been circulating undetected for about a decade. In contrast, the currently sampled S-OIV shared a common ancestor around January 2009 (no earlier than August 2008; Table A14-1). The long, unsampled history observed for every segment suggests that the reassortment of Eurasian and North American swine lineages may not have occurred recently, and it is possible that this single reassortant lineage has been cryptically circulating rather than two distinct lineages of swine flu. Thus, this genomic structure may have been circulating in pigs for several years before emergence in humans, and we urge caution in making inferences about human adaptation on the basis of the ancestry of the individual genes.

A search for amino acid residues in the S-OIV outbreak sequences that have been previously identified as phenotypic markers showed no evidence of virulence-associated variation or adaptations to human hosts (CDC, 2009a; Shortridge et al., 1977; Shope and Lewis, 1931), consistent with the outbreak being of swine origin and causing relatively mild symptoms. Full molecular characterization of the human swine H1N1 viruses is provided in Supplementary Information.

We did detect a difference in the viral molecular evolution in the outbreak clade when compared to that observed in related swine influenza sequences: all S-OIV genes showed a comparatively higher non-synonymous to synonymous (d_N/d_S) substitution rate ratio (Supplementary Tables A14-2 and A14-3). This d_N/d_S ratio rise could be due to the increased detection of mildly deleterious mutations resulting from intensive epidemic surveillance; such mutations would more typically be eliminated and escape detection (CDC, 2009a). Alternatively, these mutations could be adaptations to the new host species.

Because this d_N/d_S ratio rise may affect our estimate of the TMRCA of the S-OIV outbreak strains (which was estimated using long-term rates of swine influenza evolution), we compared the mean d_N/d_S values of outbreak versus non-outbreak data sets, thereby approximating the degree of excess of non-synonymous

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mutations in the outbreak sequences (Methods). Once the d_N/d_S ratio rise is corrected for, the mean TMRCA of the S-OIV outbreak became 1 to 5 months more recent for each gene (Supplementary Tables A14-2 and A14-3). Furthermore, the adjusted TMRCA estimates are more uniform across genes, and are more similar to that obtained using internally calibrated S-OIV complete genomes (Table A14-1; a comparable estimate for the TMRCA of the HA gene only was recently reported [CDC, 2009a]). Irrespective of whether the d_N/d_S ratio rise is due to increased detection of deleterious mutations or to increased adaptive evolution, its presence may be a general feature of intensively sampled emerging epidemics, and should be accounted for in the evolutionary analysis of such events.

Movement of live pigs between Eurasia and North America seems to have facilitated the mixing of diverse swine influenza viruses, leading to the multiple reassortment events associated with the genesis of the S-OIV strain. Domestic pigs have been described as a hypothetical 'mixing-vessel', mediating by reassortment the emergence of new influenza viruses with avian or avian-like genes into the human population, and triggering a pandemic associated with antigenic shift (Shortridge et al., 1977). Previous research has suggested that occupational exposure to pigs increases the risk of swine influenza virus infection, and that swine workers should be considered in any surveillance programs (Shortridge et al., 1977).

The emergence of S-OIV provides further evidence of the role of domestic pigs in the ecosystem of influenza A. As reported recently, all three pandemics of the twentieth century seem to have been generated by a series of multiple reassortment events in swine or humans, and to have emerged over a period of years before pandemic recognition (Shortridge et al., 1977). Our results show that the genesis of the S-OIV epidemic followed a similar evolutionary pathway: H1N1 viruses with human pandemic potential had been identified, transmission from swine to humans was known (Webby et al., 2000) and the disease had been made notifiable. Yet despite widespread influenza surveillance in humans, the lack of systematic swine surveillance allowed for the undetected persistence and evolution of this potentially pandemic strain for many years.

Methods Summary

We compared 15 newly sequenced Hong Kong swine influenza genomes and two genomes from the S-OIV outbreak with 796 genomes representing the spectrum of influenza A diversity (comprising 285 human, 100 swine and 411 avian isolates). Phylogenetic trees were constructed for each genomic segment independently (Supplementary Fig. A14-3). Next, for each genomic segment, viruses with known isolation dates that were genetically similar to the current outbreak were identified, and more detailed analysis using a Bayesian 'relaxed molecular clock' approach was performed (Drummond and Rambaut, 2007), thereby estimating rates of viral evolution and dates of divergence (Fig. A14-3). Finally, a similar

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Bayesian molecular clock approach was applied to the 30 individual viruses isolated from the human outbreak since the end of March 2009 (Supplementary Table A14-5 and Supplementary Fig. A14-4). This analysis was performed assuming a model of exponential growth in the number of infections.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Author Contributions

J. B., S. J. L., O. G. P., A. R., G. J. D. S., D. V. and M. W. conceived the study, performed analyses, co-wrote the paper, and all contributed equally to this work. J. S. M. P. co-wrote the paper, Y. G. conceived the study and co-wrote the paper, S. B. and J. R. performed analyses, S. K. M. conducted surveillance, and C. L. C. conducted sequencing. All authors commented on and edited the paper.

Author Information

Newly reported sequences have been deposited at GenBank under accession numbers GQ229259–GQ229378. Reprints and permissions information is available at www.nature.com/reprints. This paper is distributed under the terms of the Creative Commons Attribution-Non-Commercial-Share Alike licence, and is freely available to all readers at www.nature.com/nature. Correspondence and requests for materials should be addressed to A. R. (a.rambaut@ed.ac.uk) or Y. G. (yguan@hku.hk).

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Methods

Sequence Selection for Phylogenetic Analysis

We downloaded 3,986 complete influenza genomes of any subtype and sampling year (2,490 human, 185 swine and 1,311 avian) from the NCBI Influenza Virus Resource (Bao et al., 2008) on 29 April 2009. Each sequence set was given a unique ID of the form (ID number)_(Subtype)_(Host)_(isolate name), in which the isolate name is in lower case.

To reduce the number of very similar sequences, we listed all isolates in which the coding region in segment 1 (PB2) was at least one nucleotide different from the others. This left 1,759 human, 166 swine and 1,117 avian complete genome sets. Next we sampled the human, swine and avian sets, selecting one genome set per specific host (as defined in the isolate name, for example, chicken, duck), per specific location (for example, state or province), per year (although isolate name synonyms, for example, duck = dk, hongkong = hk were not accounted for). Two avian and four swine sequence sets were removed owing to bad sequences in one or more segments (for example, frameshifts), leaving 286 human (including S-OIVs), 100 swine and 411 avian sequences in the sampled subset. A further outbreak sequence set (A/Canada-ON/RV1527/2009), and the 15 new swine sequence sets were also added, making a total of 813 complete genome sets for analysis. For the more detailed, temporal analyses, all available S-OIV sequences were used.

The nucleotides in the coding regions of segments 1 (PB2), 2 (PB1), 3 (PA) and 5 (NP) were aligned using ClustalW (Thompson et al., 1994) followed by manual alignment to codon position. The full nucleotide sequences of segments 7 (M1 and M2) and 8 (NS1 and NS2) were also aligned using ClustalW, and the sequences were edited such that all of the codons in first open reading frame (ORF) were followed by the remaining codons in the second ORF (that is, nucleotides were not repeated between the two ORFs). The HA and NA genes (segments 4 and 6) were aligned to codon positions using Muscle (Edgar, 2004). Further H1, H3, N1 and N2 only alignments were also performed.

New Swine Influenza Sequences from Hong Kong

To evaluate the evolutionary history of swine/human influenza A H1N1 viruses, 15 viruses isolated from swine in Hong Kong during 1993 to 2009 were sequenced. Viral RNA was directly extracted from infected allantoic fluid or cell culture using QIAamp viral RNA minikit (Qiagen, Inc.). Complementary DNA was synthesized by reverse transcription reaction, and gene amplification by PCR was performed using specific primers for each gene segment. PCR products were purified with the QIAquick PCR purification kit (Qiagen Inc.) and sequenced by synthetic oligonucleotides. Reactions were performed using Big Dye-Terminator

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v3.1 Cycle Sequencing Reaction Kit on an ABI PRISM 3730 DNA Analyser (Applied Biosystems) following the manufacturer's instructions. All sequences were assembled and edited with Lasergene version 8.0 (DNASTAR). Full genome sequences of these viruses are available for download at GenBank under accession numbers GQ229259–GQ229378.

Molecular Evolution and Adaptation

We used the programs SLAC (Single-Likelihood Ancestor Counting) (Kosakovsky Pond and Frost, 2005) and SNAP (Synonymous Non-synonymous Analysis Program) (Korber, 2000) to compare the mean ratio of non-synonymous changes per non-synonymous site to synonymous changes per synonymous site (d_N/d_S) of outbreak versus non-outbreak sequences. SLAC calculates inferred ancestral sequences for each internal node in a phylogeny using a codon model (and disallowing stop codons), and then counts the synonymous and non-synonymous mutations by comparing each codon to its immediate ancestor. SNAP counts the possible synonymous and non-synonymous codon changes across all pairs of sequences.

In brief, we calculated the effect of the excess of non-synonymous changes in the outbreak data as follows. Assume that S is the number of synonymous sites in a data set, N is the number of non-synonymous sites (typically ~3.5S for these data), and ω is the d_N/d_S ratio. If the proportional contribution to the overall rate from synonymous sites is s, then the proportional contribution to the overall rate from non-synonymous sites is equal to $(N/S)(\omega)s$. N, S and ω are all readily estimated from the data. Assuming the same rate of synonymous substitution in both the outbreak and reference data sets, the relative rate expected in the outbreak sequences compared to the reference sequences is thus equal to

$$(s+(N/S)(\omega_{\text{outbreak}})s)=(s+(N/S)(\omega_{\text{reference}})s)$$

Phylogenetic Analyses

Phylogenetic trees were inferred using the neighbour joining distance method, with genetic distances calculated by maximum likelihood under the Hasegawa–Kishino–Yano (HKY) model with gamma-distributed rates among sites (HKY+Γ). Parameters of this model were estimated using maximum likelihood on an initial tree. Temporal phylogenies and rates of evolution were inferred using a relaxed molecular clock model that allows rates to vary among lineages within a Bayesian Markov chain Monte Carlo (MCMC) framework (Drummond and Rambaut, 2007).This was used to sample phylogenies and the dates of divergences between viruses from their joint posterior distribution, in which the sequences are constrained by their known date of sampling. A model comprising a codon-position specific HKY+ Γ substitution model was used. The

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limited sampling timespan of the S-OIV samples required a simpler model to avoid over-parameterization, so a single HKY+Γ model over all sites was used. For the analyses using Bayesian MCMC sampling, in all cases chain lengths of at least 50 million steps were used with a 10% 'burn-in' removed. Furthermore, at least two independent runs of each were performed and compared to ensure adequate sampling.

References

Bao, Y. *et al*. The influenza virus resource at the national center for biotechnology information. *J. Virol*. **82**, 596–601 (2008).

Brown, I. H. The epidemiology and evolution of influenza viruses in pigs. *Vet. Microbiol*. **74**, 29–46 (2000).

Brown, I. H., Harris, P. A., McCauley, J. W. & Alexander, D. J. Multiple genetic reassortment of avian and human influenza A viruses in European pigs, resulting in the emergence of an H1N2 virus of novel genotype. *J. Gen. Virol*. **79**, 2947–2955 (1998).

Centers for Disease Control and Prevention. Swine influenza A (H1N1) infection in two children—Southern California, March–April 2009. *Morb. Mortal. Wkly Rep*. **58**, 400–402 (2009).

Centers for Disease Control and Prevention. Novel influenza A virus infections—2007 case definition. <http://www.cdc.gov/ncphi/disss/nndss/casedef/novel_influenzaA.htm. (24 May 2009).

Choi, Y. K. *et al*. H3N2 influenza virus transmission from swine to turkeys, United States. *Emerg. Infect. Dis*. **10**, 2156–2160 (2004).

Drummond, A. J. & Rambaut. A. BEAST: Bayesian evolutionary analysis by sampling trees. *BMC Evol. Biol*. **7**, 214(2007).

Edgar, R. C. MUSCLE: multiple sequence alignment with high accuracy and high throughput. *Nucleic Acids Res*. **32**, 1792–1797 (2004).

Fraser, C. *et al*. Pandemic potential of a strain of influenza A (H1N1): Early findings. *Science* doi:10.1126/science.1176062 (in the press).

Garten, R. J. *et al*. Antigenic and genetic characteristics of swine-origin 2009 A (H1N1) nfluenza viruses circulating in humans. *Science* doi:10.1126/science.1176225 (in the press).

Hatta, M., Gao, P., Halfmann, P.& Kawaoka, Y. Molecular basis of high virulence of Hong Kong H5N1 influenza A viruses. *Science* **7**, 1840–1842 (2001).

Jung, K. & Song, D. S. Evidence of the cocirculation of influenza H1N1, H1N2 and H3N2 viruses in the pig population of Korea. *Vet. Rec*. **161**, 104–105 (2007).

Korber, B. *HIV Signature and Sequence Variation Analysis. Computational Analysis of HIV Molecular Sequences* (eds Rodrigo, A. G. & Learn, G. H.) Ch. 4, 55–72 (Kluwer Academic Publishers, 2000).

Kosakovsky Pond, S. L. & Frost, S. D. W. Not so different after all: a comparison of methods for detecting amino acid sites under selection. *Mol. Biol. Evol*. **22**, 1208–1222 (2005).

Le, Q. M., Sakai-Tagawa, Y., Ozawa, M., Ito, M. & Kawaoka, Y. Selection of H5N1 influenza virus PB2 during replication in humans. *J. Virol*. **83**, 5278–5281 (2009).

Myers, K. P. *et al*. Are swine workers in the United States at increased risk of infection with zoonotic influenza virus? *Clin. Infect. Dis*. **42**, 14–20 (2006).

Newman, A. P. *et al*. Human case of swine influenza A (H1N1) triple reassortant virus infection, Wisconsin. *Emerg. Infect. Dis*. **14**, 1470–1472 (2008).

Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N. Engl. J. Med*. doi:10.1056/NEJMoa0903810 (in the press).

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The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic Global Challenges, Global ...

Obenauer, J. C. *et al*. Large-scale sequence analysis of avian influenza isolates. *Science* **311**, 1576–1580 (2006).

Peiris, J. S. M. *et al*. Cocirculation of avian H9N2 and contemporary ''human'' H3N2 influenza A viruses in pigs in southeastern China: potential for genetic reassortment? *J. Virol*. **75**, 9679–9686 (2001).

Pensaert, M., Ottis, K., Vanderputte, J., Kaplan, M. M. & Buchmann, P. A. Evidence for the natural transmission of influenza A virus from wild ducks to swine and its potential for man. *Bull. World Health Organ*. **59**, 75–78 (1981).

Pybus, O. G. *et al*. Phylogenetic estimation of deleterious mutation load in RNA viruses and its contribution to viral evolution. *Mol. Biol. Evol*. **24**, 845–852 (2007).

Shinde, V. *et al*. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. *N. Engl. J. Med*. doi:10.1056/NEJMoa0903812 (in the press).

Shope, R. E.& Lewis, P. Swine influenza: experimental transmission and pathology. *J. Exp. Med*. **54**, 349–359 (1931).

Shortridge, K. F., Webster, R. G., Butterfield, W. K. & Campbell, C. H. Persistence of Hong Kong influenza virus variants in pigs. *Science* **196**, 1454–1455 (1977).

Smith, G. J. D. *et al*. Dating the emergence of pandemic influenza viruses. *Proc. Natl Acad. Sci. USA*. (in the press).

Thompson, J. D., Higgins, D. G. & Gibson, T. J. CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. *Nucleic Acids Res*. **22**, 4673–4680 (1994).

Trifonov, V., Khiabanian, H., Greenbaum, B. & Rabadan, R. The origin of the recent swine influenza A (H1N1) virus infecting humans. *Euro Surveill*. **14**, 19193 (2009).

Webby, R. J. *et al*. Evolution of swine H3N2 influenza viruses in the United States. *J. Virol*. **74**, 8243–8251 (2000).

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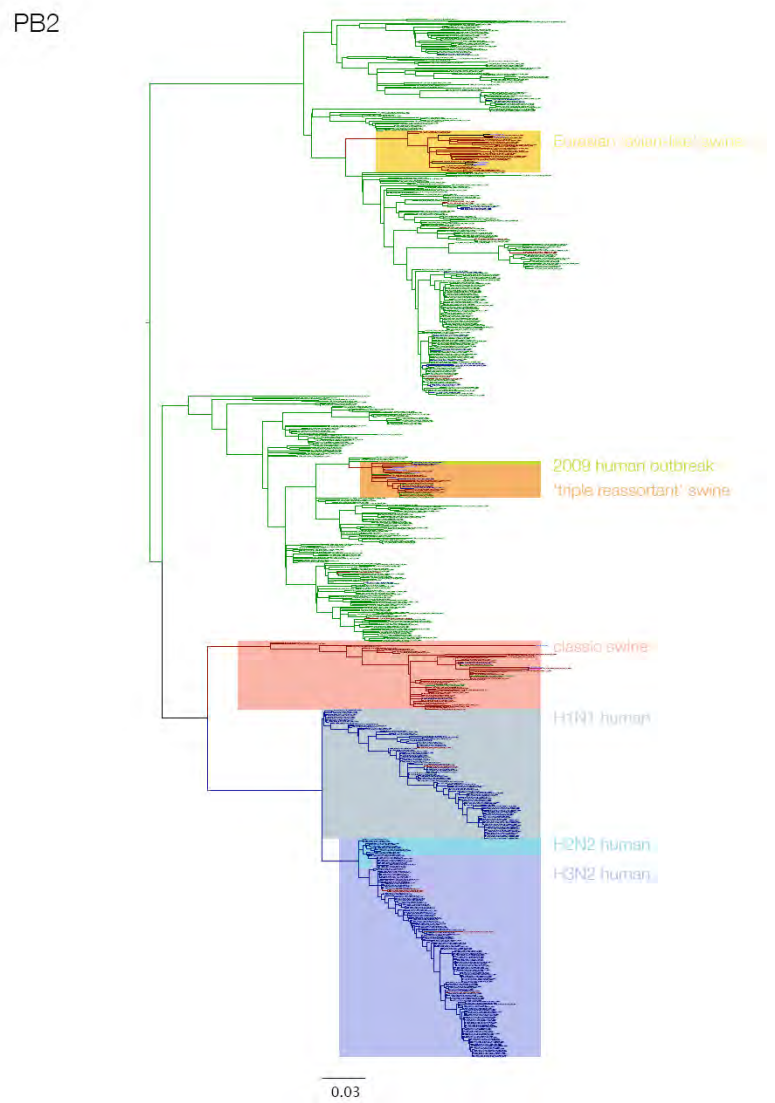
Supplementary Information



SUPPLEMENTARY FIGURE A14-3 Phylogenetic relationships of each gene segment (PB2, PB1, PA, HA, NP, NA, M & NS) of swine influenza A viruses indicating genetic components of the swine-origin influenza A (H1N1) virus. Clade labels indicate major swine lineages. Human viruses are coloured blue, swine viruses in red and avian viruses in green.

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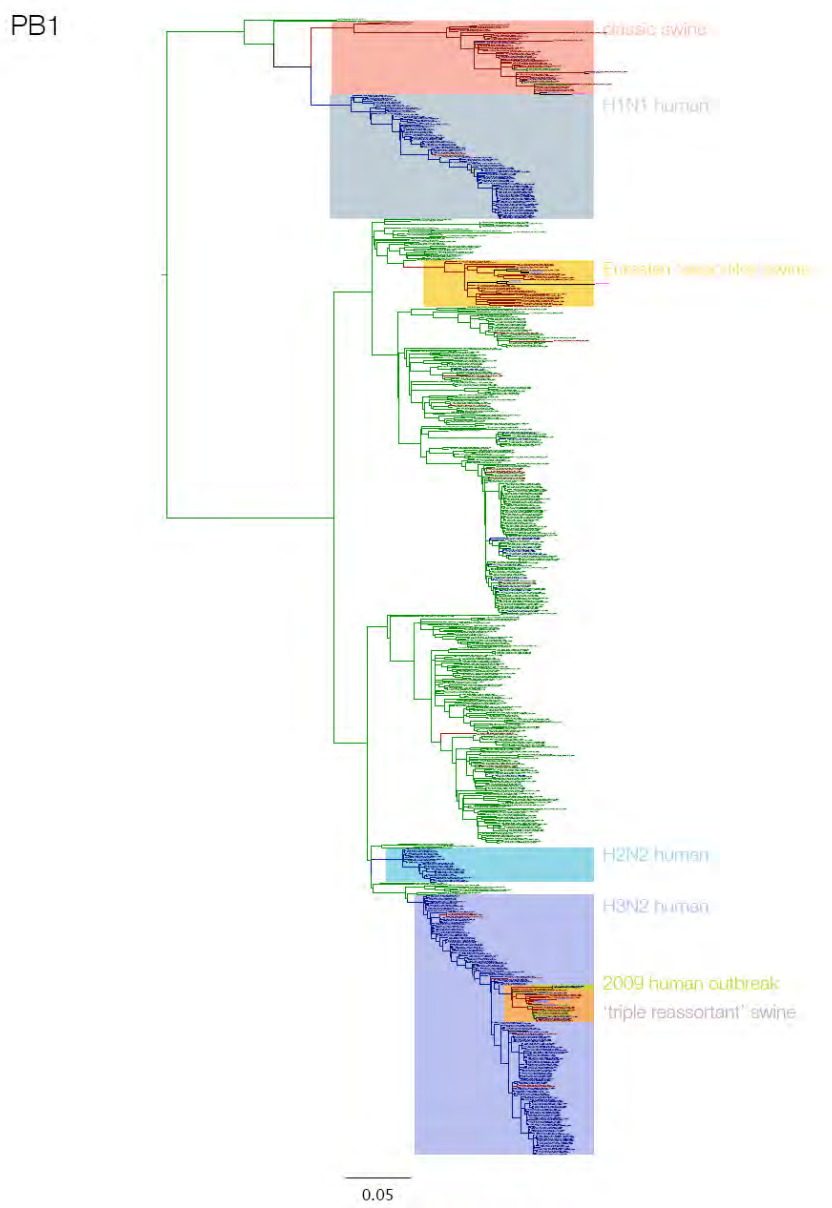

SUPPLEMENTARY FIGURE A14-3 Continued

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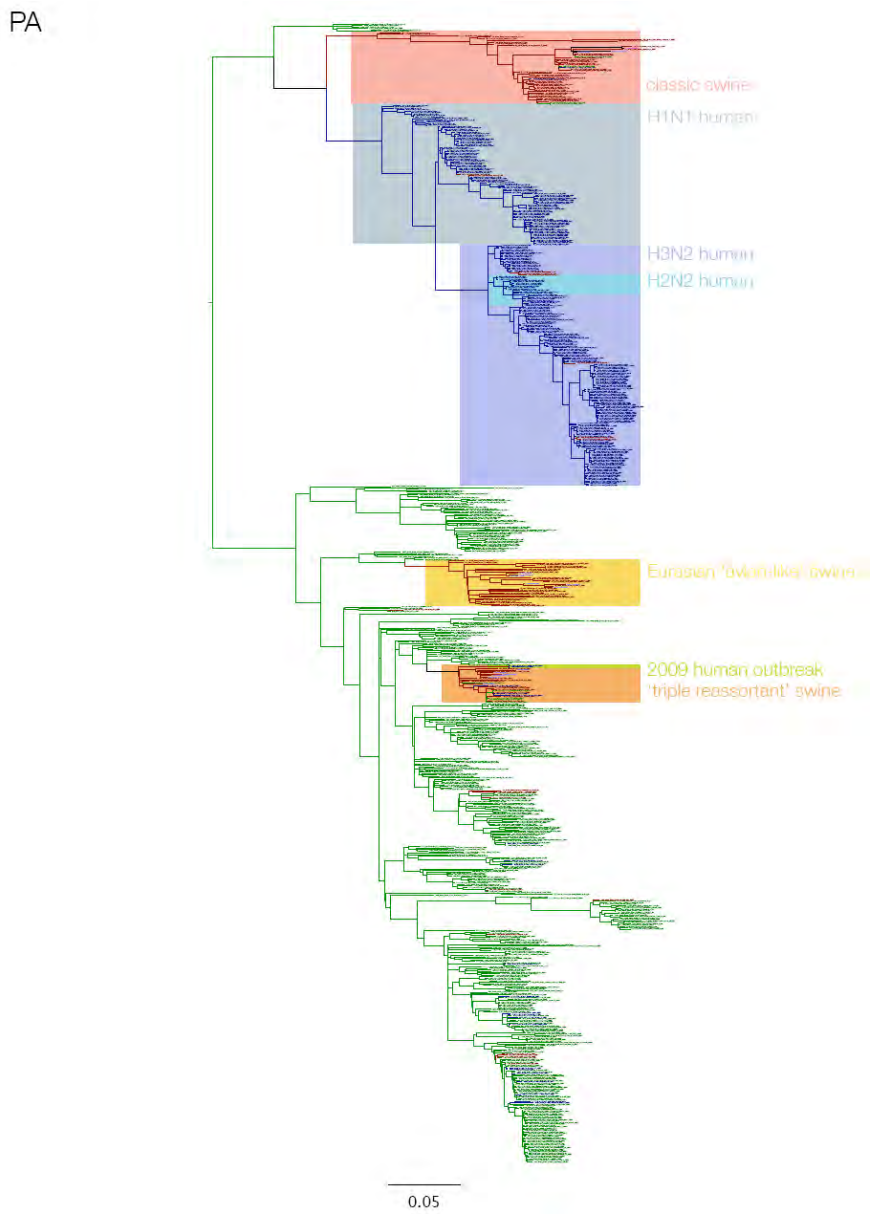

SUPPLEMENTARY FIGURE A14-3 Continued

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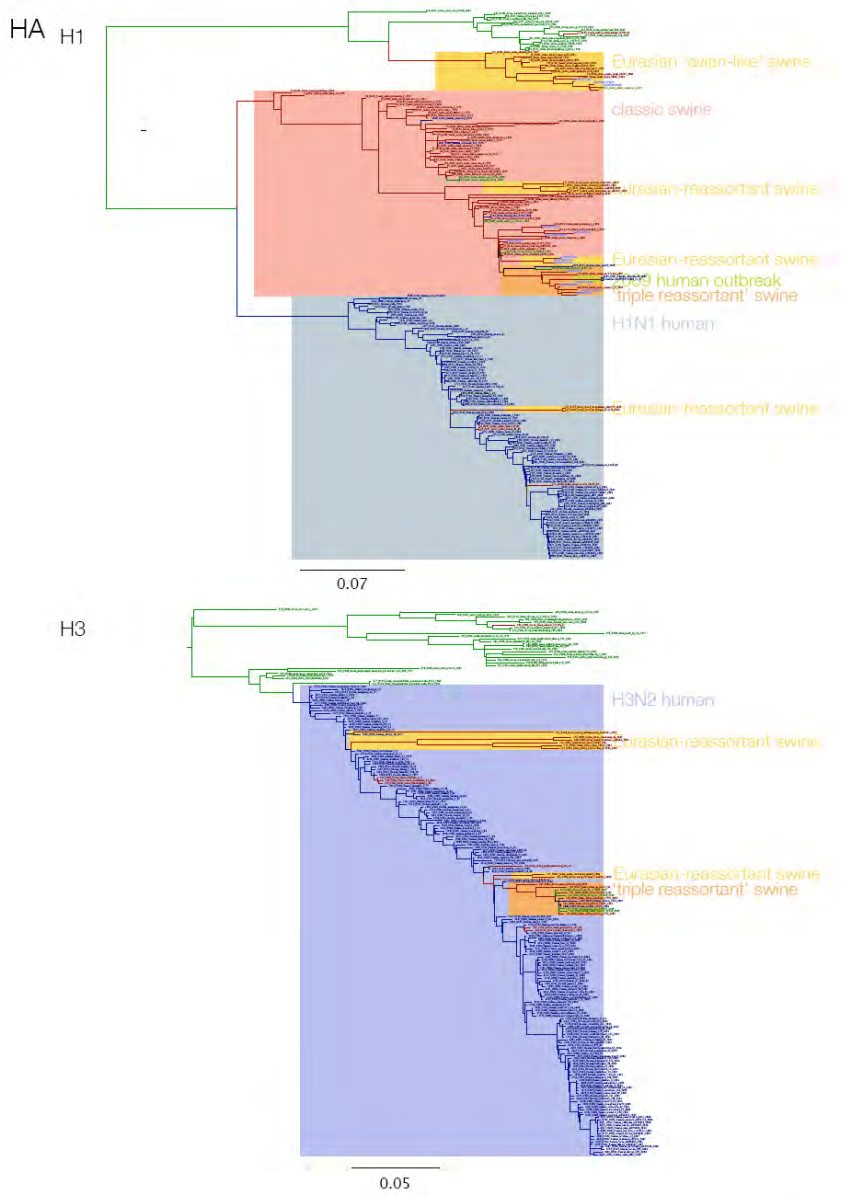

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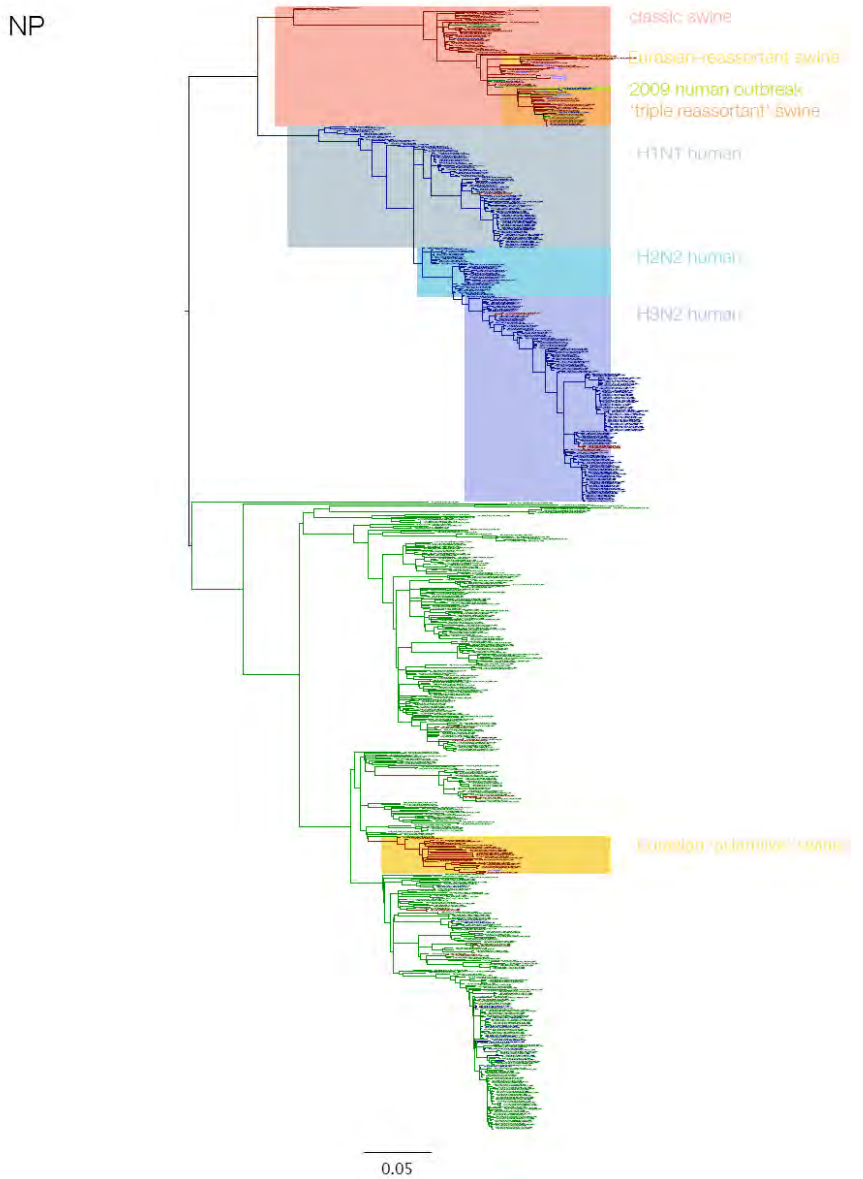

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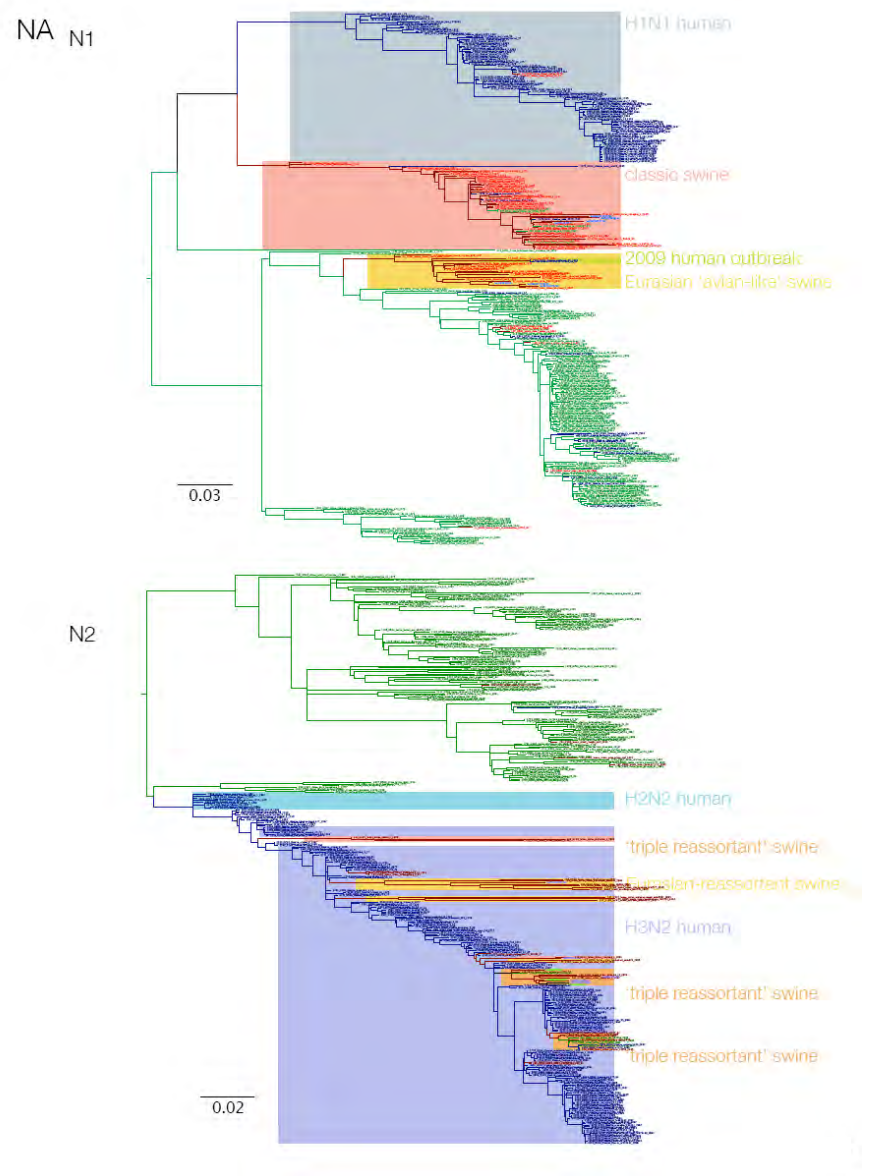

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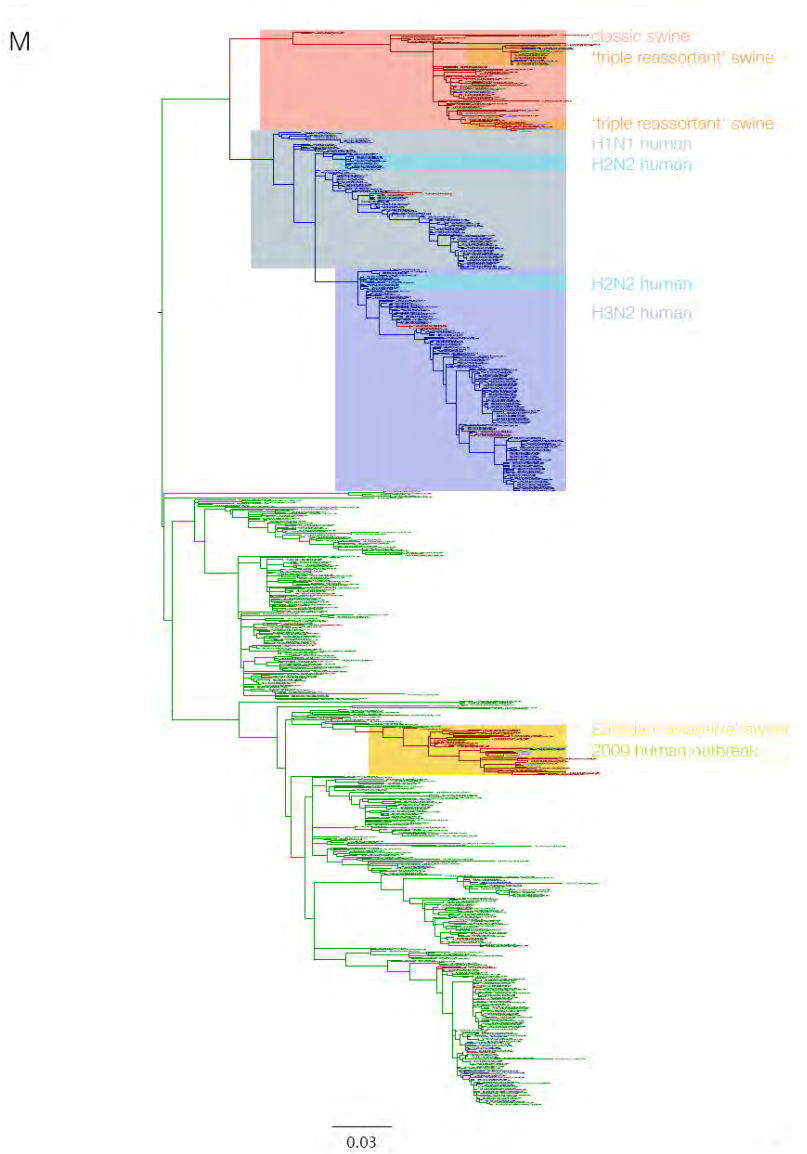

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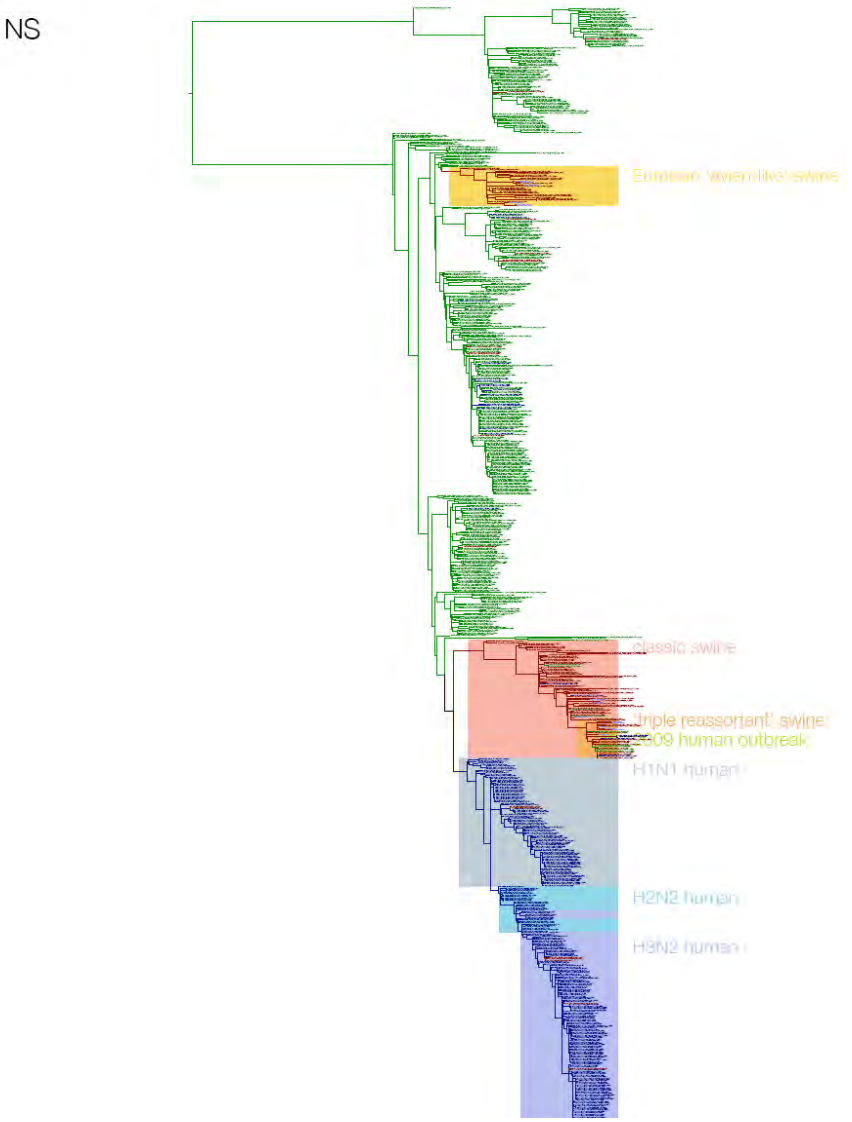

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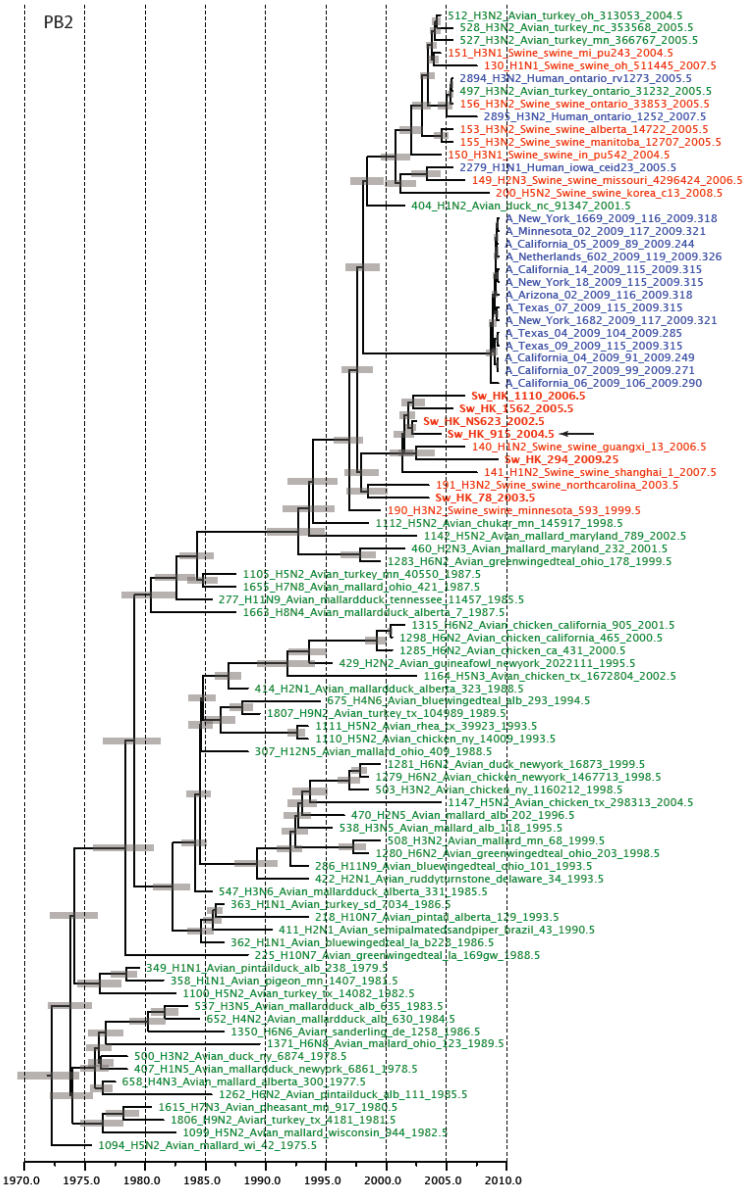

SUPPLEMENTARY FIGURE A14-4 Phylogenetic relationships scaled to time for each gene segment (PB2, PB1, PA, HA, NP, NA, M & NS) of the swine-origin influenza A (H1N1) virus as represented in Figure A14-2 of the main text but with full virus names and GenBank accession numbers. Internal nodes are reconstructed common ancestors with

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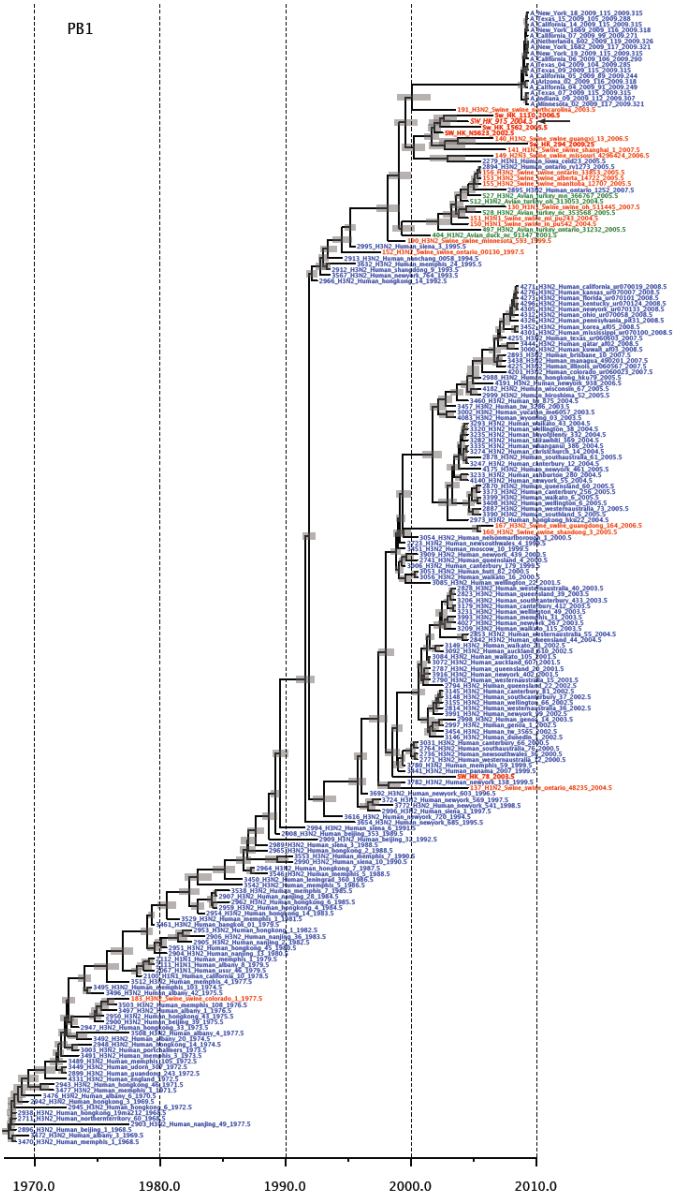

95% credible intervals on their date given by the grey bars. Human viruses are coloured blue, swine viruses in red and avian viruses in green. Newly described Hong Kong sequences have bold labels. Sw/HK/915/04 (H1N2) is highlighted with an arrow when present (see main text). Timeline is in years.

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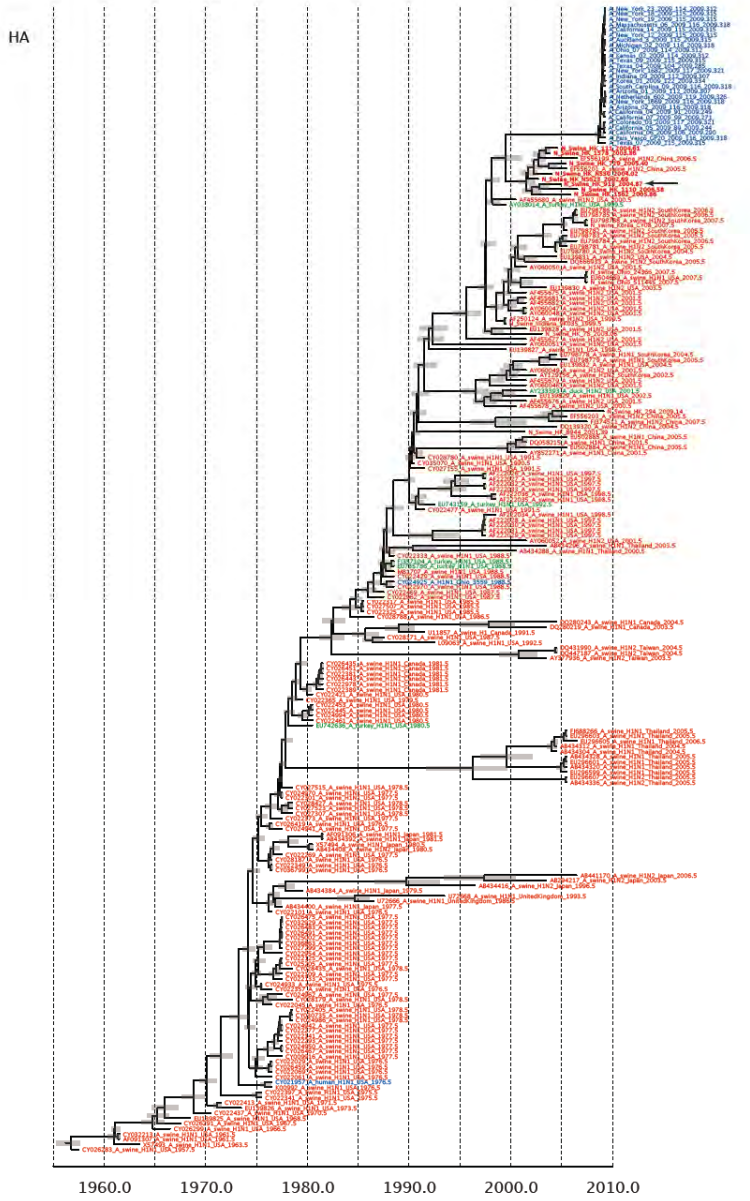

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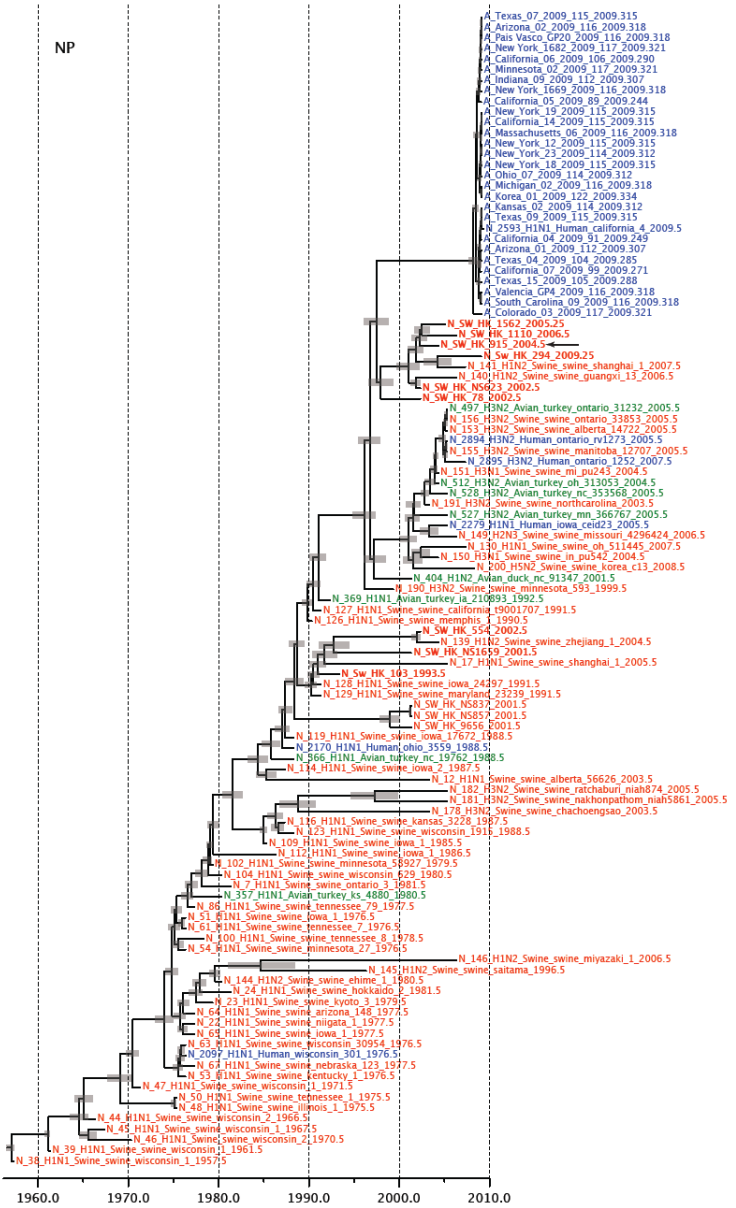

SUPPLEMENTARY FIGURE A14-4 Continued

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SUPPLEMENTARY FIGURE A14-4 Continued

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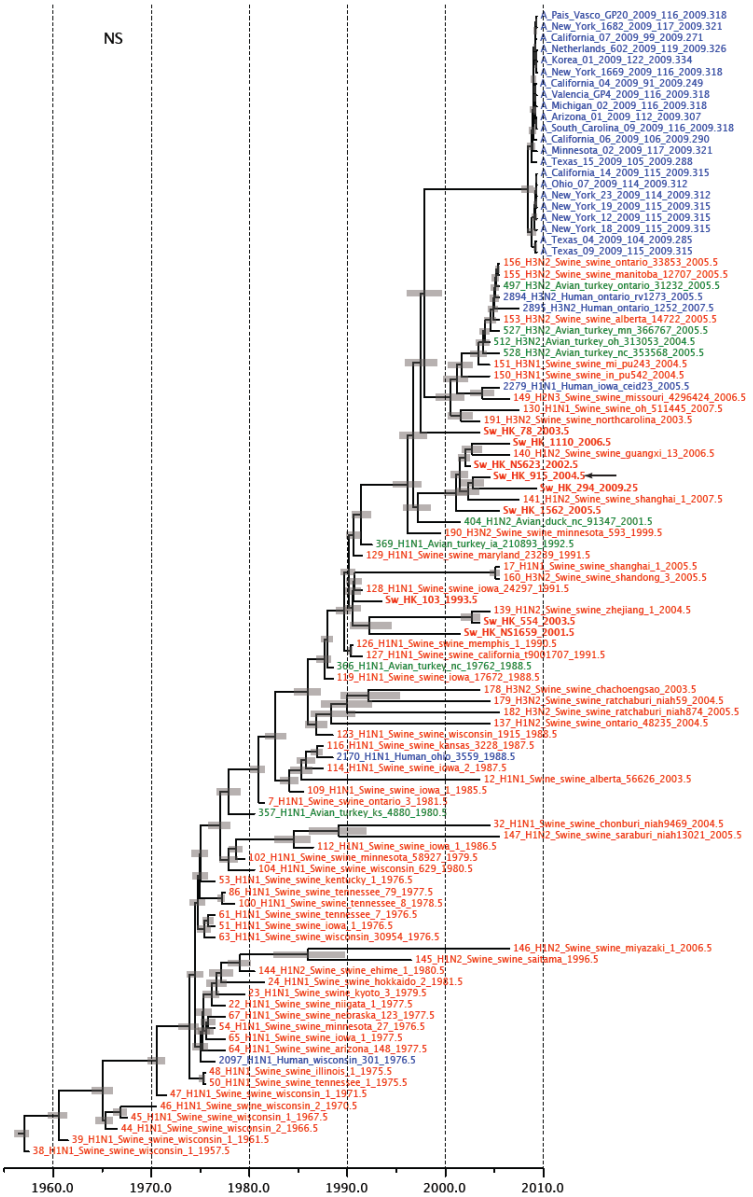

SUPPLEMENTARY FIGURE A14-4 Continued

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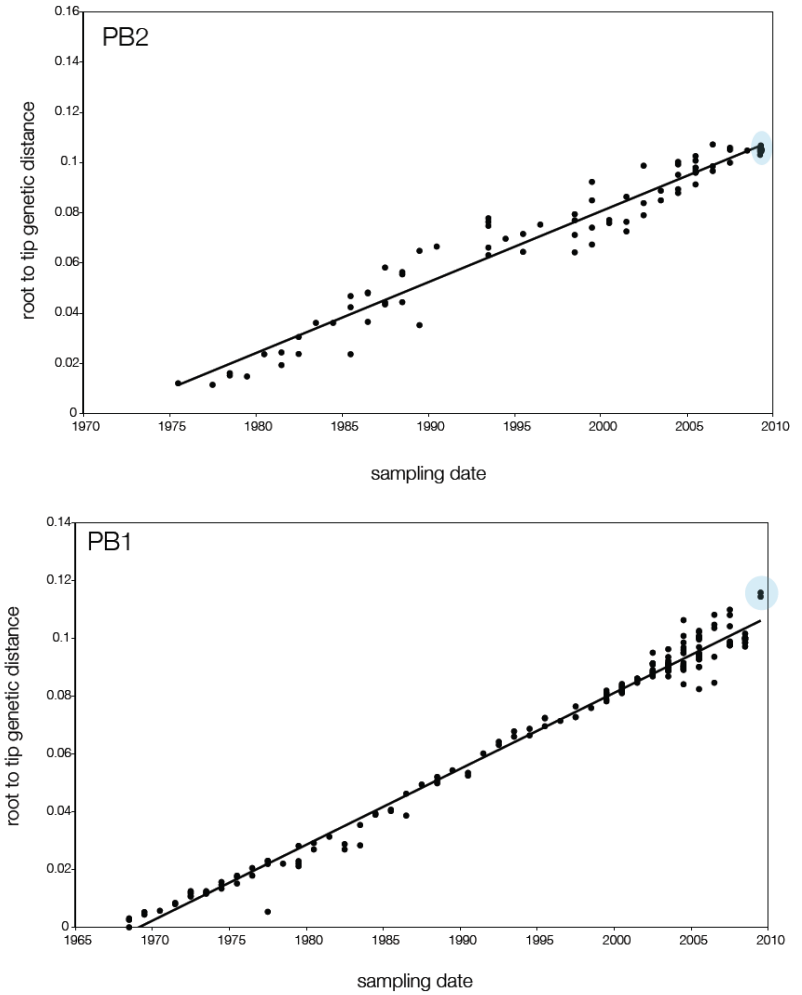

SUPPLEMENTARY FIGURE A14-5 For each gene segment (PB2, PB1, PA, HA, NP, NA, M & NS), we plot the isolation date of each influenza sequence against the genetic distance from that sequence to the root of the phylogeny. The linear regression gradient is therefore an estimate of the rate of sequence evolution and the x-intercept is an estimate of the TMRCA of the whole phylogeny. Phylogenies were estimated using neighbour-joining, with rooting chosen to maximise the regression fit. The chosen root was typically very close to the earliest sampled sequence. Residual analysis was performed to identify and remove significant outliers, which most likely result from isolation data annotation errors in the sequence database. For each gene, the degree of scatter about the linear regression reflects evolutionary rate heterogeneity among lineages, such that a "strict clock" corre-

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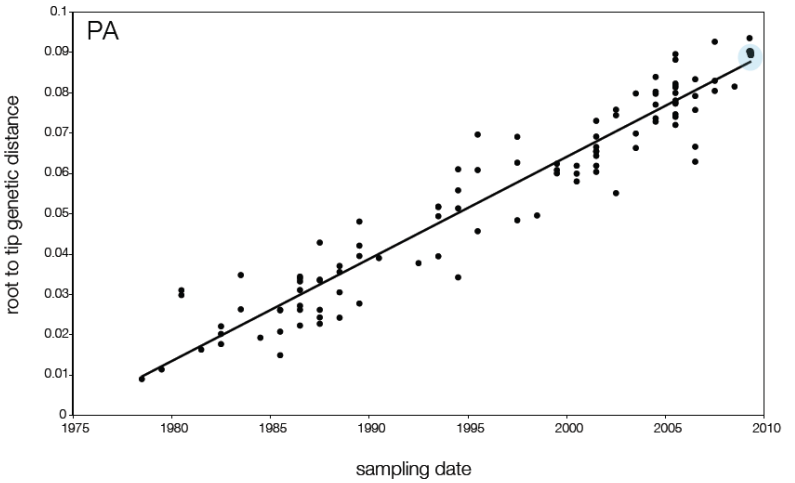

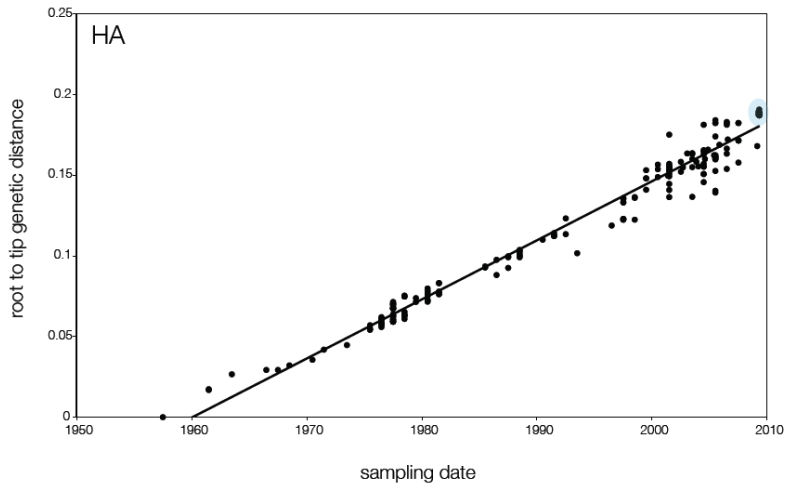

sponds to all the points falling exactly on the regression line. The 2009 outbreak sequences (highlighted in light blue) are entirely typically of the long termtrends in divergence, hence there is no evidence that the branch leading to the outbreak has evolved unusually rapidly or slowly. For further discussion of this methodology, see Drummond AJ, Pybus OG, Rambaut A. 2003. Inference of viral evolutionary rates from molecular sequences. *Advances in Parasitology* **54**:331-358.

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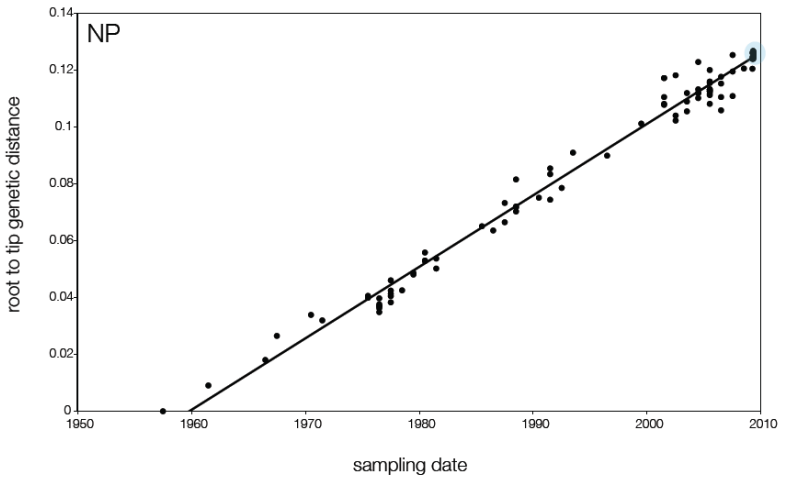

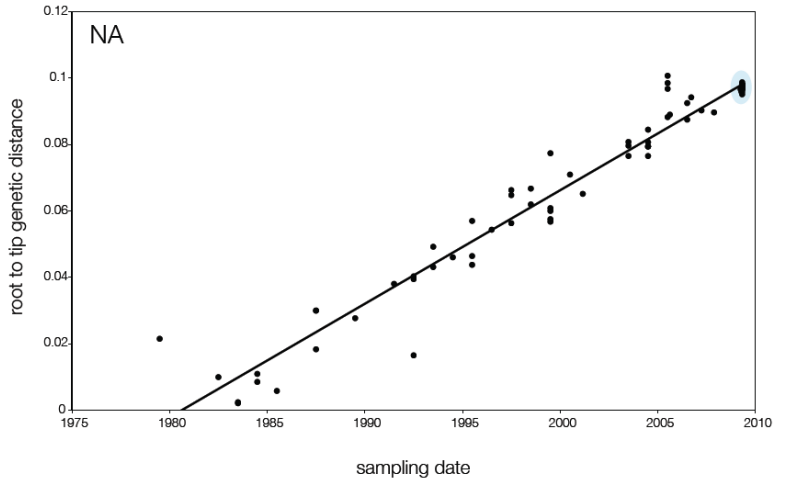

SUPPLEMENTARY FIGURE A14-5 Continued

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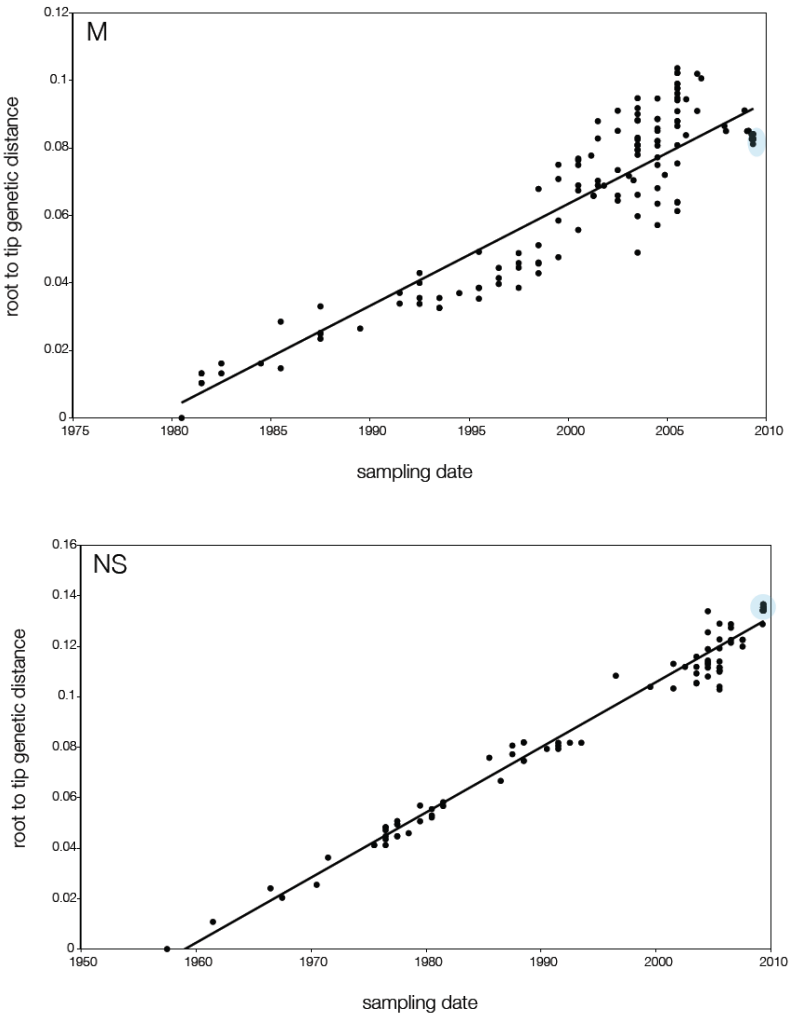

SUPPLEMENTARY FIGURE A14-5 Continued

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SUPPLEMENTARY TABLE A14-2 SLAC Results

gene	outbreak dN/dS[a]	reference dN/dS	estimated relative rate[b]	mean TMRCA	mean TMRCA (adjusted)
HA	0.32	0.21	1.22	28-Aug-2008	11-Oct-2008
NA	0.26	0.18	1.16	8-Aug-2008	12-Sep-2008
MP	0.19	0.05	1.43	3-Aug-2008	26-Oct-2008
NP	0.18	0.05	1.39	27-Mar-2008	19-Jul-2008
NS	2.15	0.23	3.85	21-May-2008	6-Feb-2009
PA	0.11	0.06	1.15	7-Oct-2008	6-Nov-2008
PB1	0.212	0.06	1.45	24-Oct-2008	22-Dec-2008
PB2	0.15	0.11	1.11	9-Sep-2008	4-Oct-2008

[a]Calculated using SLAC (S. Kosakovsky Pond, available at http://datamonkey.org)

[b]Substitution rate in outbreak clade relative to non-outbreak sequences based on excess non-synonymous mutations inferred from the higher dN/dS ratio.

SUPPLEMENTARY TABLE A14-3 SNAP Results

gene	outbreak dN/dS[a]	reference dN/dS	estimated relative rate[b]	mean TMRCA	mean TMRCA (adjusted)
HA	0.24	0.09	1.41	28-Aug-2008	9-Nov-2008
NA	0.32	0.1	1.59	8-Aug-2008	17-Nov-2008
MP	0.3	0.03	1.82	3-Aug-2008	5-Dec-2008
NP	0.14	0.02	1.39	27-Mar-2008	19-Jul-2008
NS	0.31	0.13	1.43	21-May-2008	5-Sep-2008
PA	0.18	0.05	1.43	7-Oct-2008	10-Dec-2008
PB1	0.16	0.03	1.45	24-Oct-2008	22-Dec-2008
PB2	0.13	0.07	1.15	9-Sep-2008	10-Oct-2008

[a]Calculated using SNAP (B. Korber, available at http://www.hiv.lanl.gov/content/sequemce/SNAP/SNAP.htm)

[b]Substitution rate in outbreak clade relative to non-outbreak sequences based on excess non-synonymous mutations inferred from the higher dN/dS ratio.

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SUPPLEMENTARY TABLE A14-4 Hong Kong Swine Genetic Origins. Lineage of Segments from Sw/HK Sequences Based on Phylogenetic Analysis

All Seqs	PB2	PB1	PA	HA (H1)	NP	NA	M	NS
Swine/HK/103/93	C	C	C	C	C	N1	C	C
Sw/HK/NS1659/01	C	C	C	C	C	N1	C	C
Sw/HK/8512/01	C	E	E	E	E	N1	E	E
Sw/HK/NS837/01	E	E	E	E	C	N1	E	E
Sw/HK/9656/01	E	E	E	E	C	N1	E	E
Sw/HK/NS1179/07	E	E	E	E	E	N1	E	E
Sw/HK/NS29/09	E	E	E	E	E	N1	E	E
Sw/HK/554/03	C	C	C	C	C	N2	C	C
Sw/HK/NS857/01	E	E	E	E	C	N2	E	E
Sw/HK/NS623/02	T	T	T	T	T	N2	T	T
Sw/HK/78/03	T	H	T	T	T	N2	E	T
Sw/HK/1110/06	T	T	T	T	T	N2	T	T
Sw/HK/915/04	T	T	T	T	T	N2	E	T
Sw/HK/1562/05	T	T	T	T	T	N2	T	T
Sw/HK/294/09	T	T	T	C	T	N2	T	T
A/California/04/2009	T	T	T	T	T	N1	E	T

Classical Swine	C
Eurasian Swine	E
Triple Reassortant	T
Human	H

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SUPPLEMENTARY TABLE A14-5 S-OIV Sequences Available on NCBI Influenza Virus Database at the Time of Analysis

	Days[1]	PB2[2]	PB1	PA	HA	NP	NA	MP	NS
A/Arizona/01/2009	112				GQ117067	GQ117063	GQ117064	GQ117066	GQ117065
A/Arizona/02/2009	116	GQ117076	GQ117075		GQ117079	GQ117074	GQ117077	GQ117078	
A/Auckland/3/2009	115						FJ973552	FJ973553	
A/California/04/2009	91	FJ966079	FJ966080	FJ966081	FJ966082	FJ966083	FJ966084	FJ966085	FJ966086
A/California/05/2009	89	FJ966955	FJ966952	FJ966957	FJ966952	FJ966953	FJ966956	FJ966954	
A/California/06/2009	106	FJ966963	FJ966950	FJ966964	FJ966950	FJ966961	FJ971075	FJ966962	FJ971074
A/California/07/2009	99	FJ984387	FJ969531	FJ969529	FJ981613		FJ984386	FJ966975	
A/California/14/2009	115	GQ117035	GQ117037	GQ117037	GQ117040	GQ117033	GQ117036	GQ117039	GQ117038
A/Colorado/03/2009	117				GQ117119	GQ117117	GQ117118		
A/Indiana/09/2009	112		GQ117093	GQ117095	GQ117097	GQ117092	GQ117094	GQ117096	
A/Kamsas/02/2009	114				GQ117059	GQ117057	Gq117058		
A/Korea/01/2009	122				GQ131023	GQ131024	GQ132185	GQ131025	GQ131026
A/Massachusetts/06/2009	116				GQ117043	GQ117041	GQ117042		
A/Michigan/02/2009	116			GQ117109	GQ117112	GQ117107	GQ117108	GQ117111	GQ117110
A/Minnesota/02/2009	117	GQ117070	GQ117069			GQ117068	GQ117071	GQ117073	GQ117072
A/Netherlands/602/2009	119				CY039527		CY039528		
A/New York/1669/2009	116	CY039900	CY039899	CY039898	CY039893	CY039896	CY039895	CY039894	CY039897
A/New York/1682/2009	117	CY039908	CY039907	CY039906	CY039901	CY039904	CY039903	CY039902	CY039905
A/New York/12/2009	115				FJ984337	FJ984336	FJ984335		FJ984334
A/New York/18/2009	115	FJ984351	FJ984353	FJ984354	FJ984355	FJ984352	FJ984350	FJ984348	FJ984349
A/New York/19/2009	115		FJ984392	FJ984393	FJ984394	FJ984391	FJ984390	FJ984388	FJ984389
A/New York/23/2009	114				FJ984364	FJ984363	FJ984362		FJ984361
A/Ohio/07/2009	114			FJ984401	GQ117100	GQ117098	GQ117099		
A/Paos Vasc0/GP20/2009	116				FJ985763	FJ985761	FJ985764	FJ985760	FJ985762

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A/South Carolina/09/2009	116				GQ117056	GQ117052	GQ117052	GQ117055	GQ117054	
A/Texas/04/2009	104	FJ969525	FJ981615	FJ981618	FJ981614	FJ981617	FJ981620	FJ966980		
A/Texas/07/2009	115	GQ117089	GQ117088		GQ117091	GQ117087		GQ117090		
A/Texas/09/2009	115	GQ117027	GQ117026	GQ117029	GQ117032	GQ117025	GQ117028	GQ117031	GQ117030	
A/Texas/15/2009	105		GQ122094		GQ122097	GQ122092	GQ122096	GQ122095	GQ122093	
A/Valencia/GP4/2009	116				FJ985758	FJ985756	FJ985759	FJ985755	FJ985757	

[1.]The sampling date as number of days since 1-Jan-2009.
[2.]Accession numbers for each available genomic segment.

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Supplementary Notes

Adaptation and Purifying Selection

We suggest in the main text that the increased presence of amino-acid polymorphisms may be present in the outbreak sequences relative to the swine influenza reference sequences due to the rapid growth in number of infections and the small window of time over which they were sampled. The fairly uniform distribution of nonsynonymous changes across the outbreak genomes (data not shown) and the relatively consistent dN/dS ratios across genes (Supplementary Tables A14-2 & A14-3) support this view. We predict that many of these mutations will be mildly deleterious and, given time, will be removed by purifying selection along an emergent 'trunk' lineage, and that the estimated evolutionary rate and gene-specific dN/dS pattern will approach that observed in the swine influenza data sets sampled over a time period of decades (see below). An interesting alternative is that the elevated rate in the outbreak sequences (and higher dN/dS ratio) is due to a burst of adaptive evolution in a new host, rather than a relaxation of purifying selection and that many of the 'extra' nonsynonymous mutations will become fixed in the population. If the current outbreak persists in the human population, it will be possible to distinguish these hypotheses.

Detailed Molecular Characterization

The presence of residue Asn 31 in the M2 protein invariably confers resistance to the adamantanes, a group of antiviral drugs used for treatment of human influenza (Scholtissek et al., 1998). Sequence analysis revealed that Asn 31 was present in all human isolates of the current outbreak, this mutation was also present in swine H1N1 and H1N2 viruses that were most closely related in the M gene. The widespread occurrence of the Asn 31 mutation in closely related viruses indicate that it may have descended from the swine lineage of amantadine-resistant M2 genes rather than independently acquired. It should be noted that majority of the seasonal H1N1 and H3N2 viruses are resistant to amantadine, except Brisbane-like H1N1 viruses (Barr et al., 2008). No mutations were observed in the NA gene that confers Oseltamivir resistance.

The molecular determinants of interspecies transmission of the A/California/04/2009-like virus to humans are unclear. In these viruses the amino acid residue at the receptor binding pocket of HA1– position Gln 226 and Gly 228 retain configurations (2,3-NeuAcGal linkages) predicted to have affinity for mammalian cell-surface receptors (Wiley et al., 1981; Rogers et al., 1983). Amino acid residues relevant to receptor binding were identical to those of classical swine H1N1 and North American H1N1 and recent H1N1 viruses in both the 130-loop and 190-helix. However, the amino acids at positions 133 and 135 are different from the current seasonal vaccine strain A/Brisbane/59/2007(H1N1)

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used in both the northern and southern hemispheres, indicating that these viruses may show less cross-reaction to the current vaccine strain (Winter et al., 2009; Canton et al., 1982).

Mutations Glu627Lys and Asp701Asn of the PB2 gene that are thought to be associated with adaptation to mammals and increased virulence of influenza viruses in mice were not present (Hatta et al., 2001; Gabriel et al., 2008; Le et al., 2009; Steel et al., 2009; Obenauer et al., 2006; Jackson et al., 2008). The C terminal of the NS1 gene is truncated in the A/California/04/2009-like viruses and four residues of the PDZ ligand domain are not present (Obenauer et al., 2006).

Supplementary Methods

Viral RNA was directly extracted from infected allantoic fluid or cell culture using QIAamp viral RNA minikit (Qiagen, Inc., Valencia, Calif.). cDNA were synthesized by reverse transcription reaction and gene amplification by PCR were performed using specific primers for each gene segments. PCR products were purified with the QIAquick PCR purification kit (Qiagen Inc.) and sequenced by synthetic oligonucleotides. Reactions were performed using Big Dye-Terminator v3.1 Cycle Sequencing Reaction Kit on an ABI PRISM 3700 DNA Analyzer (Applied Biosystems) following the manufacturer's instructions. All sequences were assembled and edited with Lasergene version 6.1 (DNASTAR, Madison, WI). Full genome sequences of these viruses are available for download at GISAID under the accession numbers (EPI177540 to EPI77658 and EPI177947).

References

Barr, I. G., Deng, Y. M., Iannello, P., Hurt, A. C. & Komadina, N. Adamantane resistance in influenza A (H1) viruses increased in 2007 in South East Asia but decreased in Australia and some other countries. *Antiviral Research* **80**, 200–205 (2008).

Canton, A., Brownlee, G. G., Yewdell, J. W. & Gerhard, W. The antigenic structure of the influenza virus A/PR/*/34 hemagglutinin (H1 subtype). *Cell* **31**, 417–27 (1982).

Gabriel, G. I., Herwig, A. & Klenk, H.–D. Interaction of polymerase subunit PB2 and NP with importin α1 is a determinant of host range of influenza A virus. *PLoS Pathog.* **4**, e11 (2008).

Hatta, M., Gai, P., Halfmann, P. & Kawaoka, Y. Molecular basis of high virulence of Hong Kong H5N1 influenza A viruses. *Science* **7**, 1840–1842 (2001)

Le, Q. M., Sakai-Tagawa, Y,, Ozawa, M., Ito, M. & Kawaoka, Y. Selection of H5N1 Influenza Virus PB2 during Replication in Humans. *J. Virol.* **83**, 5278–5281 (2009).

Jackson D, Hossain MJ, Hickman D, Perez DR, Lamb RA (2008) A new influenza virus virulence determinant: The NS1 protein four C-terminal residues modulate pathogenicity. *Proc. Natl. Acad. Sci. USA* **105**, 4381–4386 (2008).

Obenauer, J. C. *et al*. Large-Scale Sequence Analysis of Avian Influenza Isolates. *Science* **311**, 1576–1580 (2006).

Rogers, G. N. *et al.* Single amino acid substitutions in influenza haemagglutinin change receptor binding specificity. *Nature* **304**, 76–78 (1983).

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Scholtissek, C., Quack, G., Klenk, H. D. & Webster, R. G. How to overcome resistance of influenza A viruses against adamantane derivatives. *Antiviral Res.* **37**, 83-95 (1998).

Steel, J., Lowen, A. C., Mubareka. S. & Palese, P. Transmission of Influenza Virus in a Mammalian Host Is Increased by PB2 Amino Acids 627K or 627E/701N. *PLoS Pathog.* **5**, e1000252 (2009).

Wiley, D. C., Wilson, I. A. & Skehel, J. J. Structural identification of the antibody-binding sites of Hong Kong influenza haemagglutinin and their involvement in antigenic variation. *Nature* **289**, 373–378 (1981).

Winter, G., Fields, S. & Brownlee G. G. Nucleotide sequence of the haemagglutinin gene of a human influenza virus H1 subtype. *Nature* **292**, 72–75.

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Appendix B

Agenda

The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic: Global Challenges, Global Solutions

September 15-16, 2009
Keck Building, Room 100
500 Fifth Street, NW
Washington, DC

DAY 1: SEPTEMBER 15, 2009

8:00-8:15	Continental Breakfast
8:15-8:30	Welcoming Remarks: David A. Relman, M.D., Chair, and James M. Hughes, M.D., Vice-Chair, Forum on Microbial Threats
8:30-9:15	Keynote Address The 2009 Influenza Pandemic: Lessons for Going Forward Keiji Fukuda, M.D., M.P.H. World Health Organization
9:15-9:45	Keynote Address Swine Flu: 33 Years Onward (via DVD and teleconference) David Sencer, M.D., M.P.H.

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9:45-10:15 Discussion

10:15-10:30 Break

Session I
Evolution, Genomics, and Pathogenicity of the New H1N1 Influenza A Virus

Moderator: David A. Relman, M.D.

10:30-10:55 Rates and Dates: Origins and Emergence of the 2009 Influenza A H1N1 Pandemic Virus
Michael Worobey, D.Phil.
University of Arizona

10:55-11:20 The Ongoing Evolution of the H1N1 Pandemic
Eddie Holmes, Ph.D.
Pennsylvania State University

11:20-11:45 *In Vitro* and *In Vivo* Characterization of New Swine-Origin H1N1 Influenza Viruses
Yoshihiro Kawaoka, D.V.M., Ph.D.
University of Wisconsin

11:45-12:10 Pathology and Pathogenesis of Fatal Novel Influenza A H1N1 2009
Sherif Zaki, M.D., Ph.D.
Centers for Disease Control and Prevention

12:10-12:35 Detection and Characterization of and Response to the Emergence of 2009 H1N1 Viruses
Nancy Cox, Ph.D.
Centers for Disease Control and Prevention

12:35-1:00 Discussion of Session I

1:00-1:45 Lunch

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Session II
Potential Lessons Learned from the Southern Hemisphere Experiences

Moderator: Eduardo Gotuzzo, M.D.

1:45-2:15	Ground Zero: The Origins of a Pandemic? Guillermo Ruiz-Palacios, M.D. National Institute of Medical Sciences and Nutrition, Mexico
2:15-2:45	Clinical and Epidemiological Experience in South America Eduardo Gotuzzo, M.D. Universidad Peruana Cayetano Heredia, Peru
2:45-3:15	2009 Influenza A H1N1 Pandemic in Argentina Osvaldo Uez, M.D. Instituto Nacional de Epidemiologia, Argentina
3:15-3:30	Break
3:30-4:00	Southern Hemisphere, Northern Hemisphere: A Global Influenza World Ken Shortridge, Ph.D. The University of Hong Kong
4:00-4:30	Epidemiology of Seasonal and Pandemic Influenza A (H1N1) in South Africa, 2009 Barry Schoub, Ph.D., D.Sc. National Institute of Communicable Diseases, South Africa
4:30-5:15	Open Discussion of Session II
5:15-6:00	Open discussion of Day 1 and adjournment
6:30-9:00	Working dinner for Forum members, speakers, and staff

DAY 2: SEPTEMBER 16, 2009

8:30-9:00	Continental Breakfast
9:00-9:15	Summary of Day 1: James M. Hughes, M.D.

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Session III
Surveillance, Monitoring, Epidemiology, and Spread of Pandemic Disease

Moderator: Lonnie King, D.V.M.

9:15-9:45 Rumors of Pandemic: Monitoring Emerging Disease Outbreaks on the Internet
Larry Madoff, M.D.
University of Massachusetts

9:45-10:15 Modeling and Epidemiology of H1N1 Pandemic
Marc Lipsitch, D.Phil.
Harvard University

10:15-10:30 Break

10:30-11:00 Deciphering the Origins of Pandemics and a "Smart" Surveillance Strategy to Prevent Them
Peter Daszak, Ph.D.
Wildlife Trust

11:00-11:30 2009 Influenza A H1N1: Challenges for the Healthcare Setting
Michael Bell, M.D.
Centers for Disease Control and Prevention

11:30-12:00 Discussion of Session III

12:00-1:00 Luncheon remarks
Jesse Goodman, M.D., M.P.H.
Food and Drug Administration

Session IV
Contemporary Aspects of the Public Health Responses

Moderator: Michael Osterholm, Ph.D.

1:00-1:40 International Law and Equitable Access to Vaccines and Antiviral Medications
David Fidler, J.D.
Indiana University

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1:40-2:05	Ethical Issues in Responding to the H1N1 Pandemic Bernard Lo, M.D. University of California San Francisco
2:05-2:30	Considerations in H1N1 Vaccination John Treanor, M.D. University of Rochester
2:30-2:55	Influenza Antivirals for Pandemic H1N1: Overview Fred Hayden, M.D. University of Virginia
2:55-3:10	Break
3:10-3:35	Nonpharmaceutical Interventions Martin Cetron, M.D. Center for Disease Control and Prevention
3:35-4:00	Pandemic 2009 Influenza A (H1N1)—A Local Perspective Jeffery Duchin, M.D. Seattle-King County Department of Public Health
4:00-4:25	The H1N1 Experience in New York City—Lessons Learned and Approaches for the Fall Annie Fine, M.D. NYC Department of Health
4:25-5:00	Open Discussion
5:00-5:15	Wrap-Up and Adjournment James M. Hughes, M.D.

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Appendix C

Acronyms

ACIP	Advisory Committee on Immunization Practices
ARDS	acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
CIDRAP	Center for Infectious Disease Research and Policy
CMI	cell-mediated immunity
DOD	Department of Defense
ECDC	European Centre of Disease Prevention and Control
ED	emergency department
EFTA	European Free Trade Association
EID	emerging infectious disease
ESR	Environmental Science and Research
FDA	Food and Drug Administration
GBS	Guillain-Barré Syndrome
GDP	gross domestic product
GOARN	Global Outbreak Alert and Response Network
GP	general practitioner
GPHIN	Global Public Health Information Network

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HA	hemagglutinin
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HPAI	highly pathogenic avian influenza
IAV	influenza A virus
IHR	International Health Regulations
ILI	influenza-like illness
IOM	Institute of Medicine
ISTM	International Society of Travel Medicine
M	matrix protein
MDCK	Madin-Darby Canine Kidney
MHC	major histocompatibility complex
NA	neuraminidase
NICD	National Institute of Communicable Diseases
NIH	National Institutes of Health
NP	nuclear protein
NS	nonstructural protein
NYCDOH	New York City Department of Health and Mental Hygiene
OIE	World Organization for Animal Health
PAHO	Pan American Health Organization
PCAST	President's Council of Advisors on Science and Technology
PCR	polymerase chain reaction
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcription polymerase chain reaction
SARS	severe acute respiratory syndrome
sCFR	symptomatic case fatality ratio
SENASA	Servicio Nacional de Sanidad y Calidad Agroalimentaria
SIV	swine influenza virus
S-OIV	swine-origin influenza virus
UNICEF	United Nations Children's Fund
USDA	U.S. Department of Agriculture

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vRNA	viral ribonucleic acid
WHO	World Health Organization
WHO/AFRO	World Health Organization Regional Office of Africa

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Appendix D

Glossary

Antibody: A protein produced by the immune system in response to the introduction of a substance (an antigen) recognized as foreign by the body's immune system. Antibody interacts with the other components of the immune system and can render the antigen harmless, although for various reasons this may not always occur.

Antigen: A molecule capable of eliciting a specific antibody or T-cell response.

Antigenic: Having the properties of an antigen.

Antigenic drift: Random mutations in the genes of a virus, a process that changes the antigens of the virus. As these changes accumulate it may help the virus to evade the immune system since antigens are what the immune system recognizes (http://en.wikipedia.org/wiki/Antigenic_drift, accessed December 16, 2009).

Antigenic shift: The process by which at least two different strains of a virus (or different viruses), especially influenza, combine to form a new subtype having a mixture of the surface antigens of the two original strains (http://en.wikipedia.org/wiki/Antigenic_shift, accessed December 16, 2009).

Antiviral cytokine: A human or animal factor that is induced by interferon in virus-infected cells and mediates interferon inhibition of virus replication (http://medical-dictionary.thefreedictionary.com/antiviral+protein, accessed November 6, 2009).

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Cross-reactive cell-mediated immunity: An immune response that does not involve antibodies but rather involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen (http://encyclopedia.thefreedictionary.com/cell-mediated+immunity, accessed November 5, 2009).

Dilution: A method of obtaining a pure culture of bacteria or virus by subculturing from the highest dilution in which the organism is demonstrably present (http://medical-dictionary.thefreedictionary.com/limit+dilution, accessed November 5, 2009).

Distributive justice: Benefits and burdens imposed on the population when the emergency response measures and mitigations are shared equitably and fairly.

Endemic: The constant presence of a disease or infectious agent within a given geographic area; it may also refer to the usual prevalence of a given disease within such area.

Enzootic: A disease (can be either low or high morbidity) that is endemic in an animal community.

Epidemic: The occurrence in a community or region of cases of an illness (or outbreak) with a frequency clearly in excess of normal expectancy.

Epidemiology: The branch of science that deals with the incidence, distribution, and control of disease in a population; the sum of the factors controlling the presence or abundance of a disease or pathogen.

Epitopes: The surface portion of an antigen capable of eliciting an immune response and of combining with the antibody produced to counter that response (http://medical-dictionary.thefreedictionary.com/epitopes, accessed November 5, 2009).

Epi-X: Centers for Disease Control and Prevention's Web-based communications solution for public health professionals. Through Epi-X, CDC officials, state and local health departments, poison control centers, and other public health professionals can access and share preliminary health surveillance information—quickly and securely. Users can also be actively notified of breaking health events as they occur. For more information, see http://www.cdc.gov/epix/ (accessed November 5, 2009).

Founder effect: Changes in gene frequencies that usually accompany starting a new population from a small number of individuals. The newly founded population is likely to have quite different gene frequencies than the source population because

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of sampling error (i.e., genetic drift). The newly founded population is also likely to have a less genetic variation than the source population (http://evolution.berkeley.edu/evosite/glossary/glossary_browse.shtml, accessed December 17, 2009).

Genome: The complete genetic composition of an organism (e.g., human, bacterium, protozoan, helminth, or fungus), contained in a chromosome or set of chromosomes or in a DNA or RNA molecule (e.g., a virus).

GeoSentinel: A worldwide communication and data collection network for the surveillance of travel related morbidity. It was initiated in 1995 by the International Society of Travel Medicine (ISTM) and the CDC as a network of ISTM member travel/tropical medicine clinics. GeoSentinel is based on the concept that these clinics are ideally situated to effectively detect geographic and temporal trends in morbidity among travelers, immigrants and refugees. For more information, see http://www.istm.org/geosentinel/main.html (accessed November 5, 2009).

Global Outbreak Alert and Response Network (GOARN): A technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance. GOARN provides an operational framework to link this expertise and skill to keep the international community constantly alert to the threat of outbreaks and ready to respond. For more information, see http://www.who.int/csr/outbreaknetwork/en/ (accessed November 5, 2009).

HealthMap: Brings together disparate data sources to achieve a unified and comprehensive view of the current global state of infectious diseases and their effect on human and animal health. This freely available Web site integrates outbreak data of varying reliability, ranging from news sources (such as Google News) to curated personal accounts (such as ProMED) to validated official alerts (such as World Health Organization). Through an automated text processing system, the data is aggregated by disease and displayed by location for user-friendly access to the original alert. HealthMap provides a jumping-off point for real-time information on emerging infectious diseases and has particular interest for public health officials and international travelers. For more information, please see http://healthmap.org (accessed April 28, 2010).

Hemagglutinin: A molecule, such as an antibody or lectin, that agglutinates red blood cells.

Hemagglutinin (HA) protein: Species specific binding protein that allows for the virus to bind to the cell membrane of host respiratory cells and propagate through cellular processes (http://medical-dictionary.thefreedictionary.com/epitopes, accessed November 5, 2009).

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ILInet: A nationwide surveillance program for influenza-like illness (ILI) conducted by the CDC in collaboration with state health departments. Over 2,700 physicians in all 50 states were enrolled in this network during the 2008-2009 influenza season, during which they reported the total number of patient visits each week and number of patient visits for ILI by age group (0-4 years, 5-24 years, 25-49 years, 50-64 years, >65 years). These data are transmitted once a week to a central data repository at CDC via the Internet or fax (http://www.health.state.ny.us/diseases/communicable/influenza/recruits.htm, accessed December 17, 2009).

Immunocompromised: A condition (caused, for example, by the administration of immunosuppressive drugs or irradiation, malnutrition, aging, or a condition such as cancer or HIV disease) in which an individual's immune system is unable to respond adequately to a foreign substance.

Incidence rate: The number of new cases of a specified disease during a defined period of time divided by the number of persons in a stated population in which the cases occurred.

International air-traffic patterns: The patterns of international air traffic include travel and trade routes as well as the volume of travel and travelers between nodes in the air traffic system.

King County Healthcare Coalition: The Coalition is a network of healthcare organizations and providers that are committed to coordinating their emergency preparedness and response activities. The purpose is to develop and maintain a comprehensive system that assures effective communication, strategic acquisition and management of resources, and collaborative planning in response to emergencies and disasters (http://www.kingcounty.gov/healthservices/health/preparedness/hccoalition.aspx, accessed December 17, 2009).

M antigen: An antigen found in the cell of *Streptococcus pyogenes*; associated with virulence.

Macrophage: A type of white blood cell that ingests foreign material and is a key player in the immune response to foreign invaders such as infectious microorganisms (http://www.medterms.com/script/main/art.asp?articlekey=4238, accessed November 5, 2009).

Matrix protein: Structural proteins linking the viral envelope with the virus core (http://encyclopedia.thefreedictionary.com/matrix+protein, accessed November 5, 2009).

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Mekong Basin Disease Surveillance Group: The Mekong Basin is home to six countries: Cambodia, China, Laos, Myanmar, Vietnam, and Thailand. In 1999, delegates from these countries agreed to start disease surveillance collaborations under the name Mekong Basin Disease Surveillance. For more information, see http://www.mbdsoffice.com/ (accessed November 17, 2009).

National Influenza Program (P.L. 94-380): An act to amend the Public Health Service Act to authorize the establishment and implementation of an emergency national swine flu immunization program and to provide an exclusive remedy for personal injury or death arising out of the manufacture, distribution, or administration of the swine flu vaccine under such program. For more information, see http://thomas.loc.gov/cgi-bin/bdquery/z?d094:SN03735:@@@L&summ2=m& (accessed November 5, 2009).

Neuraminidase: Sialidase; an enzyme that catalyzes the hydrolysis of glucosidic linkages between a sialic acid residue and a hexose or hexosamine residue in glycoproteins, glycolipids, and proteoglycans. Neuraminidase is a major antigen of myxoviruses.

Neuraminidase (NA) surface protein: NA is involved in the release of viral progeny from the host (Morens, D. M., J. K. Taubenberger, and A. S. Fauci. 2009. The persistent legacy of the 1918 influenza virus. *New England Journal of Medicine* 361(3):225-229).

Nucleoprotein: Any of a group of substances found in the nuclei of all living cells and in viruses and composed of a protein and a nucleic acid (http://medical-dictionary.thefreedictionary.com/nucleoprotein, accessed November 5, 2009).

One Health: Health experts from around the world met on September 29, 2004, for a symposium focused on the current and potential movements of diseases among human, domestic animal, and wildlife populations organized by the Wildlife Conservation Society and hosted by The Rockefeller University. Using case studies on Ebola, avian influenza, and chronic wasting disease as examples, the assembled expert panelists delineated priorities for an international, interdisciplinary approach for combating threats to the health of life on Earth. The product—called the "Manhattan Principles" by the organizers of the "One World, One Health®" event—lists 12 recommendations for establishing a more holistic approach to preventing epidemic/epizootic disease and for maintaining ecosystem integrity for the benefit of humans, their domesticated animals, and the foundational biodiversity that supports us all. For more information, see http://www.oneworldonehealth.org/ (accessed July 16, 2009).

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Pandemic: Disease outbreak occurring over a wide geographic area and affecting an exceptionally high proportion of the population.

Pathogen: A specific causative agent (such as a bacterium or virus) of disease.

Pathogenicity: Reflects the ongoing evolution between a parasite and host, and disease is the product of a microbial adaptive strategy for survival.

Pathogenicity islands: Large genomic regions encoding for virulence factors of pathogenic bacteria, present on the genomes of pathogenic strains but absent from the genomes of nonpathogenic members of the same or related species.

Prevalence rate: The total number of persons sick or portraying a certain condition in a stated population at a particular time or during a stated period of time, regardless of when that illness or condition began, divided by the population at risk of having the disease or condition at the point in time midway through the period in which they occurred.

Procedural justice: The element of justice concerned with the application of laws, rather than with the content of the laws themselves. If an unjust law is applied, then procedural justice may obtain although the outcome is unjust. Similarly, an irregular procedure might be procedurally unjust, but give the right result on an occasion.

Recombination: The formation of new combinations of genes as a result of crossing over (sharing of genes) between structurally similar chromosomes, resulting in progeny with different gene combinations than in the parents.

Reservoir: Any person, animal, arthropod, plant, soil, or substance (or combination of these) in which an infectious agent normally lives and multiplies, on which it depends primarily for survival, and in which it reproduces itself in such manner that it can be transmitted to a susceptible vector.

Retrovirus: An RNA virus that is replicated in a host cell via the enzyme reverse transcriptase to produce DNA from its RNA genome. The DNA is then incorporated into the host's genome by an integrase enzyme. The virus thereafter replicates as part of the host cell's DNA. Retroviruses are enveloped viruses that belong to the viral family *Retroviridae*. any of a large family of RNA virtuses that includes lentiviruses and oncoviruses, so called because they carry reverse transcriptase.

Reverse transcription polymerase chain reaction: A variant of polymerase chain reaction (PCR), a laboratory technique commonly used in molecular biology to generate many copies of a DNA sequence, a process termed "amplification." In

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RT-PCR, however, the RNA strand is first reverse transcribed into its DNA complement (*complementary DNA*, or *cDNA*) using the enzyme reverse transcriptase, and the resulting cDNA is amplified using traditional or real-time PCR. Reverse transcription PCR is not to be confused with real-time polymerase chain reaction (Q-PCR/qRT-PCR), which is also sometimes (incorrectly) abbreviated as RT-PCR (http://en.wikipedia.org/wiki/Reverse_transcription_polymerase_chain_reaction, accessed November 6, 2009).

RNA virus: A virus that contains ribonucleic acid (RNA) as its genetic material.

Salvage therapy: A final treatment for people who are nonresponsive to or cannot tolerate other available therapies for a particular condition and whose prognosis is often poor (http://www.medterms.com/script/main/art.asp?articlekey=9380, accessed December 17, 2009).

Serological: The use of immune serum in any of a number of tests (agglutination, precipitation, enzyme-linked immunosorbent assay, etc.) to measure the response (antibody titer) to infectious disease; the use of serological reactions to detect antigen.

Strain: A subgrouping of organisms within a species, characterized by some particular quality.

Surveillance: The continuing scrutiny of all aspects of occurrence and spread of a disease that is pertinent to effective control.

Vaccine: A biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Virulence: The degree of pathogenicity of an organism as evidenced by the severity of resulting disease and the organism's ability to invade the host tissues.

Virulence factors: The properties (i.e., gene products) that enable a microorganism to establish itself on or within a host of a particular species and enhance its potential to cause disease.

Virus: A small infectious agent that can only replicate inside the cells of another organism. Viruses are too small to be seen directly with a light microscope.

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Viruses infect all types of organisms, from animals and plants to bacteria and archaea.

Zoonotic: Infection that causes disease in human populations but can be perpetuated solely in nonhuman host animals (e.g., influenza); may be enzootic or epizootic.

Zoonotic pool: The population of animals infected with nonhuman microbes that present a potential threat of transmission to humans.

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Appendix E

Forum Member Biographies

David A. Relman, M.D. (*Chair*), is professor of medicine (infectious diseases and geographic medicine) and of microbiology and immunology at Stanford University School of Medicine, and chief of the infectious disease section at the Veterans Affairs (VA) Palo Alto Health Care System. Dr. Relman received his B.S. in biology from the Massachusetts Institute of Technology and his M.D. from Harvard Medical School. He completed his residency in internal medicine and a clinical fellowship in infectious diseases at Massachusetts General Hospital, Boston, after which he moved to Stanford for a postdoctoral fellowship in 1986 and joined the faculty there in 1994. His research focus is on understanding the structure and role of the human indigenous microbial communities in health and disease. This work brings together approaches from ecology, population biology, environmental microbiology, genomics, and clinical medicine. A second area of investigation explores the classification structure of humans and nonhuman primates with systemic infectious diseases, based on patterns of genome-wide gene transcript abundance in blood and other tissues. The goals of this work are to understand mechanisms of host-pathogen interaction, as well as predict clinical outcome early in the disease process. His scientific achievements include the description of a novel approach for identifying previously unknown pathogens; the characterization of a number of new human microbial pathogens, including the agent of Whipple's disease; and some of the most in-depth analyses to date of human indigenous microbial communities. Among his other activities, Dr. Relman currently serves as chair of the Board of Scientific Counselors of the National Institutes of Health (NIH) National Institute of Dental and Craniofacial Research, is a member of the National Science Advisory Board for Biosecurity, and advises a number of U.S. government departments and agencies on matters

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related to pathogen diversity, the future life sciences landscape, and the nature of present and future biological threats. He was cochair of the Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats for the National Academy of Sciences (NAS). He received the Squibb Award from the Infectious Diseases Society of America (IDSA) in 2001, the Senior Scholar Award in Global Infectious Diseases from the Ellison Medical Foundation in 2002, an NIH Director's Pioneer Award in 2006, and a Doris Duke Distinguished Clinical Scientist Award in 2006. He is also a fellow of the American Academy of Microbiology.

James M. Hughes, M.D. (*Vice Chair*), is professor of medicine and public health at Emory University's School of Medicine and Rollins School of Public Health, serving as director of the Emory Program in Global Infectious Diseases, associate director of the Southeastern Center for Emerging Biological Threats, and senior adviser to the Emory Center for Global Safe Water. He also serves as senior scientific adviser for infectious diseases to the International Association of National Public Health Institutes funded by the Bill & Melinda Gates Foundation. Prior to joining Emory in June 2005, Dr. Hughes served as director of the NCID at the CDC. Dr. Hughes received his B.A. and M.D. degrees from Stanford University and completed postgraduate training in internal medicine at the University of Washington, infectious diseases at the University of Virginia, and preventive medicine at the CDC. After joining the CDC as an EIS officer in 1973, Dr. Hughes worked initially on foodborne and waterborne diseases and subsequently on infection control in healthcare settings. He served as director of CDC's Hospital Infections Program from 1983 to 1988, as deputy director of NCID from 1988 to 1992, and as director of NCID from 1992 to 2005. A major focus of Dr. Hughes' career has been on building partnerships among the clinical, research, public health, and veterinary communities to prevent and respond to infectious diseases at the national and global levels. His research interests include emerging and reemerging infectious diseases; antimicrobial resistance; foodborne diseases; health care-associated infections; vector-borne and zoonotic diseases; rapid detection of and response to infectious diseases and bioterrorism; strengthening public health capacity at the local, national, and global levels; and prevention of water-related diseases in the developing world. Dr. Hughes is a fellow of the AAAS, the American College of Physicians, and the IDSA, a member of IOM, and a councillor of the American Society of Tropical Medicine and Hygiene.

Ruth L. Berkelman, M.D., is the Rollins Professor and director of the Center for Public Health Preparedness and Research at the Rollins School of Public Health, Emory University, in Atlanta. She received her A.B. from Princeton Uni-

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versity and her M.D. from Harvard Medical School. Board certified in pediatrics and internal medicine, she began her career at the Centers for Disease Control and Prevention (CDC) in 1980 and later became deputy director of the National Center for Infectious Diseases (NCID). She also served as a senior adviser to the director of CDC and as assistant surgeon general in the U.S. Public Health Service. In 2001 she came to her current position at Emory University, directing a center focused on emerging infectious diseases and other urgent threats to health, including terrorism. She has also consulted with the biologic program of the Nuclear Threat Initiative and is most recognized for her work in infectious diseases and disease surveillance. She was elected to the IOM in 2004. Currently a member of the Board on Life Sciences of the National Academies, she also chairs the Board of Public and Scientific Affairs at the American Society of Microbiology (ASM).

Enriqueta C. Bond, Ph.D., is president emeritus of the Burroughs Wellcome Fund. She received her undergraduate degree from Wellesley College, her M.A. from the University of Virginia, and her Ph.D. in molecular biology and biochemical genetics from Georgetown University. She is a member of the IOM, the AAAS, the ASM, and the American Public Health Association. Dr. Bond chairs the Academies' Board on African Science Academy Development and serves on the Report Review Committee for the Academies. She serves on the board and executive committee of the Hamner Institute, the board of the Health Effects Institute, the board of the James B. Hunt Jr. Institute for Educational Leadership and Policy, the council of the National Institute of Child Health and Human Development, and the NIH Council of Councils. In addition Dr. Bond serves on a scientific advisory committee for the World Health Organization (WHO) Tropical Disease Research Program. Prior to being named president of the Burroughs Wellcome Fund in 1994, Dr. Bond served on the staff of the IOM beginning in 1979, becoming its executive officer in 1989.

Roger G. Breeze, Ph.D., received his veterinary degree in 1968 and his Ph.D. in veterinary pathology in 1973, both from the University of Glasgow, Scotland. He was engaged in teaching, diagnostic pathology, and research on respiratory and cardiovascular diseases at the University of Glasgow Veterinary School from 1968 to 1977 and at Washington State University College of Veterinary Medicine from 1977 to 1987, where he was professor and chair of the Department of Microbiology and Pathology. From 1984 to 1987 he was deputy director of the Washington Technology Center, the state's high-technology sciences initiative, based in the College of Engineering at the University of Washington. In 1987, he was appointed director of the U.S. Department of Agriculture's (USDA's) Plum Island Animal Disease Center, a Biosafety Level 3 facility for research and diagnosis of the world's most dangerous livestock diseases. In that role he initiated research into the genomic and functional genomic basis of disease

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pathogenesis, diagnosis, and control of livestock RNA and DNA virus infections. This work became the basis of U.S. defense against natural and deliberate infection with these agents and led to his involvement in the early 1990s in biological weapons defense and proliferation prevention. From 1995 to 1998, he directed research programs in 20 laboratories in the Southeast for the USDA Agricultural Research Service before going to Washington, DC, to establish biological weapons defense research programs for the USDA. He received the Distinguished Executive Award from President Clinton in 1998 for his work at Plum Island and in biodefense. Since 2004 he has been chief executive officer of Centaur Science Group, which provides consulting services in biodefense. His main commitment is to the Defense Threat Reduction Agency's Biological Weapons Proliferation Prevention Program in Europe, the Caucasus, and Central Asia.

Steven J. Brickner, Ph.D., is an independent consultant based in southeastern Connecticut. He received his Ph.D. in organic chemistry from Cornell University, and completed an NIH postdoctoral research fellowship at the University of Wisconsin-Madison. He is co-inventor of Zyvox® (linezolid), a leading antibiotic with annual worldwide sales first exceeding US$1 billion in 2008. He initiated the oxazolidinone research program at Upjohn and led the team that discovered linezolid and an earlier clinical candidate, eperezolid. Linezolid is the first member of any entirely new class of antibiotics to reach the market in the more than 35 years since the discovery of the first quinolone. Dr. Brickner is a corecipient of the Pharmaceutical Research and Manufacturers of America (PhRMA) 2007 Discoverers Award, and the 2007 American Chemical Society Award for Team Innovation. He was named the 2002-2003 Outstanding Alumni Lecturer, College of Arts and Science, Miami University (Ohio). Dr. Brickner is a synthetic organic/medicinal chemist with over 25 years of research experience focused entirely on the discovery of novel antibacterial agents during his prior tenure at Upjohn, Pharmacia & Upjohn, and Pfizer. He is an inventor or co-inventor on 21 U.S. patents and has published over 30 peer-reviewed scientific papers, particularly on the oxazolidinones and novel azetidinones. An internationally recognized drug discoverer with over 20 invited speaker presentations, he has been a member of the IOM Forum on Microbial Threats since 1997 and is on the Editorial Advisory Board of *Current Pharmaceutical Design* and the Faculty of 1000 Biology. In February 2009, he established SJ Brickner Consulting, LLC, which primarily offers consulting services on all aspects of medicinal chemistry and drug design related to the discovery and development of new antibiotics.

John E. Burris, Ph.D., became president of the Burroughs Wellcome Fund in July 2008. He is the former president of Beloit College. Prior to his appointment at Beloit in 2000, Dr. Burris served for eight years as director and CEO of the Marine Biological Laboratory in Woods Hole, Massachusetts. From 1984 to 1992 he was at the National Research Council/National Academies, where he

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served as the executive director of the Commission on Life Sciences. A native of Wisconsin, he received an A.B. in biology from Harvard University in 1971, attended the University of Wisconsin–Madison in an M.D.-Ph.D. program, and received a Ph.D. in marine biology from the Scripps Institution of Oceanography at the University of California, San Diego in 1976. A professor of biology at the Pennsylvania State University from 1976 to 1985, he held an adjunct appointment there until coming to Beloit. His research interests were in the areas of marine and terrestrial plant physiology and ecology. He has served as president of the American Institute of Biological Sciences and is or has been a member of a number of distinguished scientific boards and advisory committees including the Grass Foundation; the Stazione Zoologica "Anton Dohrn" in Naples, Italy; the AAAS; and the Radiation Effects Research Foundation in Hiroshima, Japan. He has also served as a consultant to the National Conference of Catholic Bishops' Committee on Science and Human Values.

Gail H. Cassell, Ph.D., is currently vice president, Scientific Affairs, and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company, in Indianapolis, Indiana. She is the former Charles H. McCauley Professor and chairman of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from NIH during her decade of leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the twentieth century. She obtained her Ph.D. in microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus. She is a past president of the ASM (the oldest and single-largest life sciences organization, with a membership of more than 42,000). She was a member of the NIH Director's Advisory Committee and a member of the Advisory Council of the National Institute of Allergy and Infectious Diseases (NIAID) of NIH. She was named to the original Board of Scientific Councilors of the CDC Center for Infectious Diseases and served as chair of the board. She recently served a 3-year term on the Advisory Board of the director of the CDC and as a member of the HHS secretary's Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the FDA Advisory Committee to the Commissioner. Since 1996 she has been a member of the U.S.–Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas (U.S. State Department–Japan Ministry of Foreign Affairs). She has served on several editorial boards of scientific journals and has authored more than 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the IOM and is currently serving a 3-year term on the IOM Council, its governing board. Dr. Cassell has been intimately involved in the establishment of science policy and legislation related to biomedical research and public health. For 9 years she

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was chairman of the Public and Scientific Affairs Board of the ASM; she has served as an adviser on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy (OSTP); and she has been an invited participant in numerous congressional hearings and briefings related to infectious diseases, antimicrobial resistance, and biomedical research. She has served two terms on the Liaison Committee for Medical Education (LCME), the accrediting body for U.S. medical schools, as well as other national committees involved in establishing policies for training in the biomedical sciences. She has just completed a term on the Leadership Council of the School of Public Health of Harvard University. Currently she is a member of the Executive Committee of the Board of Visitors of Columbia University School of Medicine, the Board of Directors of the Burroughs Wellcome Fund, and the Advisory Council of the School of Nursing of Johns Hopkins.

Mark B. Feinberg, M.D., Ph.D., is vice president for medical affairs and policy in global vaccine and infectious diseases at Merck & Co., Inc., and is responsible for global efforts to implement vaccines to achieve the greatest health benefits, including efforts to expand access to new vaccines in the developing world. Dr. Feinberg received a bachelor's degree magna cum laude from the University of Pennsylvania in 1978 and his M.D. and Ph.D. degrees from Stanford University School of Medicine in 1987. His Ph.D. research at Stanford was supervised by Dr. Irving Weissman and included time spent studying the molecular biology of the human retroviruses—HTLV-I (human T-cell lymphotrophic virus, type I) and HIV—as a visiting scientist in the laboratory of Dr. Robert Gallo at the National Cancer Institute. From 1985 to 1986, Dr. Feinberg served as a project officer for the IOM Committee on a National Strategy for AIDS. After receiving his M.D. and Ph.D. degrees, Dr. Feinberg pursued postgraduate residency training in internal medicine at the Brigham and Women's Hospital of Harvard Medical School and postdoctoral fellowship research in the laboratory of Dr. David Baltimore at the Whitehead Institute for Biomedical Research. From 1991 to 1995, Dr. Feinberg was an assistant professor of medicine and microbiology and immunology at the University of California, San Francisco (UCSF), where he also served as an attending physician in the AIDS-oncology division and as director of the virology research laboratory at San Francisco General Hospital. From 1995 to 1997, Dr. Feinberg was a medical officer in the Office of AIDS Research in the Office of the Director of the NIH, the chair of the NIH Coordinating Committee on AIDS Etiology and Pathogenesis Research, and an attending physician at the NIH Clinical Center. During this period, he also served as executive secretary of the NIH Panel to Define Principles of Therapy of HIV Infection. Prior to joining Merck in 2004, Dr. Feinberg served as professor of medicine and microbiology and immunology at the Emory University School of Medicine, as an investigator at the Emory Vaccine Center, and as an attending physician at Grady Memorial Hospital. At UCSF and Emory, Dr. Feinberg and colleagues

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were engaged in the preclinical development and evaluation of novel vaccines for HIV and other infectious diseases and in basic research studies focused on revealing fundamental aspects of the pathogenesis of AIDS. Dr. Feinberg also founded and served as the medical director of the Hope Clinic of the Emory Vaccine Center—a clinical research facility devoted to the clinical evaluation of novel vaccines and to translational research studies of human immune system biology. In addition to his other professional roles, Dr. Feinberg has also served as a consultant to, and a member of, several IOM and NAS committees. Dr. Feinberg currently serves as a member of the National Vaccine Advisory Committee and is a member of the Board of Trustees of the National Foundation for Infectious Diseases. Dr. Feinberg has earned board certification in internal medicine; he is a fellow of the American College of Physicians, a member of the Association of American Physicians, and the recipient of an Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation and an Innovation in Clinical Research Award from the Doris Duke Charitable Foundation.

Capt. Darrell R. Galloway, M.S.C., Ph.D., is chief of the Medical Science and Technology Division for the Chemical and Biological Defense Directorate at the Defense Threat Reduction Agency. He received his baccalaureate degree in microbiology from California State University in Los Angeles in 1973. After completing military service in the U.S. Army as a medical corpsman from 1969 to 1972, Captain Galloway entered graduate school and completed a doctoral degree in biochemistry in 1978 from the University of California, followed by two years of postgraduate training in immunochemistry as a fellow of the National Cancer Institute (NCI) at the Scripps Clinic and Research Foundation in La Jolla, California. Captain Galloway began his Navy career at the Naval Medical Research Institute in Bethesda, Maryland, where he served as a research scientist working on vaccine development from 1980 to 1984. In late 1984, Captain Galloway left active service to pursue an academic appointment at Ohio State University, where he is now a tenured faculty member in the Department of Microbiology. He also holds appointments at the University of Maryland Biotechnology Institute and the Uniformed Services University of the Health Sciences. He has an international reputation in the area of bacterial toxin research and has published more than 50 research papers on various studies of bacterial toxins. In recent years, Captain Galloway's research has concentrated on anthrax and the development of DNA-based vaccine technology. His laboratory has contributed substantially to the development of a new DNA-based vaccine against anthrax that has completed the first phase of clinical trials. Captain Galloway is a member of the ASM and has served as president of the Ohio branch of that organization. He received an NIH Research Career Development Award. In 2005, Captain Galloway was awarded the Joel M. Dalrymple Award for significant contributions to biodefense vaccine development.

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S. Elizabeth George, Ph.D., is deputy director, Biological Countermeasures Portfolio Science and Technology Directorate, Department of Homeland Security. Until it merged into the new department in 2003, she was program manager of the Chemical and Biological National Security Program in the Department of Energy's National Nuclear Security Administration's Office of Nonproliferation Research and Engineering. Significant accomplishments include the design and deployment of BioWatch, the nation's first civilian biological threat agent monitoring system, and PROTECT, the first civilian operational chemical detection and response capability deployed in the Washington, DC, area subway system. Previously, she spent 16 years at the U.S. Environmental Protection Agency (EPA), Office of Research and Development, National Health and Ecological Effects Research Laboratory, Environmental Carcinogenesis Division, where she was branch chief of the Molecular and Cellular Toxicology Branch. She received her B.S. in biology in 1977 from Virginia Polytechnic Institute and State University and her M.S. and Ph.D. in microbiology in 1979 and 1984, respectively, from North Carolina State University. From 1984 to 1986, she was a National Research Council (NRC) fellow in the laboratory of Dr. Larry Claxton at EPA. Dr. George is the 2005 chair of the Chemical and Biological Terrorism Defense Gordon Research Conference. She has served as councillor for the Environmental Mutagen Society and president and secretary of the Genotoxicity and Environmental Mutagen Society. She holds memberships in the ASM and the AAAS and is an adjunct faculty member in the School of Rural Public Health, Texas A&M University. She is a recipient of the EPA Bronze Medal and Scientific and Technological Achievement Awards and the DHS Under Secretary's Award for Science and Technology. She is the author of numerous journal articles and has presented her research at national and international meetings.

Jesse L. Goodman, M.D., M.P.H., is director of the FDA's Center for Biologics Evaluation and Research, which oversees medical, public health, and policy activities concerning the development and assessment of vaccines, blood products, tissues, and related devices and novel therapeutics, including cellular and gene therapies. He moved to the FDA full-time in 2001 from the University of Minnesota, where he was professor of medicine and director of the Division of Infectious Diseases. A graduate of Harvard College, he received his M.D. from the Albert Einstein College of Medicine; did residency and fellowship training at the Hospital of the University of Pennsylvania and at the University of California, Los Angeles (UCLA), where he was also chief medical resident; and is board certified in internal medicine, oncology, and infectious diseases. He trained in the virology laboratory of Jack Stevens at UCLA and has had an active laboratory program in the molecular pathogenesis of infectious diseases. In 1995, his laboratory isolated the etiologic agent of human granulocytic ehrlichiosis and subsequently characterized fundamental events involved in the infection of leukocytes, including their cellular receptors. He is editor of the book *Tick Borne Diseases of Humans*

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published by ASM Press in 2005, and is a staff physician and infectious diseases consultant at the NIH Clinical Center and the National Naval Medical Center-Walter Reed Army Medical Center, as well as adjunct professor of medicine at the University of Minnesota. He is active in a wide variety of clinical, public health, and product development issues, including pandemic and emerging infectious disease threats; bioterrorism preparedness and response; and blood, tissue, and vaccine safety and availability. In these activities, he has worked closely with CDC, NIH, and other HHS components, academia, and the private sector, and he has put into place an interactive team approach to emerging threats. This model was used in the collaborative development and rapid implementation of nationwide donor screening of the U.S. blood supply for West Nile virus. He has been elected to the American Society for Clinical Investigation (ASCI) and to the IOM.

Eduardo Gotuzzo, M.D., is principal professor and director at the Instituto de Medicina Tropical Alexander von Humbolt, Universidad Peruana Cayetan Heredia in Lima, Peru, as well as chief of the Department of Infectious and Tropical Diseases at the Cayetano Heredia Hospital. He is also an adjunct professor of medicine at the University of Alabama, Birmingham, School of Medicine. Dr. Gotuzzo is an active member of numerous international societies and has been president of the Latin America Society of Tropical Disease (2000-2003), the IDSA Scientific Program (2000-2003), the International Organizing Committee of the International Congress of Infectious Diseases (1994 to present), president-elect of the International Society for Infectious Diseases (1996-1998), and president of the Peruvian Society of Internal Medicine (1991-1992). He has published more than 230 articles and chapters as well as six manuals and one book. Recent honors and awards include being named an honorary member of the American Society of Tropical Medicine and Hygiene in 2002, an associate member of the National Academy of Medicine in 2002, an honorary member of the Society of Internal Medicine in 2000, and a distinguished visitor at the Faculty of Medical Sciences, University of Cordoba, Argentina, in 1999. In 1988 he received the Golden Medal for Outstanding Contribution in the Field of Infectious Diseases awarded by Trnava University, Slovakia.

Jo Handelsman, Ph.D., is a Howard Hughes Medical Institute professor in the Departments of Bacteriology and Plant Pathology and chair of the Department of Bacteriology at the University of Wisconsin (UW)–Madison. She received her Ph.D. in molecular biology from the UW–Madison in 1984 and joined the faculty of UW–Madison in 1985. Her research focuses on the genetic and functional diversity of microorganisms in soil and insect gut communities. She is one of the pioneers of functional metagenomics, an approach to accessing the genetic potential of unculturable bacteria in environmental samples. In addition to her research program, Dr. Handelsman is nationally known for her efforts to improve science education and increase the participation of women and minori-

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ties in science at the university level. She cofounded the Women in Science and Engineering Leadership Institute at UW–Madison, which has designed and evaluated interventions intended to enhance the participation of women in science. Her leadership in women in science led to her appointment as the first President of the Rosalind Franklin Society and her service on the National Academies' panel that wrote the 2006 report *Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering*, which documented the issues of women in science and recommended changes to universities and federal funding agencies. In addition to more than 100 scientific research publications, Dr. Handelsman is coauthor of two books about teaching: *Entering Mentoring* and *Scientific Teaching*. Dr. Handelsman is the editor-in-chief of *DNA and Cell Biology* and the series. Controversies in Science and Technology, and a member of the National Academy of Sciences Board on Life Sciences and the IOM Forum on Microbial Threats. She is a National Academies Mentor in the Life Sciences, a fellow in the American Academy of Microbiology and the AAAS, Director of the Wisconsin Program for Scientific Teaching, and codirector of the National Academies Summer Institute on Undergraduate Education in Biology. In 2008 she received the Alice Evans Award from the ASM in recognition of her mentoring, and in 2009 she received the Carski Award from the ASM in recognition of her teaching contributions and in 2009, *Seed Magazine* named her "A Revolutionary Mind" in recognition of her unorthodox ideas.

Carole A. Heilman, Ph.D., is the director of the Division of Microbiology and Infectious Diseases (DMID) at NIAID, a component of NIH-HHS. As director of DMID she has responsibility for scientific direction, oversight, and management of all extramural research programs on infectious diseases (except AIDS) within NIH. In addition, since 2001 Dr. Heilman has played a critical role in launching and directing NIAID's extramural biodefense research program. Previously, Dr. Heilman served as deputy director of NIAID's Division of AIDS for three years. Dr. Heilman has a Ph.D. in microbiology from Rutgers University. She did her postdoctoral work in molecular virology at the National Cancer Institute (NCI) and continued at the NCI as a senior staff fellow in molecular oncology. She moved into health science administration in 1986, focusing on respiratory pathogens, particularly vaccine development. She has received numerous awards for scientific management and leadership, including three HHS Secretary's Awards for Distinguished Service for her contributions to developing pertussis, biodefense, and AIDS vaccines.

David L. Heymann, M.D., is currently chair of the Health Protection Agency, United Kingdom, and head of the Global Health Security Programme at Chatham House, London. Until April 2009, he was assistant director-general for Health Security Environment and representative of the director-general for Polio Eradication at WHO. Prior to that, from July 1998 until July 2003, he was executive

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director of the WHO Communicable Diseases Cluster, which included WHO's programmes on infectious and tropical diseases, and from which the public health response to SARS was mounted in 2003. From October 1995 to July 1998, he was director of the WHO Programme on Emerging and Other Communicable Diseases, and prior to that was the chief of research activities in the WHO Global Programme on AIDS. Dr. Heymann has worked in the area of public health for the past 35 years, 25 of which were on various assignments from the U.S. Centers for Disease Control and Prevention (CDC), and 10 of which have been with WHO. Before joining WHO, Dr. Heymann worked for 13 years as a medical epidemiologist in sub-Saharan Africa (Cameroon, Côte d'Ivoire, Malawi, and the Democratic Republic of Congo, formerly Zaire) on assignment from the CDC in CDC-supported activities. These activities aimed at strengthening capacity in surveillance of infectious diseases and their control, with special emphasis on the childhood immunizable diseases including measles and polio, African hemorrhagic fevers, poxviruses, and malaria. While based in Africa, Dr. Heymann participated in the investigation of the first outbreak of Ebola in Yambuku (former Zaire) in 1976, then again investigated the second outbreak of Ebola in 1977 in Tandala, and in 1995 directed the international response to the Ebola outbreak in Kikwit for WHO. Prior to assignments in Africa he was assigned for two years to India as a medical epidemiologist in the WHO Smallpox Eradication Programme. Dr. Heymann's educational qualifications include a B.A. from the Pennsylvania State University, an M.D. from Wake Forest University, a diploma in tropical medicine and hygiene from the London School of Hygiene and Tropical Medicine, and practical epidemiology training in the 2-year Epidemic Intelligence Service (EIS) of CDC. He is a member of the IOM, and has been awarded the 2004 Award for Excellence of the American Public Health Association, the 2005 Donald Mackay Award from the American Society for Tropical Medicine and Hygiene, and the 2007 Heinz Award on the Human Condition. Dr. Heymann has been visiting professor at Stanford University, the University of Southern California, and the George Washington University School of Public Health; has published over 145 scientific articles on infectious diseases and related issues in peer-reviewed medical and scientific journals; and has authored several chapters on infectious diseases in medical textbooks. He is currently the editor of the 19th edition of the *Control of Communicable Diseases Manual*, a joint publication of the American Public Health Association and WHO.

Phil Hosbach is vice president, New Products and Immunization Policy, at Sanofi Pasteur. The areas under his supervision are new product marketing, state and federal government policy, business intelligence, bids and contracts, medical communications, public health sales, and public health marketing. His current responsibilities include oversight of immunization policy development. He acts as Sanofi Pasteur's principal liaison with CDC. Mr. Hosbach graduated from Lafayette College in 1984 with a degree in biology. He has 20 years of

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pharmaceutical industry experience, including the past 17 years focused solely on vaccines. He began his career at American Home Products in clinical research in 1984. He joined Aventis Pasteur (then Connaught Labs) in 1987 as clinical research coordinator and has held research and development positions of increasing responsibility, including clinical research manager and director of clinical operations. Mr. Hosbach also served as project manager for the development and licensure of Tripedia, the first diphtheria, tetanus, and acellular pertussis (DTaP) vaccine approved by the FDA for use in U.S. infants. During his clinical research career at Aventis Pasteur, he contributed to the development and licensure of seven vaccines, and he has authored or coauthored several clinical research articles. From 2000 through 2002, Mr. Hosbach served on the board of directors for Pocono Medical Center in East Stroudsburg, Pennsylvania. Since 2003 he has served on the board of directors of Pocono Health Systems, which includes Pocono Medical Center.

Stephen A. Johnston, Ph.D., is currently director of the Center for Innovations in Medicine in the Biodesign Institute at Arizona State University. His center focuses on formulating and implementing disruptive technologies for basic problems in health care. The center has three divisions: Genomes to Vaccines, Cancer Eradication, and DocInBox. Genomes to Vaccines has developed high-throughput systems to screen for vaccine candidates and is applying them to predict and produce chemical vaccines. The Cancer Eradication group is working on formulating a universal prophylactic vaccine for cancer. DocInBox is developing technologies to facilitate presymptomatic diagnosis. Dr. Johnston founded the Center for Biomedical Inventions (also known as the Center for Translation Research) at the University of Texas–Southwestern, the first center of its kind in the medical arena. He and his colleagues have developed numerous inventions and innovations, including the gene gun, genetic immunization, TEV (tobacco etch virus) protease system, organelle transformation, digital optical chemistry arrays, expression library immunization, linear expression elements, and others. He also was involved in transcription research for years, first cloning *Gal4* and later discovering functional domains in transcription factors and the connection of the proteasome to transcription. He has been professor at the University of Texas Southwestern Medical Center at Dallas and associate and assistant professor at Duke University. He has been involved in several capacities as an adviser on biosecurity since 1996 and is a member of the WRCE SAB and a founding member of BioChem 20/20.

Kent Kester, M.D., is currently the Commander of the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, Maryland. Dr. Kester holds an undergraduate biology degree from Bucknell University (1982) and an M.D. from Jefferson Medical College (1986). He completed his internship and residency in Internal Medicine at the University of Maryland Hospital/Baltimore VA Medical

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Center (1989) and a fellowship in Infectious Diseases at the Walter Reed Army Medical Center (1995). A malaria vaccine researcher with over 50 authored or coauthored scientific manuscripts and book chapters, Dr. Kester has played a major role in the development of the candidate falciparum malaria vaccine known as RTS,S, having safely conducted the largest number of experimental malaria challenge studies ever attempted to date. Dr. Kester's previous military medical research assignments have included: director of the WRAIR Malaria Serology Reference Laboratory; chief, Clinical Malaria Vaccine Development Program; Chief of the WRAIR Clinical Trials Center; and director of the WRAIR Division of Regulated Activities. He currently is a member of the Steering Committee of the IAID/USUHS Infectious Disease Clinical Research Program, as well as multiple NIAID Safety Monitoring Committees. He also serves as the consultant to the U.S. Army Surgeon General in Medical Research and Development. Board-certified in both internal medicine and infectious diseases, Dr. Kester is also a fellow of both the American College of Physicians and the IDSA. He holds faculty appointments at both the Uniformed Services University of the Health Sciences and the University of Maryland School of Medicine.

Gerald T. Keusch, M.D., is associate provost and associate dean for global health at Boston University and Boston University School of Public Health. He is a graduate of Columbia College (1958) and Harvard Medical School (1963). After completing a residency in internal medicine, fellowship training in infectious diseases, and two years as an NIH research associate at the Southeast Asia Treaty Organization (SEATO) Medical Research Laboratory in Bangkok, Thailand, Dr. Keusch joined the faculty of the Mt. Sinai School of Medicine in 1970, where he established a laboratory to study the pathogenesis of bacillary dysentery and the biology and biochemistry of Shiga toxin. In 1979 he moved to Tufts Medical School and New England Medical Center in Boston to found the Division of Geographic Medicine, which focused on the molecular and cellular biology of tropical infectious diseases. In 1986 he integrated the clinical infectious diseases program into the Division of Geographic Medicine and Infectious Diseases, continuing as division chief until 1998. He has worked in the laboratory and in the field in Latin America, Africa, and Asia on basic and clinical infectious diseases and HIV/AIDS research. From 1998 to 2003, he was associate director for international research and director of the Fogarty International Center at NIH. Dr. Keusch is a member of ASCI, the Association of American Physicians, the ASM, and the IDSA. He has received the Squibb (1981), Finland (1997), and Bristol (2002) awards of the IDSA. In 2002 he was elected to the IOM.

Rima F. Khabbaz, M.D., is the deputy director for infectious diseases at the Centers for Disease Control and Prevention (CDC). Most recently, she served as director of the National Center for Preparedness, Detection, and Control of Infectious Diseases (NCPDCID). Her other leadership roles at CDC include

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director, acting deputy director, and associate director for epidemiologic science in the National Center for Infectious Diseases (NCID) and deputy director and associate director for science in the Division of Viral and Rickettsial Diseases. Dr. Khabbaz first joined CDC as an Epidemic Intelligence Service (EIS) Officer in NCID's Hospital Infections Program and later served as a medical epidemiologist in NCIDs Retrovirus Diseases Branch. There, she made major contributions to defining the U.S. epidemiology of non-HIV retroviruses, specifically human T lymphotropic viruses (HTLV) I and II, and in developing guidance for counseling HTLV–infected persons. Following the 1993 outbreak of hantavirus pulmonary syndrome in the southwestern United States, she led CDC's efforts to set up national surveillance for this syndrome. Dr. Khabbaz also played a leading role in developing and coordinating CDC's blood safety and food safety programs related to viral diseases. She has served in leadership positions in many of CDC's responses to outbreaks of new and/or reemerging viral infections, including Nipah, Ebola, West Nile virus, SARS, and monkeypox, and led the CDC field team to the nation's capital during the public health response to the 2001 anthrax attacks. Dr. Khabbaz is a graduate of the American University of Beirut in Beirut, Lebanon, where she obtained both her bachelor's degree in science (biology/chemistry) and her medical doctorate degree. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland in Baltimore. She is also a graduate of the National Preparedness Leadership Initiative at Harvard University and of the Public Health Leadership Institute at the University of North Carolina. Dr. Khabbaz has served on several Advisory Committees including FDA's Blood Product Advisory Committee. The author/co-author of more than 100 scientific articles, book chapters, and reviews, Dr. Khabbaz is a fellow of the Infectious Diseases Society of America (IDSA), and holds membership in the American Epidemiological Society, the American Society for Microbiology, and the American Society for Tropical Medicine and Hygiene. She is also a member of IDSA's National and Global Public Health Committee and of the Institute of Medicine's Forum on Microbial Threats and serves as a clinical associate professor of medicine (infectious diseases) at Emory University.

Lonnie J. King, D.V.M., became the 10th dean of the College of Veterinary Medicine at The Ohio State University in September 2009. Dr. King most recently directed the National Center for Zoonotic, Vector-Borne and Enteric Diseases at the Centers for Disease Control. He served Michigan State University as dean for 10 years and prior to that spent 19 years with the U.S. Department of Agriculture in the Animal and Plant Health Inspection Service. As the nation's chief veterinarian, he worked extensively in global trade agreements and has testified before Congress on issues of emerging diseases and animal health. A member of the National Academies of Science, Dr. King is board certified by the American College of Veterinary Preventive Medicine. He received his bachelor's degree

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and Doctor of Veterinary Medicine degree from Ohio State, a master's degree in epidemiology from the University of Minnesota, and a master's degree in public administration from American University. An expert in "One Health" and the emergence of new diseases, he is a highly sought-after speaker regarding the convergence of human and animal health.

Stanley M. Lemon, M.D., is the John Sealy Distinguished University Chair and director of the Institute for Human Infections and Immunity at the University of Texas Medical Branch (UTMB) at Galveston. He received his undergraduate A.B. degree in biochemical sciences from Princeton University summa cum laude and his M.D. with honors from the University of Rochester. He completed postgraduate training in internal medicine and infectious diseases at the University of North Carolina at Chapel Hill and is board certified in both. From 1977 to 1983 he served with the U.S. Army Medical Research and Development Command, followed by a 14-year period on the faculty of the University of North Carolina School of Medicine. He moved to UTMB in 1997, serving first as chair of the Department of Microbiology and Immunology, then as dean of the School of Medicine from 1999 to 2004. Dr. Lemon's research interests relate to the molecular virology and pathogenesis of the positive-stranded RNA viruses responsible for hepatitis. He has had a long-standing interest in antiviral and vaccine development and has served as chair of FDA's Anti-Infective Drugs Advisory Committee. He is the past chair of the Steering Committee on Hepatitis and Poliomyelitis of the WHO Programme on Vaccine Development. He is past chair of the NCID-CDC Board of Scientific Counselors and currently serves as a member of the U.S. Delegation to the U.S.–Japan Cooperative Medical Sciences Program. He was cochair of the NAS Committee on Advances in Technology and the Prevention of Their Application to Next Generation Biowarfare Threats, and he recently chaired an IOM study committee related to vaccines for the protection of the military against naturally occurring infectious disease threats.

Edward McSweegan, Ph.D., is a program officer at NIAID. He graduated from Boston College with a B.S. in biology in 1978. He has an M.S. in microbiology from the University of New Hampshire and a Ph.D. in microbiology from the University of Rhode Island. He was an NRC associate from 1984 to 1986 and did postdoctoral research at the Naval Medical Research Institute in Bethesda, Maryland. Dr. McSweegan served as a AAAS diplomacy fellow in the U.S. State Department from 1986 to 1988, where he helped to negotiate science and technology agreements with Poland, Hungary, and the former Soviet Union. After moving to NIH, he continued to work on international health and infectious disease projects in Egypt, Israel, India, and Russia. Currently, he manages NIAID's bilateral program with India, the Indo–U.S. Vaccine Action Program, and he represents NIAID in the HHS Biotechnology Engagement Program with Russia and related countries. He is a member of AAAS, the ASM, and the

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National Association of Science Writers. He is the author of numerous journal and freelance articles.

Paul Miller, Ph.D., is chief scientific officer for antibacterials research. He received his undergraduate degree in Biology from LeMoyne College, and subsequently earned a Ph.D. in microbiology and immunology from The Albany Medical College in 1987. Following 4 years of post-doctoral studies on yeast molecular genetics at the National Institutes of Health in Bethesda, Maryland, Paul joined the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company in Ann Arbor, Michigan, in 1990 as a senior scientist in the infectious diseases department, where he developed a number of novel screens and mechanism-of-action tools. He then moved to Pfizer in 1997 as manager of the antibacterials biology research group within the Antibacterials, Immunology and Cancer Zone at the Groton, Connecticut, research labs, and has taken on increasing responsibility since that time. In his current role, he is responsible for all antibacterial research activities through early clinical development, as well as collaboratively establishing research and development strategies in this disease area. His specific research interests and expertise include genetic mechanisms of intrinsic antibiotic resistance in bacteria, as well as the use of novel genetic technologies for the elucidation of antibiotic mechanisms of action.

Stephen S. Morse, Ph.D., is professor of epidemiology and founding director of the Center for Public Health Preparedness at the Mailman School of Public Health of Columbia University. He returned to Columbia in 2000 after 4 years in government service as program manager at the Defense Advanced Research Projects Agency, where he codirected the Pathogen Countermeasures Program and subsequently directed the Advanced Diagnostics Program. Before coming to Columbia, he was assistant professor of virology at the Rockefeller University in New York, where he remains an adjunct faculty member. He is the editor of two books, *Emerging Viruses* (Oxford University Press, 1993; paperback, 1996), which was selected by *American Scientist* for its list of 100 Top Science Books of the 20th Century, and *The Evolutionary Biology of Viruses* (Raven Press, 1994). He was a founding section editor of the CDC journal *Emerging Infectious Diseases* and was formerly an editor-in-chief of the Pasteur Institute's journal *Research in Virology*. Dr. Morse was chair and principal organizer of the 1989 NIAID-NIH Conference on Emerging Viruses, for which he originated the term and concept of emerging viruses/infections. He has served as a member of the IOM-NAS Committee on Emerging Microbial Threats to Health, chaired its Task Force on Viruses, and was a contributor to the resulting report *Emerging Infections* (1992). He was a member of the IOM Committee on Xenograft Transplantation. Dr. Morse also served as an adviser to WHO and several government agencies. He is a fellow of the New York Academy of Sciences and a past chair of its microbiology section, a fellow of the American Academy of Microbiology

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of the American College of Epidemiology, and an elected life member of the Council on Foreign Relations. He was the founding chair of ProMED, the non-profit international Program to Monitor Emerging Diseases, and was one of the originators of ProMED-mail, an international network inaugurated by ProMED in 1994 for outbreak reporting and disease monitoring using the Internet. Dr. Morse received his Ph.D. from the University of Wisconsin, Madison.

Michael T. Osterholm, Ph.D., M.P.H., is director of the Center for Infectious Disease Research and Policy and director of the NIH-sponsored Minnesota Center for Excellence in Influenza Research and Surveillance at the University of Minnesota. He is also professor at the School of Public Health and adjunct professor at the Medical School. Previously, Dr. Osterholm was the state epidemiologist and chief of the acute disease epidemiology section for the Minnesota Department of Health. He has received numerous research awards from NIAID and CDC. He served as principal investigator for the CDC-sponsored Emerging Infections Program in Minnesota. He has published more than 300 articles and abstracts on various emerging infectious disease problems and is the author of the best-selling book *Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe*. He is past president of the Council of State and Territorial Epidemiologists. He currently serves on the IOM Forum on Microbial Threats. He has also served on the IOM Committee to Ensure Safe Food from Production to Consumption, and on the IOM Committee on the Department of Defense Persian Gulf Syndrome Comprehensive Clinical Evaluation Program, and as a reviewer for the IOM report *Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response*.

George Poste, Ph.D., D.V.M., is chief scientist, Complex Adaptive Systems Initiative (CASI) at Arizona State University (ASU). He assumed this post in February 2009. This program links expertise across the university in research on synthetic biology, ubiquitous sensing and healthcare informatics for personalized medicine. He is also a Regents' Professor and holds the Del E. Webb Chair in Health Innovation at ASU. From 2003 to 2008 he founded the Biodesign Institute at ASU (www.biodesign.asu.edu/). In creating this Institute, Dr. Poste designed and built 400,000 sq. ft. of new facilities, achieved cumulative research funding of $225 million and recruited over 60 faculty, including three members of the National Academies of Science and Engineering. In addition to his academic post he serves as chief executive of a consulting company, Health Technology Networks, which specializes in the application of genomic technologies and computing in healthcare. He is chairman of Orchid Biosciences, the leading company in DNA forensic analysis, and serves on the board of directors of Monsanto, Exelixis, and Caris Dx. From 1992 to 1999, he was chief science and technology officer and president, R&D of SmithKline Beecham (SB). During his tenure at SB he was associated with the successful registration of 31 drug, vaccine and diagnostic products. In 2004,

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he was named as "R&D Scientist of the Year" by *R&D Magazine* and in 2006 he received the Einstein award from the Global Business Leadership Council. He has published over 350 research papers and edited 14 books on pharmaceutical technologies and oncology. He has received honorary degrees in science, law, and medicine for his research contributions and was honored in 1999 by HM Queen Elizabeth II as a Commander of the British Empire for his contributions to international security. He is a Fellow of the Royal Society, the Royal College of Pathologists, and the UK Academy of Medicine, a Distinguished Fellow at the Hoover Institution, Stanford University, and a member of the Council for Foreign Relations. He is a member of the Defense Science Board and Health Board of the U.S. Department of Defense (DOD) and the U.S. Institute of Medicine's Board on Global Health. He is chair of the DOD Task Force on Bioterrorism and the newly launched DOD Task Force on Synthetic Biology.

John C. Pottage, Jr., M.D., has been vice president for Global Clinical Development in the Infectious Disease Medicine Development Center at GlaxoSmithKline since 2007. Previously he was senior vice president and chief medical officer at Achillion Pharmaceuticals in New Haven, Connecticut. Achillion is a small biotechnology company devoted to the discovery and development of medicines for HIV, hepatitis C virus (HCV), and resistant antibiotics. Dr. Pottage initially joined Achillion in May 2002. Prior to Achillion, Dr. Pottage was medical director of Antivirals at Vertex Pharmaceuticals. During this time he also served as an associate attending physician at the Tufts New England Medical Center in Boston. From 1984 to 1998, Dr. Pottage was a faculty member at Rush Medical College in Chicago, where he held the position of associate professor, and also served as the medical director of the Outpatient HIV Clinic at Rush-Presbyterian-St. Luke's Medical Center. While at Rush, Dr. Pottage was the recipient of several teaching awards and is a member of the Mark Lepper Society. Dr. Pottage is a graduate of St. Louis University School of Medicine and Colgate University.

Gary A. Roselle, M.D., received his medical degree from the Ohio State University School of Medicine in 1973. He served his residency at the Northwestern University School of Medicine and his infectious diseases fellowship at the University of Cincinnati School of Medicine. He is program director for infectious diseases for the Department of Veterans Affairs Central Office in Washington, DC, as well as the chief of the medical service at the Cincinnati VA Medical Center. He is a professor of medicine in the Department of Internal Medicine, Division of Infectious Diseases, at the University of Cincinnati College of Medicine. Dr. Roselle serves on several national advisory committees. In addition, he is currently heading the Emerging Pathogens Initiative for the VA. He has received commendations from the under secretary for health for the VA and the secretary of VA for his work in the Infectious Diseases Program for the VA. He has been an invited speaker at several national and international meetings and has published more than 90 papers and several book chapters.

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Kevin Russell, M.D., M.T.M.&H., F.I.D.S.A. CAPT MC USN, graduated from the University of Texas Health Science Center San Antonio Medical School in 1990; after a family practice internship he was accepted into the Navy Undersea Medicine program. He was stationed in Panama City, Florida, at the Experimental Diving Unit where he worked in diving medicine research from 1991 to 1995. After a preventive medicine residency with a masters in tropical medicine and hygiene, he was transferred to Lima, Peru, where he became head of the Virology Laboratory. His portfolio included febrile illness (largely arboviral in origin) and HIV surveillance studies in eight different countries of South America, as well as prospective dengue transmission studies. In 2001, he moved back to the states and became the director of the Respiratory Disease Laboratory at the Naval Health Research Center in San Diego, California. Febrile respiratory illness surveillance in recruits of all services was expanded into shipboard populations, Mexican border populations, support for outbreaks, and deployed settings. Validation and integration of new and emerging advanced diagnostic capabilities, utilizing the archives of specimens maintained at the laboratory, became a priority. A BSL-3-Enhanced is currently nearing completion. Projects expanded in 2006 to clinical trials support as Dr. Russell became the principal investigator for the Navy site in the FDA Phase 3 adenovirus vaccines trial, and more recently to support the Phase 4 post-marketing trial of the recently FDA-approved ACAM2000 smallpox vaccine. Dr. Russell recently became director of the Department of Defense Global Emerging Infections Surveillance and Response System (DOD-GEIS).

Janet Shoemaker is director of the American Society for Microbiology's Public Affairs Office, a position she has held since 1989. She is responsible for managing the legislative and regulatory affairs of this 42,000-member organization, the largest single biological science society in the world. Previously, she held positions as assistant director of public affairs for ASM; as ASM coordinator of the U.S.–U.S.S.R. Exchange Program in Microbiology, a program sponsored and coordinated by the NSF and the U.S. Department of State; and as a freelance editor and writer. She received her baccalaureate, cum laude, from the University of Massachusetts and is a graduate of the George Washington University programs in public policy and in editing and publications. She is a member of Women in Government Relations, the American Society of Association Executives, and AAAS. She has coauthored articles on research funding, biotechnology, biodefense, and public policy issues related to microbiology.

P. Frederick Sparling, M.D., is the J. Herbert Bate Professor Emeritus of Medicine, Microbiology, and Immunology at the University of North Carolina (UNC) at Chapel Hill, and professor of medicine, Duke University. He is director of the North Carolina Sexually Transmitted Infections Research Center and also the Southeast Regional Centers of Excellence in Biodefense and Emerging Infections. Previously he served as chair of the Department of Medicine and chair of the Department of Microbiology and Immunology at UNC. He was presi-

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dent of the Infectious Diseases Society of America from 1996 to 1997. He was also a member of the IOM Committee on Microbial Threats to Health (1990-1992) and the IOM Committee on Emerging Microbial Threats to Health in the 21st Century (2001-2003). Dr. Sparling's laboratory research has been on the molecular biology of bacterial outer membrane proteins involved in pathogenesis, with a major emphasis on gonococci and meningococci. His work helped to define the genetics of antibiotic resistance in gonococci and the role of iron-scavenging systems in the pathogenesis of human gonorrhea.

Terence Taylor is director of the Global Health and Security Initiative and president and director of the International Council for the Life Sciences (ICLS). He is responsible for the overall direction of the ICLS and its programs, which have the goal of enhancing global biosafety and biosecurity. From 1995 to 2005, he was assistant director of the International Institute for Strategic Studies (IISS), a leading independent international institute, and president and executive director of its U.S. office (2001-2005). He studies international security policy, risk analysis, and scientific and technological developments and their impact on political and economic stability worldwide. He was one of IISS's leading experts on issues associated with nuclear, biological, and chemical weapons and their means of delivery. In his previous appointments, he has had particular responsibilities for issues affecting public safety and security in relation to biological risks and advances in the life sciences. He was one of the commissioners to the United Nations Special Commission on Iraq, for which he also conducted missions as a chief inspector. He was a science fellow at the Center for International Security and Cooperation at Stanford University, where he carried out, among other subjects, studies of the implications for government and industry of the weapons of mass destruction treaties and agreements. He has also carried out consultancy work for the International Committee of the Red Cross (ICRC) on the implementation and development of the laws of armed conflict and serves as a member of the editorial board of the *ICRC Review*. He has served as chairman of the World Federation of Scientists' Permanent Monitoring Panel on Risk Analysis. He was a career officer in the British Army on operations in many parts of the world, including counterterrorist operations and United Nations peacekeeping. His publications include monographs, book chapters, and articles for, among others, Stanford University, the World Economic Forum, Stockholm International Peace Research Institute (SIPRI), the Crimes of War Project, the *International Herald Tribune*, the *Wall Street Journal*, the *International Defence Review*, the *Independent* (London), *Tiempo* (Madrid), the *International and Comparative Law Quarterly*, the *Washington Quarterly*, and other scholarly journals, including unsigned contributions to IISS publications.

Murray Trostle, Dr.P.H., is a foreign service officer with the U.S. Agency for International Development (USAID), presently serving as the deputy director of

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the Avian and Pandemic Influenza Preparedness and Response Unit. Dr. Trostle attended Yale University, where he received a master's in public health in 1978, focusing on health services administration. In 1990, he received his doctorate in public health from UCLA. His research involved household survival strategies during famine in Kenya. Dr. Trostle has worked in international health and development for approximately 38 years. He first worked overseas in the Malaysian national malaria eradication program in 1968 and has since focused on health development efforts in the former Soviet Union, Africa, and Southeast Asia. He began his career with USAID in 1992 as a postdoctoral fellow with AAAS. During his career he has worked with a number of development organizations such as the American Red Cross, Project Concern International, and the Center for Development and Population Activities. With USAID, Dr. Trostle has served as director of the child immunization cluster, where he was chairman of the European Immunization Interagency Coordinating Committee and the USAID representative to the Global Alliance on Vaccines and Immunization. Currently, Dr. Trostle leads the USAID Infectious Disease Surveillance Initiative as well as the Avian Influenza Unit.

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