Seasonal and Pandemic Influenza: A 2007 Update on Challenges and Solutions

Arnold S. Monto,1,2 and Richard J. Whitley3,4,5,6,7
1Department of Epidemiology, University of Michigan School of Public Health, 2University of Michigan Bioterrorism Preparedness Initiative, Ann Arbor; 3Departments of Pediatrics, 4Microbiology, and 5Medicine, 6Division of Neurosurgery, and 7Center for Biodefense and Emerging Infections, University of Alabama at Birmingham, Birmingham

The second annual Seasonal and Pandemic Influenza Conference, which took place in February 2007 in Arlington, Virginia, focused on recent progress in basic and clinical research regarding preparedness for outbreaks of influenza. Sporadic outbreaks of avian influenza A in Asia and the Middle East remind us that the threat of another influenza pandemic remains real. Although the exact mechanisms underlying avian influenza A human pathogenicity remain unclear, preclinical studies in animal models provide insights into the mechanisms of avian influenza A virus infection and transmission from bird to human and, rarely, from human to human. With regard to prevention, developmental studies of adjuvant-supplemented vaccines indicate promising immunogenicity and cross-reactivity. The pipeline of new antiviral agents in development is also increasing, including a new neuraminidase inhibitor and agents aimed at completely new targets. Global strategic planning efforts focus on assuring sufficient stocks of vaccines and antiviral agents, as well as timely nonpharmacological interventions to potentially delay or contain spread of an outbreak. These initiatives will also help control outbreaks of seasonal influenza.

Since the 1918 influenza pandemic, which accounted for >50 million human deaths worldwide [1], the world has been on alert for the next pandemic—one that could be even more devastating, unless global public health systems are fully prepared. Sporadic outbreaks of avian influenza A (H5N1) virus infection and the high mortality associated with this infection in humans are a grim reminder of what could occur. This awareness justifies the current, unprecedented global effort to have effective vaccines and antiviral drugs in stock and/or ready for production and distribution when needed and to prepare for implementation of nonpharmacological interventions with short notice. In February 2007, experts from around the world convened at the Seasonal and Pandemic Influenza Conference in Arlington, Virginia, to discuss progress that has been made in preparing for the next influenza season and for an influenza pandemic. The key findings are summarized here.

THE PANDEMIC THREAT: H5N1 VIRUS IN 2006–2007

Outbreaks of H5N1 virus infection in poultry were reported in 38 countries from the end of 2003 through the middle of March 2007 [2]. H5N1 virus was associated with the deaths of >230 million birds during that time. Human infection due to the H5N1 virus has been reported in 12 countries, resulting in 330 known cases and an associated mortality rate of ~60% as of 8 October 2007 (table 1) [3]. The greatest number of human deaths due to H5N1 influenza virus infection has been reported from Indonesia, but the region of highest incidence has been continually evolving. Indonesia recently reported 108 cases and 87 deaths due to H5N1 virus infection, confirming its current rank as the world leader in the number of human H5N1 influenza cases. Cases have been consistently reported from Indonesia since 2005. Vietnam, however, which currently has the
second highest overall number of cases of H5N1 virus infection and deaths due to the infection, reported no cases in 2006 and only a small number of cases thus far in 2007. This may reflect, at least in part, relative control of infection in poultry as a result of a vaccination program.

A review of 256 confirmed cases of H5N1 influenza illustrated that the median duration from onset of symptoms to hospital admission was 4 days and the time to death was 9 days. Nearly 90% of the cases were in adults aged <40 years (median age, 18 years), and mortality was highest among persons aged 10–19 years (mortality, 76%) [4]. Human-to-human transmission of H5N1 virus infection is inefficient, and most patients with H5N1 virus infection had direct contact with sick or dead poultry. Twenty percent to 25% of confirmed cases have occurred in clusters, and nearly all involved family members. Consequently, neither limited human-to-human transmission nor a potential role of shared genetic susceptibility can be excluded [5].

Although H5N1 influenza is associated with a higher viral load, wider tissue tropism, and greater cytokine dysregulation than seasonal influenza, the exact mechanism of increased pathogenicity is unclear [6, 7]. A high level of viral replication over a sustained period predicts increased levels of proinflammatory cytokines. Of concern, several amino acid changes identified in the 1918 virus as potential contributors to human adaptation have been identified in the H5N1 virus circulating today [8]. Importantly, however, death has been associated with a lack of decrease in viral titers, indicating the potential value of antiviral treatment [9].

**PREVENTION AND CONTROL WITH VACCINES**

Awareness of the toll exacted by seasonal influenza, coupled with the threat of an influenza pandemic, has driven an increase of influenza funding from the National Institute of Allergy and Infectious Diseases from $15 million in 2001 to an estimated $215 million in 2007 [10]. Through this funding, the full genomic sequences of >2000 human and avian isolates have been made available for public study, resulting in seminal work that has shed light on all aspects of influenza virology [11]. As a result of this massive federal investment, many human vaccine studies have been completed or are under way and have been providing important information. Several issues warrant note. First, there is a need to use the smallest amount of antigen in the vaccine. Because of the time constraints involved, this is necessary to facilitate the production of the greatest number of doses, especially because 2 doses of vaccine are likely to be needed. Second, there are several clades and subclades identified in the H5N1 subtype, and the vaccine should protect against >1 clade. This could be accomplished by using 1 clade for the first dose, and another, perhaps the actual pandemic virus, for the second dose. However, underlying all this is the fact that efficacy studies are not feasible. Thus, a specific antibody titer will have to be used to predict protection on the basis of experience with seasonal influenza, whereby protection correlates with a hemagglutination inhibition titer of 1:40.

Data for same-clade, multiple-dose vaccines in humans were obtained from a study comparing 4 doses of a subvirion H5N1 (clade 1) vaccine with placebo in 451 healthy adults (age range, 18–64 years) [12]. Each subject received 2 intramuscular injections of the vaccine or placebo and was observed for 56 days. An immune response was observed at all dose levels (7.5, 15, 45, and 90 μg) after a single dose, although subjects who received the 2 injections at the highest dose had the highest antibody titers (figure 1). In another study, 2 intradermal injections of H5N1 vaccine (3 μg or 9 μg, ~1 month apart) showed no clear advantage over the intramuscular route [13]. A third dose at 7 months did not substantially increase immune responses. Currently, a trial is under way to study a 30-μg dose of H5N1 vaccine given intramuscularly versus intra dermatally.

Encouraging data emerged from a phase I study of inactivated split influenza A/Vietnam/1194/2004 (H5N1) vaccine formulations given as 3 doses of hemagglutinin (7.5, 15, and 30 μg) with or without aluminium hydroxide adjuvant [14]. Individuals received 2 doses of vaccine 3 weeks apart. In this study, all formulations were well tolerated and were immunogenic, even after only 1 dose in some individuals. A Chinese study of similar design confirmed those trends. When volunteers were treated with 4 HA doses (1.25, 2.5, 5, and 10 μg) of an inactivated whole-virion H5N1 vaccine with aluminium hydroxide adjuvant on days 0 and 28 [15], all 4 doses were well tolerated, with seroconversion elicited in 78% of the subjects in the 10-μg arm after 2 doses of vaccine; similar results were shown in other studies [16]. All available evidence indicates that vaccine formulations containing an adjuvant, such

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of cases</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>108</td>
<td>87</td>
</tr>
<tr>
<td>Vietnam</td>
<td>100</td>
<td>46</td>
</tr>
<tr>
<td>Egypt</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Thailand</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>China</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Turkey</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Cambodia</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Iraq</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Djibouti</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>330</td>
<td>202</td>
</tr>
</tbody>
</table>
as MF59, have been more successful and have allowed for the use of lower amounts of antigen [17].

**ANTIVIRAL DRUGS FOR HUMAN TREATMENT**

Four antiviral medications are licensed for influenza prophylaxis and treatment: 2 M2 channel blockers (amantadine and rimantadine; effective against influenza A) and 2 neuraminidase inhibitors (oseltamivir and zanamivir; effective against influenza A and B). However, antiviral resistance to the adamantanes has become so common among seasonal influenza strains and among some (but not all) clones of H5N1 virus that use of adamantanes has become problematic. In 2001, increased viral resistance to amantadine was noted in Asia, and during 2005–2006, some 92% of US influenza A H3N2 viruses tested at the Centers for Disease Control and Prevention (CDC) were amantadine resistant [18]. A recent comprehensive analysis of influenza A H3N2 and H1N1 strains isolated globally during 2005–2006 indicated that 761 (96.4%) of H3N2 strains circulating in the United States were adamantane resistant, as were 100% of strains from some Asian countries. Among H1N1 strains isolated worldwide, 15.5% were adamantane resistant, and in the United States, 4.0% of strains were resistant [18].

Little spontaneous resistance to neuraminidase inhibitors has been documented to date, and no spontaneously resistant influenza viruses were identified prior to the introduction of the drugs [9, 19]. Although resistance to oseltamivir is less common than resistance to the adamantanes and although the resistant viruses may not be as transmissible as the sensitive strains, it is possible that resistance to oseltamivir could become a problem. Zanamivir is considered to be an alternative for oseltamivir-resistant viruses. Finally, a recent report regarding the emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors has raised some concerns, although the possible greater implications of evidence limited to seasonal outbreaks of influenza B virus infection remain to be fully assessed [20].

For patients with H5N1 influenza virus infection, the World Health Organization currently recommends oseltamivir (75 mg twice daily for 5 days; the same dosage used for seasonal pandemic infections). However, it is still not certain whether this dosage is optimal for treating H5N1 virus infection. Although these recommendations are based on the limited available evidence and the optimal dosage and duration of treatment are unknown [21], recent studies using a ferret model of H5N1 virus infection found that oseltamivir effectively decreased the mortality of the infection, inhibited re-infection, decreased the level of inflammation, and blocked the spread of the virus to visceral organs [22]. However, an increased dose was needed for these effects to be observed with some clones.

Irrespective of these encouraging data, proper treatment may require using >1 drug, and more options for antiviral therapy are clearly desirable. Antiviral agents in development include a new neuraminidase inhibitor and completely novel classes of antiviral drugs with new molecular targets. The most advanced investigational therapeutics include the parenterally administered neuraminidase inhibitor peramivir [23], the RNA polymerase inhibitor T-705 [24], and a sialidase fusion construct, DAS181 [25]. Peramivir is a selective inhibitor of influenza A and B neuraminidases and a potent inhibitor of viral replication in cell culture [23]. Intramuscular peramivir is in phase II clinical trials.
INTERNATIONAL STRATEGIC PLANNING FOR AN INFLUENZA PANDEMIC

Pandemic preparedness activities on a global scale include World Health Organization–coordinated surveillance activities. Individual countries are establishing their own pandemic preparedness plans, with many following World Health Organization pandemic phase definitions. All European Union member states, for example, now have pandemic preparedness programs in place, and efforts are under way to make these programs operational. Harmonizing these individual national plans among member states remains a critical aspect of strategic planning [26]. France has a highly integrated plan characterized by strong regional coordination. This plan contemplates mass distribution of face masks and taking other measures to preserve critical economic activities; it is constantly being refined via simulation exercises [27]. Canada has also developed a coordinated pandemic preparedness plan [28]. In addition, Canada, Mexico, and the United States have formed the Security and Prosperity Partnership, a group working to minimize the disruption in the flow of people, goods, and services among the 3 countries by adopting a consistent approach to the influenza problem across North America [29].

The CDC and other agencies have identified 3 primary strategies for combating an influenza pandemic in the United States: vaccination, antiviral therapy, and nonpharmacologic community mitigations [30, 31]. The US preparedness plan assumes an attack rate of 30% (40% among children), with 50% of those affected seeking outpatient care, a 2-day incubation period (with viral shedding occurring 1 day before symptoms emerge and peaking on day 2), and a transmission rate of 2 cases per infected person. Other evidence suggests that viral shedding, at least in the case of H5N1, may last substantially longer than 2 days and perhaps as long as 16 days [6]. Current US health care facilities might be capable of managing a pandemic with the transmissibility, virulence, and mortality of the pandemics of 1957 and 1968; however, if a pandemic similar to that in 1918 occurred, the current system would most likely fail (table 2) [32]. This is likely because there is an 8% deficit in nurses (∼100,000 nurses), 48% of hospital emergency departments are functioning at or over capacity, and the numbers of hospitals, emergency departments, and total beds are decreasing [33].

THE PANDEMIC SEVERITY INDEX

Because a sufficient amount of vaccine is unlikely to be available during the first wave of infection and because recourse to antiviral agents may be limited by suboptimal existing stocks and distribution logistics, nonpharmacologic community intervention will be key during this period. To address this need, the CDC recently developed an interim prepandemic planning guide to define mitigation strategies in the community, based on pandemic severity category [34]. The guide is the product of a working group composed of federal, state, and local public health officials and representatives from various stake holding organizations, with input from academia, private industry, and the public sector [34].

The group and many others have examined data from past pandemics (in 1918, 1957, and 1968) to estimate the projected mortality of a modern epidemic. Computational models that used observations from seasonal transmission and, as much as possible, data from past pandemics as input were also examined. The Institute of Medicine reported on the modeling process and its evaluation [35]. By determining differences in the case-fatality ratio (the proportion of fatalities among clinically ill persons), they derived pandemic severity categories and created the US pandemic severity index, with ranges of projected US deaths based on a constant 30% illness rate without any intervention (figure 2) [34]. For example, in a category 4–5 pandemic (equivalent to the 1918 pandemic), an illness rate of 30% (based on the 2006 US population) would yield 1,800,000 US deaths based on a constant 30% illness rate without any intervention (figure 2) [34]. For example, in a category 4–5 pandemic (equivalent to the 1918 pandemic), an illness rate of 30% (based on the 2006 US population) would yield 1,800,000 deaths. This tool will be used to implement early, targeted, and layered community mitigation strategies. For example, a category 2 pandemic, similar to the 1957 and 1968 pandemics, would require voluntary isolation of the ill person at home but neither quarantine of household members nor child and adult social distancing at schools and workplaces. A category 4–5 pandemic, however, would be cause for household quarantine.

Table 2. Two scenarios for pandemic influenza in the United States in the 21st century [32].

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of persons affected</th>
<th>No. of services for patient care available in the United States in 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiencing illness</td>
<td>90,000,000</td>
<td>...</td>
</tr>
<tr>
<td>Requiring outpatient care</td>
<td>45,000,000</td>
<td>...</td>
</tr>
<tr>
<td>Requiring hospital care</td>
<td>865,000</td>
<td>90,000</td>
</tr>
<tr>
<td>Requiring intensive care unit beds</td>
<td>128,750</td>
<td>90,000</td>
</tr>
<tr>
<td>Requiring mechanical ventilation</td>
<td>64,875</td>
<td>10,500</td>
</tr>
<tr>
<td>Death</td>
<td>209,000</td>
<td>1,903,000</td>
</tr>
</tbody>
</table>

Seasonal and Pandemic Influenza • CID 2008:46 (1 April) • 1027
and antiviral prophylaxis, if feasible, in addition to child and adult social distancing in the community (figure 3) [34].

SEASONAL INFLUENZA AND CHANGING IMMUNIZATION STRATEGIES

Seasonal influenza is estimated to cause 250,000–500,000 deaths per year globally. However, during the 2006–2007 season, mortality associated with pneumonia and influenza remained below the epidemic threshold of 7.9% [36]. The efficacy rates of the 2 available types of vaccine, trivalent inactivated vaccine and live attenuated influenza vaccine, ranged from 50% to 90% [37, 38]. Vaccine production reached ∼121 million doses during 2006–2007, and the rate of vaccine use increased from 33% among persons aged ≥65 years in 1989 to 65% among the same population in 2004 [39]. However, 4%–15% of vaccine doses produced since 2000–2001 remain unused each year, including 1 million doses in the CDC's strategic reserve in 2007 [40, 41]. Unused influenza vaccine is typically disposed of prior to its expiration date, costing pharmaceutical companies millions of dollars and providing a disincentive for industry to continue vaccine production.

Innovative initiatives are clearly required to increase rates of vaccination, as exemplified by a health clinic in Colorado, where 94,000 vaccine doses were administered in 2 days by establishing a “drive-through vaccination” approach [42]. The usefulness of school-based vaccination programs was demonstrated in Minnesota, where free vaccine provided to school children in kindergarten through grade 12 resulted in the vaccination of 41% of nearly 40,000 students in 101 schools [43]. Although transmission of health care–associated influenza has been documented in many clinical settings and infections have been linked epidemiologically to unvaccinated health care workers, <50% of health care workers are vaccinated each year [44–46]. Innovative approaches may be needed to increase rates of vaccination among health care workers, just as they are needed for the general population. For example, a recent program reported that rates of vaccination of long-term care facility health care workers in southern California could be improved by providing free vaccinations at the work site during a well-publicized “Vaccine Day” [47].

SUCCESES AND FAILURES OF 2006 TO INFORM 2007

Steady progress in vaccine development is being made, with several human studies reporting promising results and a rich pipeline of preclinical candidates. In fact, the first human anti-H5N1 influenza vaccine was approved by the US Food and
Drug Administration in April 2007. In July 2007, the US Department of Health and Human Services announced that it had stockpiled enough H5N1 avian influenza vaccine to protect ∼6 million persons and that federal and state stockpiles contain enough antiviral medication to treat >48 million persons [41]. New classes of antiviral drugs expected to enhance treatment and containment options are also emerging.

Most importantly, international cooperation for pandemic preparedness has resulted in strategic surveillance and planning activities around the world. In the United States, the formulation of nonpharmacologic community mitigation interventions promoted by the CDC is a critical step in pandemic preparedness. Also, all 192 World Health Organization member states have an avian influenza preparedness plan in place or in preparation—a marked improvement over 2 years ago, when only 50 countries did so [41]. However, many problems persist. Production of adequate amounts of vaccine will likely require no less than 6 months after isolation of the pandemic strain; using a related but different strain for priming is being investigated. Also, supplies during the first 6 months will be just enough to vaccinate ∼14% of the world’s population, and no vaccine will be available for poor countries unless recently proposed plans for local production are implemented.

Because of our global “just-in-time delivery” economic pattern, inventories are kept to a minimum, and even beyond vaccine production, virtually no production surge capacity exists for health care, food supplies, and many other products and services [48]. The availability of mechanical ventilators illustrates this point effectively. To date, in the United States, ∼80% of the existing mechanical ventilators are in use on any day. Because normal seasonal epidemics require ∼100% of the available ventilators, it is safe to assume that, in a pandemic, unless a massive surge takes place, most patients who need mechanical ventilation would not have access to it. To compound those problems, detailed plans for establishing and staffing the temporary hospitals that would have to be set up are nonexistent. Health care delivery systems and managed-care organizations have done little planning and are essentially unprepared to face the expected shortage of key health care workers. Finally, bringing businesses to a satisfactory level of preparedness is a daunting challenge, because only 19% of businesses appear to have plans in place that workers are aware of for responding to a pandemic outbreak of influenza [49]. Clearly, much has been learned in the past year about our preparedness for an influenza pandemic, and much still remains to be done. For example, because of the recent successes in developing vaccines of increased antigenicity for the H5N1 strain, we may soon have vaccine candidates available for stockpiling. How this should be done needs to be clearly specified nationally and internationally on the basis of evolving data.

**SCIENTIFIC PLANNING COMMITTEE**

**Seasonal and Pandemic Influenza Meeting, 1–2 February 2007, Arlington, VA.** Dr. Arnold S. Monto (co-chair; Department of Epidemiology, University of Michigan School of Public Health), Dr. Richard J. Whitley (co-chair; Departments of Pediatrics, Microbiology, Medicine, and Neurosurgery, Center for Biodefense and Emerging Infections, The University of Alabama at Birmingham), Dr. John G. Bartlett (Department of Medicine, Johns Hopkins University School of Medicine), Dr. Frederick G. Hayden (Departments of Clinical Virology, and Medicine and Pathology, University of Virginia School of Medicine), Dr. Andrew T. Pavia (Division of Pediatric Infectious Diseases, University of Utah), and Dr. Michael L. Tapper (Continuing Medical Education course director; Department of Medicine, New York University School of Medicine, Division of Infectious Diseases, Lenox Hill Hospital).

**Acknowledgments**

We thank Elyse Grusky and Filippo Cavalieri for receiving payment from the commercial supporters for research and editing assistance. **Financial support.** This article is derived from the Seasonal and Pandemic Influenza Conference (2007), which was jointly sponsored by the New York University Postgraduate Medical School and Lenox Hill Hospital (New York City) and was endorsed by the American Academy of Pediatrics, the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America, with participation by the Centers for Disease Controls and Prevention. Independent educational grants for this program, including this article, have been provided by Gilead Sciences, Roche Laboratories, GlaxoSmithKline, and BioCryst Pharmaceuticals. **Potential conflicts of interest.** A.S.M. has been a consultant for Roche, GlaxoSmithKline, Novartis, and Solvay and has received an investigator-initiated grant from Sanofi-Pasteur. R.J.W. serves on the scientific advisory board and is a consultant for Gilead Sciences.

**References**

9. de Jong MD, Thanh TT, Khanh TH, et al. Oseltamivir resistance during...
13. Patel SM, Atmar RL, Sahly HE, Cate TR, Keitel WA. A randomized, open-label, phase I clinical trial comparing the safety, reactogenicity, and immunogenicity of booster immunization with inactivated influenza A/H5N1 vaccine administered by the intradermal (ID) or the intramuscular (IM) route among healthy adults [abstract LB-5]. In: Program and abstracts of the 44th Annual Meeting of the Infectious Diseases Society of America (Toronto). Alexandria, VA: Infectious Diseases Society of America, 2006; 64.
46. Joint Commission on the Accreditation of Healthcare Organizations. Joint commission establishes infection control standard to address in-
