A Primer on Strategies for Prevention and Control of Seasonal and Pandemic Influenza

The United States has made considerable progress in pandemic preparedness. Limited attention, however, has been given to the challenges faced by populations that will be at increased risk of the consequences of the pandemic, including challenges caused by societal, economic, and health-related factors. This supplement to the *American Journal of Public Health* focuses on the challenges faced by at-risk and vulnerable populations in preparing for and responding to an influenza pandemic.

Here, we provide background information for subsequent articles throughout the supplement. We summarize (1) seasonal influenza epidemiology, transmission, clinical illness, diagnosis, vaccines, and antiviral medications; (2) H5N1 avian influenza; and (3) pandemic influenza vaccines, antiviral medications, and nonpharmaceutical interventions. (*Am J Public Health.* 2009;99: S216–S224. doi:10.2105/AJPH.2009.164848)

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ALTHOUGH THE UNITED States has made considerable progress in pandemic preparedness, limited attention has been given to the challenges faced by populations who may be at risk or vulnerable to the consequences of a severe influenza pandemic.[1–4] The US Department of Health and Human Services (HHS) working definition of "at-risk individuals" is described in the *Federal Guidance to Assist States in Improving State-Level Pandemic Influenza Operating Plans*[5] (see the box on the next page). In this commentary, we summarize key information about the prevention and control of seasonal and pandemic influenza in the United States to support articles in this special supplement to the *American Journal of Public Health*. We do not cover specific at-risk and vulnerable populations and the potential affects of an influenza pandemic on these groups in this article; rather, these groups are covered in detail in subsequent articles in this supplement.

HUMAN INFLUENZA VIRUSES

Of the 3 human influenza virus types—A, B, and C—only influenza A viruses historically have caused pandemics among humans. Influenza A viruses are subtyped according to their hemagglutinin and neuraminidase surface proteins. Protection from infection primarily is based on antibody against the hemagglutinin, although antibody against the neuraminidase can reduce spread of the virus but cannot prevent infection.[6] The antigens change either through (1) antigenic drift, or gradual changes in the hemagglutinin antigens that result in new influenza virus variants, allowing for seasonal influenza epidemics, or (2) antigenic shift, during which a new influenza A virus subtype emerges as the result of genetic reassortment or recombination. This change results in influenza A viruses against which few or no people any have immunity. Influenza pandemics result when new influenza A virus subtypes for which humans have little or no immunity

A student in a child-friendly classroom in Cambodia using the Avian Influenza kit, which teaches young people about the dangers of the illness. Printed with permission of Magnum.

Department of Health and Human Services Working Definition of "At-Risk Individuals"

Before, during, and after an incident, members of at-risk populations may have additional needs in one or more of the following functional areas:

- *Independence*—individuals in need of support to be independent in daily activities
- *Communication*—individuals who have limitations that interfere with the receipt of and response to information
- *Supervision*—individuals who require the support of caregivers, family, or friends or who have limited ability to cope in a new environment
- *Transportation*—individuals who cannot drive owing to the presence of a disability or who do not have a vehicle
- *Medical care*—individuals who are not self-sufficient or do not have adequate support from caregivers and need assistance with managing medical conditions

In addition to those individuals specifically recognized as at risk in the Pandemic and All-Hazards Preparedness Act (e.g., children, senior citizens, and pregnant women), individuals who might need additional assistance during a response should include those who have disabilities, live in institutionalized settings, are from diverse cultures, have limited English proficiency or are non-English speaking, are transportation disadvantaged, have chronic medical disorders, and have pharmacological dependency.

Source. Federal Guidance to Assist States in Improving State-Level Pandemic Influenza Operating Plans.[5]

cause human illness and spread efficiently from person to person.[7]

Seasonal Influenza

Epidemiology. Seasonal influenza epidemics of varying intensity and duration occur from late fall to early spring each year in the United States.[8] During the 1990s, an average of 36 000 deaths (range = 17 000–51 000) and 226 000 hospitalizations (range =55 000–431 000) occurred each year because of seasonal influenza. Rates of serious morbidity and mortality from seasonal influenza are highest in persons 65 years or older, children younger than 2 years, and persons with medical conditions that place them at high risk for serious complications from influenza. Persons 65 years or older account for more than 90% of the deaths and 60% of the hospitalizations related to seasonal influenza. Persons aged 50 to 64 years have an increased prevalence of high-risk medical conditions. Children and adults with chronic illnesses and children younger than 5 years are also at greater risk for influenza complications than is the general population.[9,10] Higher rates of chronic conditions in racial/ethnic minority populations increase the risk of severe disease from influenza.[11]

Transmission. Influenza is thought to spread primarily from person to person when infected people cough, sneeze, or talk, sending respiratory droplets into the air that then have pertinent contact with susceptible individuals. These droplets can infect a person through direct contact with mucous membranes, such as in the eyes, nose, or mouth. Transmission might also occur when people touch contaminated objects and then touch their own nose, mouth, or eyes with their hands, or when they inhale small, droplet nuclei.[12] The relative contribution of the different types of contact—airborne, large droplet, droplet nuclei, indirect exposure, and direct contact—in transmitting influenza is unknown.[13]

Infected individuals have a typical incubation period of about 1 to 4 days (average = 2 days) from exposure to development of symptoms.[7] Although infected adults can shed the virus from the day before until 5 to 10 days after the onset of symptoms,[14,15] the amount of virus shed decreases rapidly at 3 to 5 days after onset.[16,17] Children have the highest rates of influenza virus infection, may shed the virus longer,[18] and are a key source of transmission in community-wide epidemics.[19–21] Severely immunocompromised people can shed the virus for weeks or months.[22–25]

Clinical illness. Influenza signs and symptoms include the abrupt onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis,[26] which typically resolve in 3 to 7 days. Complications include primary influenza viral pneumonia; exacerbation of chronic medical conditions such as congestive heart failure and asthma; secondary bacterial pneumonia, sinusitis, or otitis media; and coinfection with other viruses or bacteria, including both methicillin-resistant and methicillin-sensitive strains of *Staphylococcus aureus* and *Streptococcus pneumoniae.*[27–29]

Diagnosis. It is difficult to distinguish, by signs and symptoms alone, influenza-related illnesses from those caused by other respiratory pathogens. The sensitivity and predictive value of clinical case definitions vary depending on the level of influenza activity and the prevalence of other respiratory pathogens circulating in the community at the time. The clinical diagnosis of influenza in persons with an influenza-like illness is much more likely to be accurate during influenza season than during periods when there is little influenza in the community. The clinical diagnosis of influenza is confirmed by laboratory tests that detect viral antigen, particles, or antibody in specimens of human secretions, tissue, or serum. Diagnostic tests for influenza include viral culture, serology, rapid antigen testing, reverse transcriptase–polymerase chain reaction, and immunofluorescence assays.[30] The sensitivity and specificity of these tests vary by laboratory, type of test used, type and quality of specimen, and timing of specimen collection in relation to illness. Results should be interpreted in the context of other clinical and epidemiological information. Additional information on influenza laboratory diagnostic procedures is available on the Centers for Disease Control and Prevention (CDC) Web site at http://www.cdc.gov/flu/professionals/diagnosis/labprocedures.htm.

Vaccines. The most effective way to prevent seasonal influenza and its complications is by getting vaccinated every year. Influenza vaccines, which are reformulated each year on the basis of global surveillance, currently contain 3 influenza virus strains: 1 influenza A(H3N2) virus, 1 influenza A(H1N1) virus, and 1 influenza B virus. Estimates of vaccine effectiveness—the prevention of

TABLE 1—US Formulations for Live, Attenuated Influenza Vaccine (LAIV) Compared With Trivalent Inactivated Influenza Vaccine (TIV) for Seasonal Influenza

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
No. of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Frequency of update of vaccine virus strains	Annually	Annually
Frequency of administration	Annually[a]	Annually[a]
Approved age for vaccination	2–49 y[b]	≥6 mo
Interval between 2 doses recommended for children aged ≥6 mo through 8 y who are receiving influenza vaccine for the first time	4 wk	4 wk
Can be given to persons with medical risk factors for influenza-related complications[b]	No	Yes
Can be given to children with asthma or children aged 2–4 y with wheezing in the past year[c]	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipients)	No	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunosuppressed	Yes	Yes
Can be simultaneously administered with other vaccines	Yes[d]	Yes[e]
If not simultaneously administered, can be administered within 4 wk of another live vaccine	Prudent to space 4 wk apart	Yes
If not simultaneously administered, can be administered within 4 wk of an inactivated vaccine	Yes	Yes

[a]Children aged 6 months through 8 years who have never received influenza vaccine before should receive 2 doses. Those who only receive 1 dose in their first year of vaccination should receive 2 doses in the following year, spaced 4 weeks apart.
[b]Persons at higher risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Persons at higher risk for complications of influenza infection because of underlying medical conditions include adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression; children and adolescents receiving long-term aspirin therapy (at risk for developing Reye syndrome after wild-type influenza infection); persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; pregnant women; and residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions.
[c]Clinicians and immunization programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2 to 4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health care providers should consult the medical record, when available, to identify children aged 2 to 4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2 to 4 years should be asked: "In the past 12 months, has a health care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer yes to this question and children who have asthma or who had a wheezing episode noted in the medical record within the past 12 months should not receive FluMist (MedImmune, Inc, Gaithersburg, MD).
[d]Live attenuated influenza vaccine coadministration has been evaluated systematically only among children aged 12 to 15 months who received measles, mumps, and rubella vaccine.
[e]Inactivated influenza vaccine coadministration has been evaluated systematically only among adults with pneumococcal polysaccharide vaccine.

laboratory-confirmed influenza illness in vaccinated populations—vary from less than 50% in years with poorly matched vaccines to 50% to 90% in years with well-matched vaccines.[31] These estimates largely depend on the degree of similarity between the viruses in the vaccine and those circulating in the community at the time, the age and immunocompetence of the vaccine recipient, and the health outcome being measured.

Two vaccines are available in the United States: (1) injectable, inactivated vaccines recommended for anyone who is 6 months or older and (2) live, attenuated vaccines recommended for healthy, nonpregnant persons aged 2 to 49 years (Table 1). Recommendations from the Advisory Committee on Immunization Practices (ACIP) focus on vaccinating persons at higher risk for complications from seasonal influenza (e.g., persons aged ≥50 years, children aged 6 months–4 years, persons with chronic medical conditions, pregnant women) and their contacts who might be sources of infection for them (e.g., household contacts, health care personnel; see the box on page S219). In 2008, ACIP expanded recommendations to include all children aged 6 months through 18 years (see the box on page S219) based on evidence of vaccine effectiveness and safety, adverse impacts of influenza among school-aged children and their contacts, and expectation that a simplified recommendation will improve vaccine coverage among children considered at high risk for influenza and especially needing vaccination. Sufficient vaccination coverage among children may reduce influenza among persons who have close contact with children and reduce overall transmission within communities.[31]

Estimated vaccination coverage levels in 2007 among persons older than 65 years were 70% for non-Hispanic Whites, 58% for non-Hispanic Blacks, and 54% for Hispanics.[33] Although seasonal influenza vaccination coverage

Summary of Seasonal Influenza Vaccination Recommendations by Advisory Committee on Immunization Practices

Children and adolescents aged 6 months through 18 years

Vaccination of all children aged 6 months through 18 years is recommended during the 2009–2010 influenza season.
Children and adolescents at higher risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children and adolescents, including:

- those who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus);
- those who are immunosuppressed (including immunosuppression caused by medications or by HIV);
- those who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- those who are receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection;
- those who are residents of chronic-care facilities; and
- those who will be pregnant during the influenza season.

Children aged younger than 6 months cannot receive the influenza vaccination. Household and other close contacts (e.g., day care providers) of children younger than 6 months, including older children and adolescents, should be vaccinated.

Adults

Annual vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others. Vaccination is recommended for all adults in the following groups because these persons are either at higher risk for influenza complications or are close contacts of persons at higher risk:

- persons aged 50 years or older;
- women who will be pregnant during the influenza season;
- persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus);
- persons who have immunosuppression (including immunosuppression caused by medications or by HIV);
- persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- residents of nursing homes and other chronic-care facilities;
- health care personnel;
- household contacts and caregivers of children aged younger than 5 years and adults aged 50 years or older, with particular emphasis on vaccinating contacts of children aged younger than 6 months; and,
- household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

Source. Reprinted with permission from Centers for Disease Control and Prevention.[32]

has increased in recent years, coverage remains low or below the target range in all groups for whom annual vaccination is recommended.[34] Some reasons for low coverage are the relatively short time frame for annual vaccination, lack of access to vaccination, lack of knowledge about influenza burden and vaccine indications, concerns about vaccine effectiveness and safety, lack of prioritization of influenza immunization by the public, and lack of advocacy for vaccination by some health care providers.

Antiviral medications. Antiviral medications can be used for influenza treatment or chemoprophylaxis. The US Food and Drug Administration (FDA) approved 2 classes of antiviral drugs for the treatment of influenza A: the adamantanes (or M2 protein inhibitors), amantadine and rimantadine, and the neuraminidase inhibitors, oseltamivir and zanamivir (Table 2).[31] A national sample of outpatient and emergency department visits during the 1995–2002 influenza seasons found that physicians prescribed antiviral agents to 19% of patients diagnosed with influenza, although it could not be determined whether this represented underprescribing, overprescribing, or appropriate prescribing.[35]

When taken by otherwise healthy children or adults within 48 hours of onset of illness, zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by about 1 day.[36,37] Some observational studies of the effectiveness of oseltamivir have shown reductions in severe outcomes among hospitalized patients.[38,39] Neuraminidase inhibitors also can be used to prevent influenza in household contacts of people with influenza[40,41] and in institutional settings.[42,43]

Oseltamivir and zanamivir are generally well tolerated. Based on reports from Japan of transient neuropsychiatric events among persons, usually adolescents, receiving neuraminidase inhibitors, the FDA advises that people receiving oseltamivir or zanamivir be monitored closely for abnormal behavior.

TABLE 2—Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Chemoprophylaxis: United States

Antiviral Agent and Treatment/Propylaxis	Aged 1–6 Years	Aged 7–9 Years	Aged 10–12 Years	Aged 13–64 Years	Aged ≥ 65 Years
Zanamivir[a]					
Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
Chemoprophylaxis, influenza A and B	NA for ages 1–4	Ages 5–9, 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir[b]					
Treatment,[c] influenza A and B	Dose varies by child's weight[d]	Dose varies by child's weight[d]	Dose varies by child's weight[d]	75 mg twice daily	75 mg twice daily
Chemoprophylaxis, influenza A and B	Dose varies by child's weight[d]	Dose varies by child's weight[e]	Dose varies by child's weight[e]	75 mg/day	75 mg/day
Amantadine[f]					
Treatment, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses[g]	5 mg/kg body weight/day up to 150 mg in 2 divided doses[g]	100 mg twice daily[h]	100 mg twice daily	≤ 100 mg/day
Prophylaxis, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses[g]	5 mg/kg body weight/day up to 150 mg in 2 divided doses[g]	100 mg twice daily[h]	100 mg twice daily[h]	less than or equal to 100 mg/day
Rimantadine[i]					
Treatment,[j] influenza A	NA	NA	NA	100 mg twice daily[h]	100 mg/day
Prophylaxis, influenza A	5 mg/kg body weight/day up to 150 mg in 2 divided doses[g]	5 mg/kg body weight/day up to 150 mg in 2 divided doses[g]	100 mg twice daily[h]	100 mg twice daily[d]	100 mg/day[k]

Note. NA = not applicable. Recommended duration for antiviral treatment is 5 days. For chemoprophylaxis, recommended duration is 10 days when given after a household exposure and 5 to 7 days after last known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, the Centers for Disease Control and Prevention recommends antiviral chemoprophylaxis for a minimum of 2 weeks, and up to 1 week after the last known case was identified. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children younger than 1 year of age. This information is based on data published by the Food and Drug Administration (FDA).

Source. Adapted from Table: Recommended Daily Dosage of Seasonal Influenza Antiviral Medications for Treatment and Chemoprophylaxis for the 2008-09 Season–United States (available at: http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table).

[a]Zanamivir is manufactured by GlaxoSmithKline (Relenza: inhaled powder) and is approved for treatment of persons 7 years and older and approved for chemoprophylaxis of persons 5 years and older. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease.

[b]Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu: tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged 1 year and older.

[c]A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance less than 30 mL/min.

[d]The treatment dosing recommendation for children who weigh 15 kg or less is 30 mg twice a day. For children who weigh more than 15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh more than 23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh more than 40 kg, the dose is 75 mg twice a day.

[e]The chemoprophylaxis dosing recommendation for children who weigh 15 kg or less is 30 mg once a day. For children who weigh more than 15 kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh more than 23 kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh more than 40 kg, the dose is 75 mg once a day.

[f]Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel: tablet and syrup); Geneva Pharms Tech (Amantadine HCL: capsule); USL Pharma (Amantadine HCL: capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, Pharmaceutical Associates (Amantadine HCL: syrup), and Sandoz. The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance less than or equal to 50 mL/min/1.73 m^2.

[g]Fifty-five milligrams per kilogram of body weight of amantadine or rimantadine syrup=1 tsp/22 lbs.

[h]Children aged 10 years and older who weigh less than 40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg body weight/day.

[i]Rimantadine is manufactured by Forest Laboratories (Flumadine: tablet and syrup); Corepharma, Impax Labs (Rimantadine HCL: tablet), and Amide Pharmaceuticals (Rimantadine HCL: tablet). A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance less than 10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

[j]Rimantadine is approved by the FDA for treatment of influenza A only among adults. However, certain specialists in the management of influenza consider rimantadine appropriate for treatment of influenza A among children. Studies evaluating the efficacy of amantadine and rimantadine in children are limited, but they indicate that treatment with either drug diminishes the severity of influenza A infection when administered within 48 hours of illness onset.

[k]Older nursing home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged 65 years and older if they experience possible side effects when taking 200 mg/day.

Resistance to oseltamivir has been observed among seasonal H1N1 viruses in some countries. The CDC monitors the prevalence of H1N1 virus strains resistant to oseltamivir and issues interim recommendations for antiviral treatment and chemoprophylaxis of influenza. In the United States during the 2008–2009 influenza season, most seasonal H1N1 viruses have been resistant to oseltamivir and most H3N2 viruses have been resistant to amantadine and rimantadine. Health care providers should consult the CDC's "Interim Recommendations for Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance Among Circulating Influenza A (H1N1) Viruses" (available at http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279) for guidance pending new ACIP recommendations for use of antiviral medications.[43]

Avian Influenza

H5N1 is one of several avian influenza viruses of concern. In 1997, an outbreak of severe human infections with H5N1 in Hong Kong was attributed to human exposure to infected birds.[44–46] Because H5N1 was not known to cause human disease in the 20th century, levels of clinical immunity to the strain are low to nonexistent throughout the world. H5N1 reemerged in 2003 and has caused large outbreaks among poultry and wild birds in more than 50 countries. Cases of human infection with highly pathogenic H5N1 have existed primarily among persons with direct or close unprotected contact with sick or dead birds associated with the avian outbreaks in Asia, Africa, Europe, and the Middle East.[47–52] As of June 2, 2009, of 433 confirmed human H5N1 cases reported to the World Health Organization, 262 have been fatal.[53] Although transmission has been predominantly bird to human, ongoing outbreaks among both wild and domesticated birds, with occasional human infection, raise concern that this virus may develop the ability to be efficiently transmitted from person to person, leading to an influenza pandemic.[54] Limited person-to-person transmission of H5N1 has likely occurred in some disease clusters.[54,55]

Pandemic Influenza

Influenza pandemics can occur when an influenza A virus subtype develops the ability to be efficiently transmitted from person to person in human populations around the world that lack immunity. The 3 influenza pandemics that occurred during the 20th century varied in severity:

- The 1918 H1N1 pandemic caused 20 million to 50 million deaths worldwide,
- The 1957 H2N2 pandemic caused 1 million to 2 million deaths worldwide, and
- The 1968 H3N2 pandemic caused 700 000 to 1 million deaths worldwide.

A severe influenza pandemic could overwhelm health and medical capabilities and potentially lead to hundreds of thousands of deaths, millions of hospitalizations, and hundreds of billions of dollars in direct and indirect costs. In addition, a severe pandemic could change daily life, including limiting travel and public gatherings, disrupting businesses, and dismissing children and adults from schools.[56] Even less severe pandemics would likely pose substantial challenges to the health care system and lead to higher rates of work and school absenteeism.

Vaccines. Vaccines that are specifically formulated to work against a pandemic virus usually will not be available until 4 to 5 months after a pandemic begins.[57] Researchers are developing vaccines for various clades and subclades of H5N1 viruses currently circulating among birds and for other influenza A viruses with pandemic potential. These vaccines might provide immunologic priming, thus potentially reducing the number of doses required to induce some degree of protective immunity once a strain-matched vaccine is given, or even provide partial protection against a pandemic strain prior to a strain-matched vaccine being given.

Vaccines against the various H5N1 virus clades and subclades and other novel influenza A viruses are likely to require 2 doses to induce a protective immunologic response on the basis of experience with studies of seasonal influenza vaccine in populations that have not been previously exposed to the particular virus strain, the reemergence of H1N1 in 1977, the 1976 swine flu vaccine, and studies of prepandemic vaccines.[58,59] The H5N1 vaccines have been shown to be immunogenic and safe in initial trials among healthy, young nonpregnant adults.[59–63] However, little information is available on immunogenicity or safety in older people, people with chronic illness, pregnant women, or infants and young children,[64,65] and effectiveness data will not be available before a pandemic. One vaccine against clade 1 H5N1 is licensed in the United States and another is licensed in Europe.[66] These vaccines are being produced for government stockpiles and are not commercially available.

Pandemic vaccines with adjuvants to increase their immunogenicity are being developed to improve immunogenicity and to reduce the amount of hemagglutination-inhibition (HI) antigen needed in vaccines because the amount of HI antigen required to induce a protective response is much greater than that required for seasonal vaccines. These adjuvanted vaccines appear to be safe and immunogenic, and they induce cross-reactive immune responses in healthy adults while requiring considerably less HI antigen than is needed to induce an immune response to unadjuvanted vaccines.[60,67]

Vaccination will likely need to be prioritized during the early stages of a pandemic. The persons prioritized to receive vaccination vary according to the severity of the pandemic. For more severe pandemics with high case–fatality ratios, persons prioritized for vaccination include health care personnel and emergency responders, a subset of persons working in occupations that support critical infrastructure, and pregnant women and young children. Although the prepandemic draft allocation guidance for the United States did not directly prioritize other at-risk and vulnerable populations, these groups benefit indirectly. For example, it is essential to maintain critical infrastructure (e.g., water, electric, and gas services) so that people are able to heat their homes and have sanitation services and safe water to avoid becoming ill from drinking contaminated water.

HHS's Biomedical Advanced Research and Development Authority oversees procurement of vaccine, including vaccines against various clades and subclades of

H5N1 viruses and vaccines intended to be used with adjuvants. The US government has contracted with vaccine manufactures to hold the vaccines, primarily in bulk storage, until they receive an order to fill and deliver them. Vaccine storage and distribution is coordinated through the CDC. Vaccines developed prior to a pandemic might be recommended during the early stages of a pandemic while vaccines against the specific pandemic influenza virus are being developed. Vaccination of critical personnel such as health care workers prior to a pandemic has also been proposed.[63] Experts are planning for how best to use antiviral agents and other medical countermeasures during a severe pandemic.

Antiviral medications. Recommendations for antiviral treatment and chemoprophylaxis during an influenza pandemic, including the dose and duration, will depend on the antiviral sensitivity patterns of the pandemic strain of influenza virus. Currently, many of the H5N1 strains causing human infections are resistant to adamantine and M2 inhibitors. Neuraminidase inhibitors are currently recommended for H5N1 treatment and chemoprophylaxis. Data are not sufficient, however, for determining treatment effectiveness and optimal dosing,[54] and resistance to neuraminidase inhibitors has been observed rarely in some H5N1 viruses.

Neuraminidase inhibitors are currently licensed only for use in some age groups (Table 2). Oseltamivir and zanamivir are both "Pregnancy Category C" medications because no clinical studies have been conducted to assess the safety of these medications for pregnant women. Because the potential risk to the fetus appears to be outweighed by the benefits of using anti-influenza medications during a pandemic, no basis currently exists for modifying recommendations for pregnant women from the ones that are provided for treating the general population. Further, pregnant women should be considered a high priority for receiving anti-influenza medications for treatment or prophylaxis, given their presumed high risk of influenza-associated morbidity and mortality.[31,68,69]

Strategic National Stockpile. The Strategic National Stockpile (SNS) stores pharmaceuticals and other resources that can be requested by state governors during large-scale public health emergencies. SNS assets include antiviral agents (such as oseltamivir and zanamivir) and medical supplies and personal protective equipment (ventilators, N95 respirators, surgical masks, face shields, surgical gowns, gloves, antimicrobial agents, needles and syringes) available for use in an influenza pandemic. Governors do not need to request these assets through the usual SNS process. Once directed by federal officials to do so, SNS officials automatically deliver influenza pandemic assets to states on a pro rata basis. The SNS does not store or distribute vaccine.

Response to an influenza pandemic will depend on state-level antiviral stockpiles and federal-level supplies. In addition to the resources in the SNS, states are tasked with procuring their own stockpiles, which account for 41% of the national inventory of antiviral medications for the treatment of the general population. Both federal and state stockpiles are essential components of prevention and control strategies.

Nonpharmaceutical interventions. Slowing the spread of an influenza pandemic would provide more time to isolate and identify the pandemic virus strain; produce, distribute, and administer a strain-matched vaccine[57]; and reduce the enormous impact of a pandemic on the health care system. Nonpharmaceutical interventions may serve as one component of a comprehensive community mitigation strategy that includes both pharmaceutical and nonpharmaceutical measures. Assessments of the impact of actions taken during previous pandemics and mathematical modeling studies indicate that nonpharmaceutical interventions could have a substantial impact on the epidemiology of an influenza pandemic.[70–72] When an influenza pandemic starts, government officials will consider factors such as severity (primarily based on infection and case fatality rate among patients infected with the pandemic strain of influenza) and, on the basis of the severity, recommend appropriate responsive actions at all levels of society.

Actions that might be recommended are presented in *Interim Pre-Pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States—Early, Targeted Layered Use of Nonpharmaceutical Interventions.*[57] Community mitigation actions may include the following:

- Asking ill people to voluntarily remain at home and not go to work or out into the community for about 7 to 10 days—or until they are well and can no longer spread the infection to others (voluntary isolation).
- Asking members of households where a person is ill to voluntarily remain at home for about 7 days (voluntary quarantine).
- Treating ill individuals and providing prophylaxis to members of their households through influenza antiviral medications, if available.
- Dismissing students from public and private schools, colleges and universities, school-based activities, and child care programs for up to 12 weeks.
- Reducing out-of-school social contacts and community mixing by limiting contact of children and adolescents at malls, movie theaters, and similar venues.
- Reducing contact between adults in the community and workplace, including cancellation of large public gatherings, religious services, and social events. Reducing contact also could include temporarily changing workplace environments and schedules to avoid large numbers of people mixing together at one time.

Respiratory diseases may be reduced through reasonable and inexpensive hygiene efforts such as hand washing and using masks.[73–75] Although few data are available to assess the effects of community-level respiratory disease mitigation strategies (e.g., closing schools, avoiding mass gatherings) on reducing influenza virus transmission,[71,76] review of interventions used in past pandemics, modeling, and common sense indicate that these strategies may be our most effective mitigation tools. For these strategies to be improved, additional research is needed to better understand how influenza is transmitted and determine the most effective strategies for reducing that transmission.

Certain at-risk and vulnerable populations may be disproportionately affected by a pandemic and by actions taken to reduce the impact of a pandemic (see the box on page S217). For example, some individuals may not have

enough money to follow recommendations to stockpile supplies or stay home from work. Children in single-parent homes, homeless people, travelers, and socially, culturally, or geographically isolated people may lack support networks to help them follow these recommendations or obtain antiviral medications or vaccines when they become available. Vulnerable persons are more likely to experience adverse consequences when the usual systems they rely on are overloaded or unavailable. Thus, community planning for support for such individuals is crucial. (These groups will be covered in detail in subsequent articles in this supplement.)

CONCLUSIONS

Seasonal influenza epidemics cause considerable morbidity and mortality in the United States. Although the country has made substantial progress in preparing for an influenza pandemic, challenges remain. Strategies to mitigate the impact of a pandemic are still being developed, but are based on limited data. Stakeholders who plan for the impact of a pandemic on at-risk and vulnerable populations must consider how to equitably distribute vaccine, antiviral agents, and other countermeasures and how to minimize—for all groups—the disruption that may be caused by nonpharmaceutical interventions. Although no simple solutions exist, we hope that the articles included in this supplement will help address these issues. ■

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Contributors

S. Santibañez, T.L. Merlin, and S. Redd conceptualized the article. S. Santibañez led the authors in writing and editing, compiled contributions from all authors, and conducted key components of the literature review. A.E. Fiore contributed to the literature review and writing of the sections on seasonal influenza, vaccines, and antiviral agents. All authors helped to conceptualize ideas, interpret findings, and review and revise drafts of the manuscript.

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Note. Pandemic (H1N1) 2009 virus (initially referred to as "swine flu") is a new influenza virus that was first detected in the United States in April 2009. In June 2009, the World Health Organization signaled that an (H1N1) 2009 influenza pandemic was underway. This article and supplement represent prepandemic planning. Readers are encouraged to go to www.cdc.gov/H1N1flu and www.flu.gov for the most up-to-date information about pandemic (H1N1) 2009 influenza.

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