Vaccines for Seasonal and Pandemic Influenza

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Seasonal influenza continues to have a huge annual impact in the United States, accounting for tens of millions of illnesses, hundreds of thousands of excess hospitalizations, and tens of thousands of excess deaths. Vaccination remains the mainstay for the prevention of influenza. In the United States, 2 types of influenza vaccine are currently licensed: trivalent inactivated influenza vaccine and live attenuated influenza vaccine. Both are safe and effective in the populations for which they are approved for use. Children, adults <65 years of age, and the elderly all receive substantial health benefits from vaccination. In addition, vaccination appears to be cost-effective, if not cost saving, across the age spectrum. Despite long-standing recommendations for the routine vaccination of persons in high-priority groups, US vaccination rates remain too low across all age groups. Important issues to be addressed include improving vaccine delivery to current and expanded target groups, ensuring timely availability of adequate vaccine supply, and development of even more effective vaccines. Development of a vaccine against potentially pandemic strains is an essential part of the strategy to control and prevent a pandemic outbreak. The use of existing technologies for influenza vaccine production would be the most straightforward approach, because these technologies are commercially available and licensing would be relatively simple. Approaches currently being tested include subvirion inactivated vaccines and cold-adapted, live attenuated vaccines. Preliminary results have suggested that, for some pandemic antigens, particularly H5, subvirion inactivated vaccines are poorly immunogenic, for reasons that are not clear. Data from evaluation of live pandemic vaccines are pending. Second-generation approaches designed to provide improved immune responses at lower doses have focused on adjuvants such as alum and MF59, which are currently licensed for influenza or other vaccines. Additional experimental approaches are required to achieve the ultimate goal for seasonal and pandemic influenza prevention—namely, the ability to generate broadly cross-reactive and durable protection in humans.

Seasonal influenza is a major cause of vaccine-preventable disease mortality, causing an estimated 250,000–500,000 deaths annually worldwide and 30,000–50,000 deaths in the United States [1]. In a typical year in the United States, there are an estimated 25–50 million cases of influenza, resulting in hundreds of millions of days of illness and tens of millions of days of work and school lost (table 1) [2]. The estimated number of annual influenza-associated hospitalizations averaged 290,000 (range, 85,000–550,000) for the 1979–1980 through 2000–2001 seasons in the United States, with the increase in the numbers of these hospitalizations over the past 2 decades due, in part, to the aging of the population [3]. Although it is difficult to estimate the impact of the next pandemic, because of so many unknown factors, provisional estimates based on extrapolations from moderate (1957/1968-like) and severe (1918-like) pandemics suggest that, in the United States, illness attack rates will be ~30%, resulting in the deaths of 200,000 (moderate pandemic) or, potentially, 1.9 million (severe pandemic) people (A. S. Monto, personal communication).

The primary strategy for prevention and control of influenza is vaccination. Seasonal influenza epidemics...
current status of vaccination coverage in the United States. We also review the recent development of inactivated and live attenuated pandemic vaccines and the results of trials assessing their safety and immunogenicity, including research into potential strategies to improve responsiveness.

## SEASONAL INFLUENZA: VACCINES AND PREVENTION

There are several important options for preventing and controlling influenza. The benefits of simple methods such as hand hygiene, cough etiquette, and contact avoidance cannot be overemphasized and would have a significant impact on decreasing the number of cases during an outbreak [5]. However, the primary strategy for reducing the morbidity and mortality of influenza is vaccination.

### Current Influenza Vaccines

Trivalent inactivated vaccine (TIV) and live attenuated influenza virus vaccine (LAIV) are developed each year for protection against the expected predominant influenza strains. Both vaccines contain the predicted antigenic variants of influenza A(H3N2), A(H1N1), and B viruses [6]. The main differences between the 2 vaccines are route of administration (TIV is given as an intramuscular injection, LAIV as an intranasal spray) and structure (TIV contains purified hemagglutinin [HA] and neuraminidase, whereas LAIV contains a weakened virus); hence, they provoke different responses. TIV elicits a higher mean serum IgG antibody response than does LAIV. LAIV elicits a better IgA mucosal response, which occurs at the site where the virus enters the body, thus helping to prevent infection before significant viral replication occurs [7]. The 2 vaccines are generally well tolerated. Except for an injection-site reaction, adverse effects due to TIV do not differ significantly from those due to placebo. LAIV causes transient (2-day) respiratory symptoms—for example, runny nose. In the United States, TIV is indicated for individuals >6 months of age, and LAIV is indicated for healthy people 5–49 years of age [6], although these latter recommendations may be altered on the basis of recent clinical trial data.

### Vaccine Efficacy and Effectiveness

Vaccine efficacy and effectiveness studies tend to evaluate different outcomes, making comparisons between studies difficult. Cause-specific outcomes—that is, where there is laboratory confirmation of the influenza virus causing illness or infection—provide the highest and most precise estimate of vaccine impact, because there are fewer false-positive results. “All-cause” outcomes—for example, clinical illness without laboratory confirmation, all respiratory illnesses, or all otitis media episodes—are less specific, because they would not all be caused by influenza, and, hence, vaccination will give a lower percentage reduction. However, although all-cause outcomes have a lower relative risk reduction ratio (RRR), they have an increased absolute risk reduction (ARR), because including all-cause outcomes enhances sensitivity. The evidence of vaccine efficacy and effectiveness in children, adults, and the elderly is provided by several systematic reviews and meta-analyses.

#### Children

Two recent systematic reviews evaluated the efficacy (reduction in laboratory-confirmed cases) and effectiveness (reduction in clinical illness) of inactivated vaccine and LAIV in children (<16 and <18 years of age) [8, 9]. LAIV resulted in a higher percentage reduction (RRR) in laboratory-confirmed influenza (79%–80%) than did inactivated vaccine (65%). The effect on clinical illness, a less specific outcome, was less clear (34%–38% vs. 28%–33%), although the results suggest that LAIV may be somewhat more effective. Recent data from a pivotal phase 3 study of cold-adapted trivalent influenza vaccine in children 6–59 months of age demonstrated a 55% reduction in culture-confirmed influenza-like illness, compared with TIV [10].

#### Adults

Similarly, in a meta-analysis of 25 studies of healthy adults (14–60 years of age), inactivated vaccine reduced serologically confirmed illness by 69%–70%, compared with pla-

### Table 1. Estimated annual impact of epidemic influenza in the United States.

<table>
<thead>
<tr>
<th>Impact measurement</th>
<th>Estimate [reference]</th>
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<tbody>
<tr>
<td>Cases, no.</td>
<td>25 to &gt;50 million</td>
</tr>
<tr>
<td>Days of illness</td>
<td>100–200 million</td>
</tr>
<tr>
<td>Days of work and school loss</td>
<td>Tens of millions</td>
</tr>
<tr>
<td>Hospitalizations, no.</td>
<td>85,000–550,000</td>
</tr>
<tr>
<td>Deaths, no.</td>
<td>34,000–51,000</td>
</tr>
<tr>
<td>Cost</td>
<td>Billions of dollars</td>
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</tbody>
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* d Based on 294,000 excess hospitalizations, at $7000 per hospitalization, plus indirect costs [4].
cebo or noninfluenza vaccine, and prevented 6.1–6.8 serologically confirmed illnesses [11]. The RRR for clinical illness was lower, at 22%–25%, because many of the influenza-like illnesses were caused by other viruses; however, the ARR was 12.1–13.5 per 100 people, indicating that vaccination prevented clinical illness in ∼13% of participants. The finding of a higher ARR seen in studies that looked at “clinical illnesses prevented” versus “serologically confirmed influenza illnesses prevented” is not surprising, because serologic confirmation of influenza illness is only ∼60% sensitive for confirmed influenza illness [12].

**Individuals at high risk.** Vaccination has also been shown to be beneficial for people <65 years of age with high-risk medical conditions [13]. Among high-risk children and adolescents <18 years of age, 43% of general practitioner visits were prevented; among high-risk adults 18–64 years of age, vaccination prevented 78% of deaths, 87% of hospitalizations, and 26% of general practitioner visits; among elderly persons (≥65 years of age), vaccination prevented 50% of deaths and 48% of hospitalizations. These data demonstrate the benefit of vaccination in high-risk persons of any age during an epidemic.

**Elderly.** Two meta-analyses in community-dwelling elderly people ≥65 years of age showed consistent estimates for the impact of vaccination in this group [14, 15]. Vaccination significantly reduced all-cause mortality (RRR, 50% and 47%) and hospitalizations for pneumonia or influenza (RRR, 33% and 27%) and for respiratory conditions (RRR, 30% and 22%). The benefit was somewhat greater among elderly people living in long-term-care facilities—2 meta-analyses showed that vaccination was associated with significant reductions in hospitalizations (RRR, 48% and 45%) and death (RRR, 68% and 60%) [15, 16]. These 2 analyses also showed reduction in respiratory/influenza-like illness (RRR, 56% and 23%) and pneumonia (RRR, 53% and 46%).

Influenza vaccination also has indirect benefits relevant for control of both seasonal and pandemic influenza. Children transmit influenza virus to others very efficiently [17], and health care workers (HCWs) are often the source of influenza outbreaks in health care institutions [18]. Vaccination of children and HCWs, to reduce transmission of influenza to others, has been evaluated in several studies. Vaccination of children in day care protected family contacts against febrile respiratory illnesses (42% reduction, compared with contacts of control children) [19]. In school-age siblings, there was an 80% reduction in febrile respiratory illnesses and a ≥70% reduction in school days missed, physician visits, antibiotic use, and parental work loss to care for sick children. Three key studies evaluated the effects of vaccinating children on the wider community. The Tecumseh study compared 2 cities in Michigan, one (Tecumseh) where 86% of all schoolchildren were vaccinated and another (Adrian) where there was no childhood vaccination program [20]. Respiratory illness rates were found to be 3 times higher in the unvaccinated town than in the vaccinated town (4.2 vs. 1.4 adjusted excess weekly respiratory illnesses per 100 people). Another study, in Texas, showed that vaccination of children resulted in lower illness rates in adults >35 years of age [21]. A study in Japan evaluated the impact of a national child vaccination program on death rates in the community [22]. During the program, in which ∼80% of schoolchildren were vaccinated, the number of excess winter deaths (all-cause and pneumonia and influenza, principally in the elderly) fell dramatically, by 37,000–49,000 per year. When vaccination of children became optional and there was negligible vaccine uptake, the mortality rate increased. Although these studies suggest that universal vaccination of schoolchildren against influenza is an effective way to decrease influenza in the community, a recent systematic review highlights several limitations in the design and execution of these studies and recommends that further well-designed studies be performed to define the impact on influenza-related morbidity and mortality in the community and the potential cost-saving benefits [23]. Vaccination of HCWs has been shown to be highly effective in protecting high-risk patients [24, 25]. Vaccination of ∼50% of HCWs in 10 long-term-care hospitals was associated with a substantial decrease in mortality among patients (13.6% vs. 22.4% in 10 hospitals where vaccine uptake was 4.9%) [24]. A recent systematic review of 18 studies concluded that vaccination of HCWs provides indirect protection to those at high risk, is cost-effective, and may be cost saving [25]. However, despite recommendations, the uptake of vaccination in HCWs is very low (<25%) [25].

**Cost-Effectiveness of Vaccination**

In contrast to studies of vaccine efficacy and effectiveness, in which a highly specific clinical case definition for influenza-like illness is required to give a high positive predictive value and highest estimate of relative risk reduction, economic analyses need more-sensitive definitions to avoid missing cases and to capture all influenza-associated morbidity and the benefits of vaccination. The impact of different case definitions and outcome periods on estimates of the effectiveness and cost benefit of influenza vaccination was explored using data from a trial of LAIV in healthy working adults [26]. As expected, febrile upper respiratory tract illnesses occurring during the peak influenza period provided the highest estimates of vaccine effectiveness (i.e., RRR), whereas events occurring on a day with any symptom occurring during the entire outcome period—the most sensitive clinical case definition—provided the lowest estimates of vaccine effectiveness. However, this sensitive definition gave the highest estimates for absolute reduction in events (ARR: 186.4 vs. 42.4 work loss days prevented per 1000; 271.5 vs. 79 impaired productivity days prevented per 1000; and 44.8 vs. 16.5 health care provider visits prevented per 1000).
Clearly, more-sensitive criteria are appropriate when evaluating the total population impact and potential cost-effectiveness of vaccination; the use of very specific definitions applied only to the peak influenza period would underestimate the economic benefits of vaccination.

Several studies around the globe have evaluated the economic implications of vaccinating children, healthy adults, and the elderly. Although the quality of data is lower than for other age groups, studies of children generally indicate that influenza vaccination is likely to be cost-effective and may be cost saving [27, 28]. Cost savings are most apparent in children of any age with high-risk conditions and are less consistent in non–high-risk children [28]. It is worth noting that a substantial part of the economic benefit associated with vaccination of children is due to reductions in indirect costs, particularly parental work loss days for the care of sick children. Although healthy adults are not at increased risk for serious complications, influenza illness results in increased work absenteeism and impaired work productivity that impact the economic costs of illness. Hence, when indirect costs associated with work absenteeism are included, economic analyses have generally shown that vaccination of healthy adults is cost-effective and, in many cases, cost saving [27, 29, 30]. The elderly are one of the groups at highest risk for serious complications of influenza, such as secondary bacterial pneumonia and exacerbation of underlying chronic medical conditions, that may result in costly hospitalizations. Consequently, influenza vaccination provides substantial economic benefits in this group. Studies suggest that vaccinating the elderly is almost always cost-effective and is frequently cost saving [27, 31].

Current Vaccination Rates
The Advisory Committee on Immunization Practices recommendations for influenza vaccination target those who are at high risk for serious complications, those likely to be at high risk, and those who can transmit the virus to high-risk groups (Appendix) [6]. In the United States, more people die of influenza than of any other vaccine-preventable disease. However, vaccination rates for the elderly have been <70% at the national level, substantially below the Healthy People 2010 goal of 90%. Vaccination rates for other groups are even lower: <50% for other target groups, including high-risk children and adults, and <10% for low-priority groups (table 2) [32].

AVIAN AND PANDEMIC INFLUENZA VACCINE DEVELOPMENT
Although several avian influenza viruses are being monitored for their potential to infect and cause disease in humans [33], the increasing numbers of infections in animals and humans with the highly pathogenic avian influenza A(H5N1) viruses suggest that H5N1 may be the most likely to initiate a human influenza pandemic. Development of a vaccine will be an essential part of the strategy to control and prevent a pandemic outbreak, and current research is evaluating several vaccine options. Licensure and deployment of a pandemic influenza vaccine would be greatly simplified if the vaccine resembled currently licensed vaccines as closely as possible, because the regulatory authorities could view this as a strain change. Hence, the primary focus of initial studies has been on approaches using inactivated and live vaccine resembling the currently licensed inactivated and live vaccines, respectively. Approaches currently being tested include subvirion inactivated vaccines and cold-adapted, live attenuated vaccines.

Inactivated Vaccine Approach
An inactivated vaccine approach has the advantages that it uses a proven technology previously used in the 1957 and 1968 pandemics, that extensive efficacy data exist for both pandemic and interpandemic years, and that there is a large worldwide experience of clinical use of inactivated vaccines for controlling influenza. In addition, the largest manufacturing capacity is currently that for inactivated vaccine, although this is still too limited to cope with the quantities required in a pandemic. An inactivated vaccine is unlikely to induce mucosal immunity and, therefore, might be less likely to prevent person-to-person spread as effectively as a live vaccine, and the protection induced may be very strain specific. Furthermore, an unprimed population would probably require at least 2 doses to induce immunity.

Initial approaches in the development of inactivated vaccines against H5N1 influenza have dealt with the highly pathogenic nature of the virus (related to the high cleavability of the HA) in 1 of 3 ways: (1) by using an antigenically related but not highly pathogenic H5 virus, such as Duck/Singapore/97(H5N3); (2) by

<table>
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<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>65.5</td>
<td>62.7</td>
</tr>
<tr>
<td>High-risk adults, 18–64 years of age</td>
<td>34.2</td>
<td>25.5</td>
</tr>
<tr>
<td>Health care workers</td>
<td>40.1</td>
<td>35.7</td>
</tr>
<tr>
<td>Nonpriority adults</td>
<td>19.6</td>
<td>8.8</td>
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<tr>
<td><strong>Children</strong></td>
<td></td>
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<tr>
<td>Children, 6–23 months of age</td>
<td>7.7</td>
<td>48.4</td>
</tr>
<tr>
<td>High-risk children, 2–17 years of age</td>
<td>...</td>
<td>34.8</td>
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<tr>
<td>Nonpriority children</td>
<td>...</td>
<td>12.3</td>
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**NOTE.** Data are percentage coverage values and are from [32].

a Data collected by the National Health Interview Survey.
b Data collected by the Behavioral Risk Factor Surveillance System.
using recombinant approaches to express the HA in a system that does not involve handling live virus (baculovirus-expressed recombinant H5 [rH5] HA derived from the H5N1 human isolate, A/Hong Kong/156/97); or (3) by reverse genetic manipulation of the HA to remove the amino acid sequence responsible for high cleavability (subvirion rgA/Vietnam/1203/04[H5N1]). These approaches eliminate the need for sophisticated containment procedures and allow the preparation of vaccines in facilities used to prepare traditional inactivated vaccines.

**Duck/Singapore vaccine.** The H5 neutralizing antibody response to a nonadjuvanted Duck/Singapore vaccine was poor, with the best response occurring after two 30-μg doses [34]. The modest generation of postvaccination antibodies suggested that the H5 HA might be significantly less immunogenic than the H1 vaccines in unprimed populations in 1976 and 1977.

**Recombinant H5 rHA vaccine.** Two-dose administration of increasing amounts of baculovirus-expressed H5 rHA demonstrated a dose-response relationship, with the magnitude of the response determined by the number of micrograms of rHA administered [35]. Potentially protective neutralizing antibody responses were detected in 52% of individuals who received 2 doses of 90 μg of vaccine—that is, only at the highest doses evaluated. Compared with the responses seen with H1 or H3 rHA vaccines in humans [36–38], these results also suggested that an H5 rHA vaccine would be significantly less immunogenic.

**Subvirion rgA/Vietnam/1203/04 vaccine.** A recent phase 1 double-blind, placebo-controlled trial in 451 healthy adult volunteers showed that 2 intramuscular injections of the H5N1 vaccine were safe and well tolerated at all doses (7.5–90 μg). Neutralizing antibody responses were seen at all doses, but only the highest doses (2 doses of 45 μg and 90 μg) gave potentially protective responses in a substantial number of subjects [39]. The results of this study were consistent with the previous evaluation of the H5 rHA vaccine [35].

**Strategies to improve immunogenicity.** Because of the gap between influenza vaccine demands in an influenza pandemic and the limited vaccine supplies available, a number of strategies have been investigated to improve the immunogenicity of the vaccine and allow the use of lower doses: (1) a booster strategy that would include the vaccine in annual vaccinations to prime the population, which may avoid the need for a 2-dose schedule and potentially achieve better responses at lower doses; (2) the use of adjuvants with dose-sparing potential; and (3) the use of alternative routes of administration that may be dose sparing.

The finding that subjects born before 1968 (when H2N2 viruses were circulating) had a significantly greater hemagglutination-inhibition response to H9N2 vaccines than did those born after 1968 (when H2N2 was displaced by H3N2) and were then shown to have a greater prevaccination titer of antibody to H9 suggested that previous exposure to H2N2 viruses might prime subjects for a vigorous response to subsequent H9 vaccination [40]. This unexplained relationship between H9 and H2 suggests that cross-priming may be possible. In another study, revaccination of subjects with Duck/Singapore/97(H5N3) 16 months after initial vaccinations appeared to enhance protective H5N1 antibody titers, compared with those achieved after 2 doses in the original study [34, 41].

A study is currently ongoing in subjects who received the recombinant H5 rHA vaccine 5 years ago [35], to evaluate boosting with subvirion rgA/Vietnam/1203/04 vaccine. In addition, subjects in the current study of the rgA/Vietnam/1203/04 vaccine will receive a third dose of vaccine 6 months later. There are also studies proposed to evaluate interaction between seasonal TIVs and the H5 vaccine.

Aluminum-based adjuvants have been evaluated for their potential dose-sparing effects for pandemic vaccines. In an unprimed population, 2 doses of alum-adjuvanted H2N2 vaccine (1.9, 3.8, and 7.5 μg of HA) achieved protective antibody titers almost equivalent to that induced by 2 doses of 15 μg unadjuvanted vaccine [42, 43]. However, because no unadjuvanted 7.5-μg dose was included for comparison, a definitive conclusion cannot be made as to whether alum was, in fact, dose sparing.

The 30-μg dose of an alum-adjuvanted formulation of H5 subvirion vaccine recently met the immunogenicity criteria for annual administration defined by the European Agency for the Evaluation of Medicinal Products, but alum did not enhance the response to lower doses [44]. The National Institutes of Health is currently conducting a dose-ranging study of H5 with or without alum in healthy adults. On the basis of the current data with other influenza vaccines, it is likely that alum will have only a modest adjuvant effect, resulting in similar immunogenicity at approximately half the antigenic dose. Ongoing studies should provide more-definitive estimates.

The most promising adjuvant approach evaluated so far appears to be the inclusion of the MF59 oil-in-water emulsion, currently licensed in some European countries as an adjuvant for conventional influenza vaccine. Addition of MF59 to Duck/Singapore/97(H5N3) vaccine significantly enhanced the antibody responses to all the vaccine doses (7.5, 15, and 30 μg), compared with nonadjuvanted vaccine [34]. Oddly, there was an inverse dose-response relationship, with the 7.5-μg dose giving the highest seroconversion rates. Since the amount of MF59 was the same in each dose formulation, it may be the ratio of MF59 to antigen that determines the immune-enhancing effect [34]. In the revaccination study mentioned above, Stephenson et
al. also showed that MF59 significantly increased antibody titers, compared with those induced by revaccination with non-adjuvanted vaccine [41].

Effective use of MF59 for pandemic control will require adequate manufacturing capacity for MF59, as well as agreements that will make this adjuvant available for use with vaccines from different manufacturers. Among the many additional potential adjuvants worthy of evaluation are monophosphoryl lipid A and CPG, a Toll-like receptor 9 agonist that appears to be particularly potent at stimulating antibody responses.

Finally, the administration of vaccines intradermally may have dose-sparing effects. Intradermal vaccination of healthy adults with 6 \( \mu \)g of conventional vaccine gave antibody responses very similar to those seen with 15 \( \mu \)g administered intramuscularly [45]. However, in those \( \geqslant 60 \) years of age, the response rates and titers achieved were poorer with the intradermal formulation. A small pilot study has recently been reported in which intradermal administration of subvirion H5 vaccine did not appear to be an especially effective dose-sparing strategy [46].

**Live Vaccine Approach**

The live vaccine approach is a promising option for pandemic vaccination, because live viruses are highly immunogenic in unprimed populations, potentially allowing for the use of very low doses, and they tend to induce more rapid and robust immune responses in unprimed individuals than do inactivated vaccines. Furthermore, a live vaccine would be expected to induce mucosal immune responses and, therefore, could be more effective than an inactivated vaccine in reducing virus transmission. Live vaccines also will be useful in the development of challenge models that might allow the identification of better correlates of immunity against H5N1 and other potential pandemic viruses. Live attenuated vaccines may be cross-reactive with other antigenic variants and, therefore, offer cross-protection against different variants of the same virus. However, LAIVs are not licensed in all populations. There is a critical need to expand the safety database, particularly in young children, and to define correlates of protective immunity that could be extended to the elderly. There are concerns regarding transmission and reassortment of virus, although this can be dealt with by restricting the deployment of the vaccine until after the initiation of a pandemic, understanding the expected shedding patterns, and defining the biological behavior of possible vaccine–wild-type reassortants. Live attenuated H5N1 and H9N2 vaccine candidates based on the licensed cold-adapted influenza vaccine are currently being evaluated in clinical trials.

**Experimental Approaches**

There are a number of experimental approaches currently under evaluation for pandemic vaccines, including nasal inactivated vaccines, vaccines that provide cross-protective peptides/epitopes, virus-like particles, live vaccines other than cold-adapted influenza vaccine, vectored vaccines (e.g., adenovirus vectored), and DNA vaccines. These approaches require validation in clinical studies and, because none of these approaches are licensed for conventional influenza, regulatory approval would require extensive safety evaluation and validation. In addition, specific markers of efficacy will need to be developed for some approaches. Early determination of which approaches have potential advantages over conventional approaches would facilitate development of the most promising methodology.

**CONCLUSIONS**

Seasonal influenza presents a consistently huge burden from year to year. Despite the availability of safe and effective vaccines that provide benefits across the age spectrum for both low- and high-risk groups, uptake of vaccination is still too low. New strategies are needed to improve vaccination, including ensuring the timely availability of adequate vaccine supply, improving vaccine delivery to current or expanded target groups, and development of even-more-effective vaccines. Vaccination rates need to increase substantially to achieve a reasonable baseline preparedness that will grant the capacity for a surge in vaccination in the event of an influenza pandemic.

Since the studies to date have shown that H5 inactivated vaccines tend to induce modest antibody responses, a critical issue is to elucidate whether H5 as an antigen is intrinsically less immunogenic and, if so, what can be done to circumvent this problem. However, the ultimate goal, for both seasonal and pandemic influenza, is to generate durable, cross-protective immune responses—for instance, using vaccines that provide cross-protective peptides/epitopes that would be effective against different variants, approaches that modify M2-based immunity, and cytotoxic lymphocyte approaches. The development of a vaccine that could achieve cross-protective immunity would be an enormous breakthrough for influenza.

**Acknowledgments**

The “Seasonal and Pandemic Influenza 2006: At the Crossroads, a Global Opportunity” conference was sponsored by the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the National Institute of Allergy and Infectious Diseases, and the Centers for Disease Control and Prevention. Funding for the conference was supplied through an unrestricted educational grant from Gilead Sciences, GlaxoSmithKline, Roche Laboratories, MedImmune, Sanofi Pasteur, Biota Holdings, and BioCryst Pharmaceuticals.

**Supplement sponsorship.** This article was published as part of a supplement entitled “Seasonal and Pandemic Influenza: At the Crossroads, a Global Opportunity,” sponsored by the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of America, the National Institute of Allergy and Infectious Diseases, and the Centers for Disease Control and Prevention.
APPENDIX


The following should be considered to be high-priority groups for vaccination:

1. Those at high risk for serious complications
   - Persons ≥65 years of age
   - Persons with chronic medical conditions
   - Persons with conditions that compromise respiratory function or ability to handle secretions
   - Residents of long-term-care facilities
   - Pregnant women
   - Children/adolescents receiving chronic aspirin therapy
   - Children 6 months to 5 years of age

2. Those who are likely to be at high risk (50–64 years of age)

3. Persons who can transmit to high-risk groups
   - Household contacts of high-risk persons
   - Health care workers

In addition, influenza vaccine should be administered to any other person who wishes to avoid influenza illness or transmitting influenza to others, depending on vaccine availability (the vaccine can be administered to those ≥6 months of age).

References


