Epidemiology of Pandemic Influenza:
Use of Surveillance and Modeling for Pandemic Preparedness

Arnold S. Monto,1 Lorraine Comanor,2 David K. Shay,3 and William W. Thompson3
1Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor; 2Independent Clinical Research Consultant, Truckee, California; 3Centers for Disease Control and Prevention, Atlanta, Georgia

Along with continual enhancement of current influenza surveillance programs, pandemic preparedness also involves application of current surveillance techniques to past pandemics to identify their viruses and patterns, as well as estimation of the potential burden of future pandemics. Although mortality surveillance has been in place in selected locations for more than a century, the recent development of molecular diagnostics has shed new light on the origin and structure of the viruses responsible for the past 3 pandemics, allowing for comparisons with new viruses identified through ongoing viral surveillance. Models previously used to estimate hospitalizations and mortality associated with past epidemics and pandemics have evolved to estimate the burden and required surge capacity of future pandemics of different severities.

Annual or seasonal influenza epidemics are caused by the previous seasons’ viruses or by ones with slight antigenic changes. In contrast, a pandemic is caused by an influenza A virus that contains hemagglutinin (HA) for which there is no preexisting immunity, facilitating the virus’s rapid spread throughout the world. During the past 117 years, 4 pandemics have occurred; of these, the 1918 pandemic caused the most-severe morbidity and mortality. Although some mortality surveillance has been in place in selected areas since the 1889 pandemic, new surveillance techniques have increased our understanding of features of the past 3 pandemics [1–3]. Careful consideration of surveillance data from previous pandemics may suggest activities that will allow us to better prepare for the next pandemic, whether caused by an influenza A(H5N1) virus or another, novel influenza virus [3, 4].

This review will cover the lessons learned from the past pandemics, focusing chiefly on the origin and structure of the causative viruses, the mortality estimates associated with each, and modeling efforts to estimate surge capacity needs in the event of a future moderate or severe pandemic.

LESSONS FROM THE PAST: CONTRIBUTION OF SURVEILLANCE

A review of the currently available data from past pandemics confirms that a consistent pattern in pandemic epidemiological profiles does not exist—not for the periodicity, for the mechanisms of strain formation, for the origin, for the timing between waves, or for the shape of mortality curves [5, 6] (table 1). Despite these varied patterns, common themes can be found in the continuing evolution of morbidity, mortality, and viral surveillance techniques.

Establishment of viral benchmarks through viral sequencing and reconstruction. Perhaps the most important factor to discover about any pandemic is its cause. At the time of the 1889 and 1918 pandemics, identification of the causative pathogens was beyond society’s scientific capability. Unfortunately, no speci-
Table 1. Information collected from the 3 pandemics of the 20th century.

<table>
<thead>
<tr>
<th>Pandemic</th>
<th>Influenza A subtype</th>
<th>Origin</th>
<th>Viral change</th>
<th>Documentation of viral change</th>
<th>Estimated US deaths, no. [reference]</th>
<th>Shape of mortality curve</th>
<th>Population(s) at risk</th>
<th>Documentation of mortality statistics</th>
<th>Spread and crest</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957</td>
<td>H2N2</td>
<td>Asia</td>
<td>Reassortment of 3 segments from avian virus (HA, NA, and polymerase protein) in combination with 5 genetic segments of the H1N1 virus</td>
<td></td>
<td>69,800 [12]</td>
<td>U or J</td>
<td>Infants and elderly</td>
<td>NCHS</td>
<td>Major wave in Apr 1957 in Hong Kong, in May in Japan, in Jun in Chile, in Aug in the US, with a peak in Oct and a second wave in Feb 1958</td>
</tr>
</tbody>
</table>

NOTE. HA, hemagglutinin; NA, neuraminidase; NCHS, National Center for Health Statistics.
mens from the 1889 pandemic were archived from which nucleic acid could be derived; hence, any relationship between the causative virus and all subsequent pandemic viruses is impossible to determine [5]. Reconstruction of pre-1957 viruses is dependent on archived specimens from infected individuals that contain viral nucleic acid; only recently was the entire genome of the 1918 virus derived. It is now clear that the 1918 virus was fully avian in origin and resulted from a mutation; thus, it may have had little or no relation to any previous human influenza virus [5].

Complete identification of viruses responsible for past pandemics provides a reference for comparison of recently identified novel influenza viruses and may provide clues to the mechanism of their evolution and their pathogenicity [7]. The development of molecular diagnostics in the 1970s has provided the ability to determine not only viral sequences but also the steps necessary to create a new virus. Taubenberger et al. showed that all 8 separate RNA segments of the 1918 virus originated from an avian H1N1 virus that had developed a mutation in the HA gene, facilitating infection of mammals [5]. In addition, these authors pointed out that the amino acid changes in the heterotrimeric polymerase complex noted in the 1918 strain have also been noted in H5N1 and H7N7 viruses that have caused fatal human infections [8]. Using mouse models, Tumpey et al. [7] demonstrated the polygenic virulence of the 1918 virus; the greatest pathogenicity was observed only when the entire genome was present, not just the HA or neuraminidase (NA) genes. These important studies serve as a guide for future viral surveillance and its applications.

Retrospective analyses of the 1957 and 1968 viruses have shown another mechanism whereby viruses of pandemic potential evolve. Both of these viruses resulted from reassortment of a Eurasian wild waterfowl virus with a previously circulating human H1N1 virus [5]. Characterization of these viruses provided demonstrations of antigenic shift, a process whereby new viral subtypes are produced through reassortment [9]. The 1957 Asian H2N2 virus appears to have evolved from dual infection with an avian H2N2 virus and a human H1N1 virus in an individual mammal, perhaps a human or a pig [10]. The result was a new virus that contained 3 genetic segments from an avian virus in combination with 5 segments from an H1N1 virus. In 1968, the appearance of the Hong Kong H3N2 virus resulted after a reassortment during which only 2 segments were replaced (table 1). Continued viral surveillance has allowed the characterization of viruses that have caused most of the subsequent human influenza virus infections; in fact, it appears that 5 of 8 genome segments found in currently circulating H3N2 viruses originated from the 1918 virus [10]. Continual surveillance is critical to early identification of new strains for the development of influenza vaccines for the following season. It also may give clues for the identification of viruses with pandemic potential.

The role of mortality estimates and viral surveillance in pandemic preparedness. Planning for a future pandemic may benefit from the estimation of morbidity and mortality of past pandemics, including the identification of the groups at greatest risk. US mortality rates for the three 20th century pandemics have been estimated [11, 12] (table 1). Mortality rates during the latter 2 pandemics were far lower than those during the 1918 pandemic, in part because of the lower virulence of the strains involved and the availability of new medical interventions, including vaccines and antibiotics for bacterial superinfections. These estimates obviously are based on the population structure at the time and do not reflect current US demographics, in terms of either the growth of the population or the increased proportion of the population that is >65 years of age. However, they can be used as a basis for modeling future pandemic scenarios in larger populations. The surveillance activities that contributed to these estimates are described in the accompanying article by Thompson et al. [13].

Effective viral surveillance, including identification of new viruses and their culture, is critical to the development of a successful vaccination program. Early influenza vaccines, made against the previous year’s strains, were often not produced in sufficient quantity and were sometimes ineffective by the time the population was vaccinated the following year [4]. Enhanced viral surveillance over time has improved the vaccine development process, making it more likely that strains circulating during a given season have been captured in the vaccine. Additionally, by documenting the burden of influenza, surveillance data have helped in the past and should help in the future to increase compliance with the vaccination program. For example, over the past 15 years, these data have contributed to an increase in the percentage of elderly individuals receiving vaccination, a percentage that has recently plateaued [14].

Early identification of a novel strain with pandemic potential could possibly restrict its spread and provide several weeks of pandemic preparation time, particularly for the production of vaccine seed strains [15]. Although a vaccine, especially one that may require 2 doses, may not be the key to stemming the pandemic at its inception, it is likely to help minimize the impact of a second wave of pandemic.

Determination of the shape of the mortality curve: its role in planning for surge capacity. Determination of shapes of mortality curves from past pandemics is useful for characterization of the variability in mortality rates [15, 16] (figure 1). Such knowledge might facilitate planning for vaccine and antiviral prioritization and surge capacity. In most epidemics and pandemics for which we have data, the curve of influenza deaths by age at death has been U or J shaped, with most deaths occurring in the very young and the elderly and relatively few deaths occurring in those in between [5]. This pattern was observed in the late part of the 1889 pandemic occurring in
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1892 in Massachusetts, as well as in the 1957 and 1968 pandemics [3, 9]. Data from the United Kingdom during early waves of the 1889 pandemic, however, suggested a different pattern, with another mortality peak among young adults. Modeling of mortality data from the autumn wave of the 1918 pandemic clearly demonstrated a W-shaped curve. This pattern was similar to a U-shaped curve, with an added mortality peak among young adults and a relative sparing of elderly individuals. During the 1918 pandemic, individuals <65 years of age accounted for 99% of all excess influenza-related deaths, compared with 36% and 48% in the 1957 and 1968 pandemics, respectively [5].

The different mortality curves underscore one of the uncertainties associated with pandemic influenza viruses. These differences may, in part, be explained by the genetics of the virus itself, the levels of preexisting immunity to other influenza viruses (perhaps influenced by the proximity of the appearance of a pandemic virus in relation to other pandemics), and the immune response of infected individuals. For example, it is assumed that if young adults experience the highest burden of disease in a future pandemic, greater medical surge capacity might be required than if the very young and elderly are the chief targets.

**IMPLICATION OF RECENT REPORTS OF H5N1 INFECTIONS ON PANDEMIC SURVEILLANCE EFFORTS**

Reports of human infection with avian H5N1 viruses are of concern not only because of their accompanying high mortality rates but also because of the unprecedented epizootic poultry epidemic. Should this particular virus, like the 1918 virus before it, adapt to permit human-to-human transmission, a devastating pandemic could result. The first indication that this virus could infect humans came from Hong Kong in 1997, where there were 18 confirmed cases and 6 deaths [17]. The virus subsequently disappeared, and, when it reemerged, it had evolved and changed both antigenically and genetically. Ten countries—China, Vietnam, Thailand, Indonesia, Cambodia, and, more recently, Turkey, Iraq, Azerbaijan, Djibouti, and Egypt—have reported H5N1 infection cases in humans. In a few isolated circumstances, investigation suggests that a single generation of person-to-person transmission may have occurred. Nevertheless, as of 23 August 2006, 241 cases with 141 deaths have been reported [18]. Also, the current overall case mortality is 58.5%, with a median age at death of 20 years among the first 152 cases [17, 18]. To date, >200 million poultry have died or been culled in an attempt to contain the virus [18].

The Office International des Epizooties (OIE), an international organization that promotes worldwide animal disease control, is developing influenza surveillance guidelines to cover birds, domestic animals, wildlife, and humans. Currently, a number of countries report detection of H5N1 virus in poultry and/or wild birds to the World Animal Health Organization. These reports have led to increased surveillance by the World Health Organization (WHO) H5 Reference Laboratory and its closer cooperation with the WHO Working Group on Research at the Human/Animal Interface. The OIE, the Food and Agriculture Organization, and the WHO are developing a veterinary influenza network to increase surveillance and speed the diagnosis and reporting of novel strains [4].

**USE OF MODELS FOR FUTURE PROJECTIONS**

With the increase in both the US population and in the fraction of its elderly residents, we can expect an increasing annual impact of seasonal influenza on morbidity and mortality. By contrast, influenza pandemic risk assessment is considered to be an uncertain art [6]. By extrapolating estimates of mortality, hospitalizations, and attack rates from the 3 pandemics of the 20th century to a current US population, Meltzer et al. recently estimated the economic impact of moderate and severe pandemics [19]. These estimates, which do not take into account

<table>
<thead>
<tr>
<th>Event and/or required care</th>
<th>Moderate pandemic (as in 1957 and 1968)</th>
<th>Severe pandemic (as in 1918)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness</td>
<td>90 million (30%)</td>
<td>90 million (30%)</td>
</tr>
<tr>
<td>Outpatient medical care</td>
<td>45 million (50%)</td>
<td>45 million (50%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>865,000</td>
<td>9,900,000</td>
</tr>
<tr>
<td>ICU care</td>
<td>128,750</td>
<td>1,485,000</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>64,875</td>
<td>742,500</td>
</tr>
<tr>
<td>Death</td>
<td>209,000</td>
<td>1,903,000</td>
</tr>
</tbody>
</table>

**NOTE.** Estimates based on extrapolation from past pandemics in the US; they do not permit impact of interventions not available during 20th century pandemics. Data are from [20]. ICU, intensive care unit.
recent medical advances that might decrease some of the un-
toward events, as well as other variables that are impossible to
predict, are shown in table 2. The model assumes that the

greatest economic cost is due to death and, therefore, that the
greatest economic returns will come from measures that prevent
death. The most cost-effective measure would be vaccination
of 60% of the population [19]. However, if 2 vaccinations are
required, a 60% vaccination rate is unlikely during the first
wave of a pandemic [19]. Estimates of this nature are useful
in planning for implementation of vaccine programs and for
medical surge capacity.

A recently organized research network funded by the Na-
tional Institutes of Health, called Models of Infectious Disease
Agent Study (MIDAS), has been developing computer-based
simulations of pandemic influenza. By simulating outbreaks
of infection with a pandemic influenza strain, the network con-
tinues to evaluate the effects of various intervention measures,
such as school closures or vaccination programs, on containing
the spread of pandemic viruses [21–23].

Online models offered by the CDC. The CDC provides
online modeling tools, FluAid [24] and Flu Surge [25], based
on Meltzer’s studies [19], to help public health planners and
policy makers plan and prepare for the next pandemic. FluAid
provides estimates of the total number of deaths, hospitaliza-
tions, and outpatient visits before interventions are applied, for
a moderate (1968-like) or a severe (1918-like) pandemic. Es-
timates from FluSurge models demonstrate the impact of an
influenza pandemic on the demand for hospital-based re-
sources, such as intensive-care-unit beds and ventilators. Both
models assume a baseline 25% attack rate, but this rate may
be changed by the user. These software programs can use state-
specific statistics to approximate the impact of a pandemic on
a given area. By entering state-specific rates for outpatient visits,
hospitalizations, and/or deaths, state health officials can cal-
culate the expected number of these events during a pandemic.
These programs are available free of charge [24, 25].

CURRENT ISSUES IN PANDEMIC
PREPAREDNESS

Surveillance and modeling have provided invaluable lessons
from past pandemics. Improvements in both of these endeavors
will undoubtedly improve preparation for future pandemics
and increase information gained from them.

A pandemic caused by a novel virus with pathogenicity ap-
proaching that of the 1918 virus could have far more devas-
tating consequences nearly a century later, when the world’s
population has more than tripled to ~6.5 billion [26]. Even
with modern antiviral and antibacterial drugs, it is estimated
that the appearance of such a virus could cause close to 3
million deaths in the United States and >100 million deaths
worldwide [5, 19]. A pandemic caused by an H5N1 virus could
potentially cause even more deaths [5]. Both increased popu-
lation, including more elderly people who are often likely to
have an increased mortality risk, and increased global travel
suggest that estimates of such magnitude are, indeed, possible.
As an example, in 2004, 763 million people crossed interna-
tional borders, an increase of 73% over 15 years [27].

During a pandemic alert and a pandemic period, interna-
tional surveillance will help to guide the public health response.
The impact of good surveillance on outbreak containment was
demonstrated in Hong Kong in 1997, with the culling of chick-
ens after the identification of the avian H5N1 virus, as well as
during the coordinated response to severe acute respiratory
syndrome in Vancouver, Canada [9, 26, 28, 29]. Timely inter-
national surveillance, however, is not always easy to achieve.
Sovereign countries cannot be forced to report outbreaks to an
international body such as the WHO. Because identifying and
culling infected poultry have major economic consequences in
many parts of the world, compliance may be less than optimal.
The WHO may need to strengthen surveillance programs in
areas that lack the financial resources for their implementation.
Clinicians and laboratory workers worldwide will need to in-
crease efforts to recognize novel influenza A subtypes. In the
current pandemic alert period, it will be important to increase
surveillance worldwide and to keep models updated for better
estimations of medical and public health surge capacity needs.
During a pandemic, astute clinical diagnoses will provide the
mainstay of surveillance, and education will be needed to help
the clinician recognize the first few unusual cases. However,
new methods of surveillance may still become necessary, if
clinicians are overwhelmed and lack the time to report cases.

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