

Pandemic Influenza CIDRAP

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Note: Information on avian influenza is available in the overviews "Avian Influenza (Bird Flu): Agricultural and Wildlife Considerations" and "Avian Influenza (Bird Flu): Implications for Human Disease."

Agent

All past influenza pandemics in humans have been caused by influenza A viruses. General information about influenza A viruses (not specific to pandemic strains) is presented in the bullets below.

- Family: Orthomyxoviridae
 - Enveloped virions are 80 to 120 nm in diameter, are 200 to 300 nm long, and may be filamentous.
 - They consist of spike-shaped surface proteins, a partially host-derived lipid-rich envelope, and matrix (M) proteins surrounding a helical segmented nucleocapsid (6 to 8 segments).
 - The family contains five genera, classified by variations in nucleoprotein (NP and M) antigens: influenza A, influenza B, influenza C, thogotovirus, and isavirus.
- Genus: Influenzavirus A
 - Consists of a single species: influenza A virus.

- Influenza A viruses are a major cause of influenza in humans.
- The multipartite genome is encapsidated, with each segment in a separate nucleocapsid. Eight different segments of negative-sense single-stranded RNA are present; this allows for genetic reassortment in single cells infected with more than one virus and may result in multiple strains that are different from the initial ones (see [References](#): Voyles 2002).
- The genome consists of 10 genes encoding for different proteins (eight structural proteins and two nonstructural proteins). These include the following: three transcriptases (PB2, PB1, and PA), two surface glycoproteins (hemagglutinin [HA] and neuraminidase [NA]), two matrix proteins (M1 and M2), one nucleocapsid protein (NP), and two nonstructural proteins (NS1 and NS2).
- The virus envelope glycoproteins (HA and NA) are distributed evenly over the virion surface, forming characteristic spike-shaped structures. Antigenic variation in these proteins is used as part of the influenza A virus subtype definition (but not used for influenza B or C viruses).
- Influenza A virus subtypes:
 - There are 16 different HA antigens (H1 to H16) and nine different NA antigens (N1 to N9) for influenza A. Until recently, 15 HA types had been recognized, but a new type (H16) was isolated from black-headed gulls caught in Sweden and the Netherlands in 1999 and reported in the literature in 2005 (see [References](#): Fouchier 2005).
 - Human disease historically has been caused by three subtypes of HA (H1, H2, and H3) and two subtypes of NA (N1 and N2).
 - More recently, human disease has been recognized to be caused by additional HA subtypes, including H5, H7, and H9 (all from avian origin).
 - All known subtypes of influenza A can be found in birds, and feral aquatic birds are the major reservoir for influenza A viruses. Feral birds generally do not develop severe disease from influenza; however, domestic chickens and turkeys are susceptible to severe and potentially fatal influenza.
 - Certain mammals also are susceptible to influenza. Influenza A viruses have traditionally been known to cause disease in horses, pigs, whales, and seals; however, the range of several influenza A subtypes is expanding to further mammalian species. H5N1 influenza A recently has been shown to infect cats, leopards, and tigers (see [References](#): Keawcharoen 2004; Webster 2006). Cases of canine influenza have been recognized in the United States and are being caused by H3N8 influenza A, a subtype traditionally found in horses (see [References](#): Crawford 2005).
- Influenza A virus subtype strains
 - Antigenic strain nomenclature is based on: (1) host of origin (if other than human), (2) geographic origin, (3) strain number, (4) year of isolation, and (5) HA and NA type. (Examples are as follows: A/Hong Kong/03/68[H3N2], A/swine/Iowa/15/30[H1N1].)
 - H5N1 strains have been differentiated into genetic clades, with nonoverlapping case distributions. All human H5N1 strains are grouped in clade 1 (see [References](#): WHO Global Influenza Program Surveillance Network).
- Classification of influenza A strains by pandemic potential

- *Strains from past pandemics*: "Noncontemporary" strains are those from previous pandemics that pose some degree of risk to the public owing to decreased immunity in the current population. The term is currently used to describe strains from the Asian flu (H2N2) but could be applied to strains from the earlier Spanish flu pandemic (H1N1) (see [References](#): CDC: Interim CDC-NIH recommendation for raising the biosafety level for laboratory work involving noncontemporary human influenza [H2N2] viruses).
- *Nonpandemic strains*: These include strains that have recently circulated or are currently circulating in the human population (ie, those belonging to H1N1, H3N2, and H1N2 subtypes).
- *Potential pandemic strains*: Potential pandemic strains must have the following features: (1) have an antigenic makeup to which the population is immunologically naive, (2) be able to replicate in humans, and (3) efficiently transmit from human to human. Because of homosubtypic immunity (see below), new pandemic strains are most likely to be of subtypes not previously recognized in human populations. Currently, strains of H5 and H7 subtypes are of greatest concern.
- *Animal pandemic strains (including avian influenza strains)*: Animal strains such as H5N1 avian influenza are not considered human pandemic strains unless the above criteria are met, but they have significant potential to evolve into new human pandemic strains through the process of genetic reassortment (see below) or through gradual adaptation to the human host. Most avian strains are not of concern as potential pandemic strains.
- Avian influenza
 - The term "avian influenza" is used to describe influenza A subtypes that primarily affect chickens, turkeys, guinea fowls, migratory waterfowl, and other avian species.
 - "Avian influenza" is an ecological classification that does not correspond exactly to other classification schemes.
 - As with other influenza A subtypes, standard nomenclature is used to name strains (eg, A/Chicken/HK/5/98 [H5N1]).
 - Avian influenza strains in domestic chickens and turkeys are classified according to disease severity, with two recognized forms: highly pathogenic avian influenza (HPAI), also known as fowl plague, and low-pathogenic avian influenza (LPAI). Avian influenza viruses that cause HPAI are highly virulent, and mortality rates in infected flocks often approach 100%. LPAI viruses are generally of lower virulence, but these viruses can serve as progenitors to HPAI viruses. The current strain of H5N1 responsible for die-offs of domestic birds in Asia is an HPAI strain; other strains of H5N1 occurring elsewhere in the world are less virulent and, therefore, are classified as LPAI strains. All HPAI strains identified to date have involved H5 and H7 subtypes.
 - Human infections have been associated with both HPAI and LPAI strains (see [References](#): HHS: Pandemic influenza plan).
 - Evidence that HPAI strains arise from LPAI strains has led the World Organization for Animal Health to classify all H5 or H7 strains as notifiable (see [References](#): Alexander 2003, Capua 2004, OIE 2005).

- In the United States, currently only HPAI avian strains and reconstructed 1918 H1N1 strains are regulated as select agents (see Biosafety and Biosecurity, below).
- The 1918 influenza pandemic strain (H1N1) appears to be of avian origin (see [References](#): CDC: Information about pandemic influenza viruses).
- Physical characteristics of influenza A viruses
 - Strains are sensitive to lipid solvents, nonionic detergents, formaldehyde, and oxidizing agents.
 - They are inactivated by ionizing radiation, pH extremes (>9 or <5), and temperatures greater than 50°C.
 - Viruses remain infectious after 24 to 48 hours on nonporous environmental surfaces and less than 12 hours on porous surfaces (see [References](#): Bean 1982). (Note: The importance of fomites in disease transmission has not been determined.)

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Laboratory Testing for Influenza

The following statements regarding laboratory testing apply to influenza viruses in general, not just to influenza testing in a pandemic setting. During a pandemic, recommendations for laboratory testing may change, depending on a number of factors, including availability of testing reagents and laboratory staffing/surge capacity.

General Considerations

- Tests for influenza virus include viral culture, polymerase chain reaction (PCR), rapid antigen testing, and immunofluorescence. Serologic tests are used to retrospectively diagnose infection.
- Laboratory tests do not need to be conducted on all patients with suspected influenza. Factors that influence the decision to test or not test patients with signs and symptoms of influenza include:
 - *Residence in a healthcare facility*: Documentation of influenza virus infection in inpatients or residents of long-term care facilities is important for detection and control of outbreaks.
 - *Treatment options*: Testing should be performed if laboratory results influence clinical decision making.
 - *Level of influenza activity in the community*: The positive predictive value of influenza tests, especially rapid assays, increases with prevalence of influenza in the community; therefore, if the prevalence of influenza is low, the utility of the tests decreases. As influenza prevalence increases, the predictive value of clinical diagnosis without laboratory testing also increases and laboratory confirmation may not be necessary (see [References](#): CDC: Interim guidance for influenza diagnostic testing during the 2004-05 influenza season; Monto 2005).
 - *Participation in a surveillance program*: Sentinel surveillance can be useful to determine which strains are circulating in the community and to assess the

degree of the match between circulating viruses and those used to make the vaccine for that year.

- *Patients who meet the criteria for a novel influenza virus.* During a pandemic alert period, patients who meet certain criteria (such as influenza symptoms and recent travel to an area affected by a novel strain) should be considered for laboratory testing.
- *Pandemic considerations.* As noted above, recommendations for testing during a pandemic may be somewhat unique and dependent upon factors such as availability of reagents and laboratory surge capacity.
- The sensitivity and specificity of laboratory tests appears to vary with the involved strain, which has implications for emerging variants (see [References](#): Weinberg 2005).
- Laboratory tests are required for specific identification of pandemic strains. The most likely ways that a pandemic strain would be detected initially are:
 - Outbreak investigations or investigation of unexplained death in a previously healthy individual
 - Influenza surveillance with laboratory testing and characterization of unusual strains
 - Investigation of unusual laboratory findings
- State and local health departments should be prepared to process or test for the following (if they have the capability, as described below) (see [References](#): HHS: Pandemic influenza plan).
 - Avian influenza A (H5N1) and other avian influenza viruses
 - Other animal influenza viruses
 - New or re-emergent human influenza viruses (such as H2 strains)
- Testing during a pandemic (see [References](#): HHS: Pandemic influenza plan):
 - CDC will update protocols and distribute reagents as necessary.
 - The need for confirmatory testing will diminish as the pandemic progresses. Some level of continued monitoring will be necessary to monitor changes in antigenicity and antiviral susceptibility. CDC will provide appropriate guidance in such situations.
- Reporting and referral (see [References](#): HHS: Pandemic influenza plan)
 - Clinical laboratories should contact their state or local health departments if they receive specimens from patients with possible novel influenza suspected on the basis of clinical and epidemiologic criteria.
 - Public health laboratories should send specimens to CDC if the patient meets clinical and epidemiologic criteria and (1) tests positive for influenza A by reverse transcriptase–polymerase chain reaction (RT-PCR) or rapid testing or (2) tests negative for influenza A by rapid testing and RT-PCR is not available. Laboratories without capacity for testing avian strains by indirect immunofluorescence (IFA) or RT-PCR should send untypable influenza isolates to CDC.
 - Any unusual subtype should be reported to CDC through their emergency response hotline (770-488-7100).

- Laboratory-based influenza surveillance networks
 - WHO Global Influenza Surveillance Network (see [References](#))
 - CDC National Respiratory and Enteric Virus Surveillance System (NREVSS) (see [References](#))
 - State or local surveillance health department surveillance networks

Specimen Collection

- Appropriate specimens for testing include: nasal wash /aspirate, nasopharyngeal swab, throat swab, bronchoalveolar lavage, tracheal aspirate, pleural fluid tap, sputum, and autopsy specimens (see [References](#): HHS: Pandemic influenza plan [Part 2, Supplement 2]).
- Specimens from living patients optimally should be collected within 4 days after illness onset.
- Some rapid test kits require specific specimen types and storage/transport methods.
- Nasopharyngeal swabs, nasal washes, and nasal aspirates are considered to be more sensitive than throat swabs for culture of most respiratory viruses, including convention influenza strains, and are preferred for children younger than 2 years of age.
- Pharyngeal swabs collected 4 to 8 days after onset of illness may be more sensitive for detection of influenza A (H5N1) than nasal swabs (see [References](#): WHO: Writing Committee of WHO Consultation on Human Influenza A/H5I 2005).
- Only sterile Dacron or rayon swabs with plastic shafts should be used. Calcium alginate swabs or swabs with wooden sticks should not be used.
- Viral transport media should be used for nasopharyngeal and oropharyngeal swabs, and specimens should be maintained at refrigerator temperature (4°C to 8°C) until testing is performed. Freezing at -70°C is best for maintaining viability during extended storage
- With regard to autopsy specimens, large airways have the highest yield for immunohistochemistry (IHC) tests. Eight blocks or fixed-tissue specimens from each of the following sites should be obtained. Fixed tissue should be transported at room temperature (not frozen); fresh unfixed tissue should be frozen.
 - Central (hilar) lung with segmental bronchi
 - Right and left primary bronchi
 - Trachea (proximal and distal)
 - Representative pulmonary parenchyma from right and left lung
- Infection control precautions should be observed during specimen collection.
- Specimen collection procedures for animals have been described by WHO (see [References](#): WHO: Manual on animal influenza diagnosis and surveillance).

Biosafety and Biosecurity

- New safety rules and recommendations for influenza virus will be published in a revised edition of *Biosafety in Microbiological and Biomedical Laboratories (BMBL)* in early 2006 (see [References](#): CDC: Interim CDC-NIH recommendation for raising the biosafety level for laboratory work involving noncontemporary human influenza [H2N2] viruses; CDC: Update on influenza A [H5N1] and SARS: Interim

recommendations for enhanced U.S. surveillance, testing, and infection controls; HHS: Pandemic influenza plan). Current recommendations for interpandemic and pandemic alert periods include:

- Culture of influenza subtypes H1-4, H6, and H8-15 (with exceptions noted below) and culture of specimens from patients not suspected of having novel influenza strains requires BSL-2 containment and practices (Animal BSL-2 for animal models).
- Culture of noncontemporary influenza strains (H2N2) or research involving reverse genetics of the 1918 Spanish flu strain (H1N1) requires BSL-3 facilities and Animal BSL-3 practices, including containment with rigorous adherence to additional respiratory protection and clothing change protocol, use of negative pressure, high-efficiency particulate air (HEPA)-filtered respirators or positive air-purifying respirators (PAPRs), use of HEPA filtration for treatment of exhaust air, and amendment of personnel practices to include personal showers prior to exiting the laboratory.
- Culture from patients suspected of having avian influenza, other novel influenza strains, or severe acute respiratory syndrome (SARS) coronavirus should only be conducted under enhanced BSL-3 containment (also see Biosecurity below). This includes controlled access, double-door entry with changing room and shower, use of respirators, decontamination of all waste, and showering out of all personnel. These diagnostic activities must be kept separate from routine influenza diagnostic activities (eg, probably H1 or H3) to prevent recombination.
- IFA of specimens requires BSL-2 containment and practices. Culture biocontainment recommendations should be implemented when IFA is used for culture identification.
- Direct detection methods, including commercial antigen detection assays and RT-PCR, should be conducted under BSL-2 with a Class II biological safety cabinet. Serologic methods require BSL-2 containment.
- If H5N1 avian influenza virus is presumptively identified by one of the above direct methods, further work should be conducted using the enhanced BSL-3 procedures described for culture.
- Any new or re-emergent human influenza strain with suspected pandemic potential should be treated in the same manner as described for H5N1 avian influenza.
- Additional requirements and recommendations apply for laboratory work involving live animals.
- Biosecurity
 - Human influenza strains, with a few exceptions (see below), are not regulated as select agents. Inclusion of potentially pandemic strains on the select agent list is currently under consideration (see [References](#): CDC: Interim CDC-NIH recommendation for raising the biosafety level for laboratory work involving noncontemporary human influenza [H2N2] viruses; CDC: Update on avian influenza A[H5N1] and SARS). Despite the absence of regulatory authority, standard biosecurity measures should be maintained for potentially pandemic strains.
 - The US Department of Agriculture (USDA) classifies highly pathogenic avian influenza (HPAI) as an agricultural select agent regulated under 7 CFR

part 331 and 9 CFR Part 121 of the *Federal Register*, which was published as a Final Rule in the March 18, 2005, issue (see [References](#): USDA/APHIS: Agricultural Bioterrorism Protection Act of 2002). Laboratories that work with HPAI strains (H5 or H7) or perform diagnostic cultures for suspected human cases of avian influenza caused by H5 or H7 or suspected cases of SARS must be registered with the USDA.

- Both registered and exempt laboratories that identify a select agent contained in a specimen presented for diagnosis, verification, or proficiency testing must secure the agent against theft, loss, or release until transfer or destruction. Unregistered laboratories must transfer or destroy select agents within 7 days of identification. Any theft, loss, or release of the agent must be reported to the select agent authority (see [References](#): USDA/APHIS: Questions and answers).
- Effective October 20, 2005, "reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments" will be regulated as select agents under an interim rule from the US Department of Health and Human Services (HHS) (see [References](#): CDC: Select Agent Program).

Virus Isolation by Cell Culture

- Virus isolation is considered the "gold standard" of influenza testing (see [References](#): Hayden 2002, Treanor 2005).
- Cell culture measures growth rather than the presence or absence of specific targets. As cell lines are designed to support the growth of a wide range of viruses, cell culture will likely allow for detection of emerging and pandemic influenza strains (see [References](#): Australian Government Department of Health and Ageing).
- Isolates obtained from cell culture are required for strain characterization, which is an integral part of global influenza surveillance and monitoring activities during a pandemic (see [References](#): HHS: Pandemic influenza plan).
- Cell culture is subject to certain restrictions (see [Biosafety and Biosecurity](#) above).
- Specimens for culture optimally should be collected within 3 days after illness onset.
- Turnaround time for the standard method is 2 to 14 days.
- Culture consists of growth on a cell monolayer, detection of viral growth, and specific identification.
- Virus detection and identification methods for standard culture include the following:
 - Cell lines include Madin-Darby canine kidney (MDCK), primary rhesus monkey kidney (PRMK), or cynomolgus monkey kidney. Other cell lines, such as Vero, mink lung, and MRC-5, also support growth of influenza virus if trypsin is incorporated into serum-free medium.
 - Cytopathic effect (CPE) is not a consistent feature of influenza A virus. If present, CPE is nonspecific, including vacuolization or cell degeneration.
 - Assays for haemadsorption (HAd) (ie, influenza-infected cells bind red blood cells [RBCs]) are performed blindly, typically at 7 and 14 days or on cells exhibiting CPE. Other viruses, such as parainfluenza virus and mumps virus,

may also cause HAAd. The lack of HAAd specificity may be an advantage in detecting new or pandemic strains.

- Hemagglutination inhibition (HI or HAI) is used to identify the viral subtype. Cell supernatant is mixed with RBCs; identification is by quantitative inhibition of agglutination using subtype-specific antisera. Homologous strains yield high HI titers. New pandemic strains would likely be HAAd-positive with or without CPE, with low or negative titers to group-specific antisera.
- Identification of infected cells is by direct or indirect immunofluorescence (eg, DFA, IFA), enzyme-linked immunoassays (EIA), or PCR-based methods. Assays with more conserved, less specific targets are more likely to detect newly emerged strains.
- The time to detection in culture, as measured in one study conducted during two influenza seasons, ranged from 5 days (>90% of positive specimens) to 7 days (100% of positive specimens) (see [References](#): Newton 2002).
- A golden rule of laboratory testing is to never process clinical specimens from humans and swine (and presumably birds) in the same laboratory (see [References](#): WHO recommended laboratory tests to identify influenza A/H5 in specimens from patients with influenza-like illness).
- Shell vial assay (rapid culture), when combined with a rapid detection/identification method, offers a sensitive and rapid diagnostic alternative to standard culture. This method does not result in an adequate viral titer or volume for further characterization and would thus not be appropriate for pandemic influenza surveillance without subculture.

Direct Detection Methods

- Direct detection methods do not result in production of an isolate and would be inadequate for surveillance or definitive characterization of pandemic strains. Nevertheless, owing to their relatively rapid turnaround time, safety, and stability, direct detection methods play an important role in pandemic influenza preparedness.
 - Reverse transcription PCR (RT-PCR) assays
 - The sensitivity of RT-PCR has been reported to be in the range of 90% to 100% when compared with cell culture. However, several researchers have reported significantly higher numbers of total positive specimens with RT-PCR, possibly reflecting its ability to detect nonviable virions (see [References](#): Coiras 2003, Hayden 2002, Herrmann 2001, Pachucki 2004, Wallace 1999).
 - The CDC has provided state health departments with group primers for influenza A and B and with specific primers for H1, H3, H5, and H7 (see [References](#): Arizona Department of Health Services; HHS: Pandemic influenza plan). H5 primers allow for specific presumptive detection of H5 avian influenza strains; a second reference laboratory (such as CDC) should confirm any positive findings.
 - While culture of specimens from possible avian influenza (H5N1) cases is not recommended without strict containment and specific registration

- (described above), RT-PCR can be conducted using BSL-2 facilities and practices (see [References](#): HHS: Pandemic influenza plan).
- Common PCR targets include the matrix (M) protein (for genus-level identification), hemagglutinin, and neuraminidase (for subtype-level identification). PCR generally is not used for strain-level identification, which is based on serologic markers.
 - The likelihood that a RT-PCR assay will detect new pandemic strains increases when more conserved target sequences are used.
 - As with other PCR-based assays, efforts should be made to minimize and detect amplicon contamination.
 - Samples positive by RT-PCR for a novel influenza subtype should be forwarded to a public health laboratory (if testing was conducted at a private laboratory) or to CDC for confirmation (see [References](#): HHS Pandemic influenza plan).
 - A molecular microarray for influenza typing and subtyping using a flow-thru chip platform has been described (see [References](#): Kessler 2004).
 - The development of portable real-time platforms has made possible the use of PCR assays in the field (see [References](#): Perdue 2003).
- Immunofluorescence
 - IFA methods may be used to identify influenza to the species level (influenza A or B) or specific H subtypes (including H5) directly from specimens or cell culture. CDC distributes IFA typing and subtyping reagents to WHO-collaborating laboratories, including many health department laboratories. If HPAI strains are suspected, enhanced BSL-3 containment should be used (see [References](#): WHO: Recommended laboratory tests to identify avian influenza A virus in specimens from humans; FDA: Cautions in using rapid tests for detecting influenza A viruses; HHS: Pandemic influenza plan)
 - Direct immunofluorescence (DFA) methods are faster and less labor intensive than IFA but are less sensitive and are currently only available for genus-specific detection (see other rapid direct tests in the next bullet).
 - Other rapid direct tests (see [References](#): Call 2005; CDC: Interim guidance for influenza diagnostic testing during the 2004-05 influenza season; FDA: Cautions in using rapid tests for detecting influenza A viruses; HHS: Pandemic influenza plan; Treanor 2005; WHO: WHO checklist for influenza pandemic preparedness planning)
 - Rapid tests detect viral antigen (generally nucleoprotein) or enzymatic activity (neuraminidase) directly on patient specimens using a variety of platforms.
 - Rapid tests are designed to identify influenza A only, influenza A or B without identifying the type, or influenza A or B with type-specific identification.
 - Reported sensitivities range from 40% to 80%.
 - Sensitivity is generally greater in children than adults.
 - Sensitivity is greater early in the course of illness.
 - Rapid test predictive value and disease prevalence: The predictive value of rapid assays without confirmation by a reference test is strongly correlated

with disease prevalence in the community, as is clinical diagnosis without laboratory testing. When the disease prevalence is low, the tests' positive predictive value decreases and positive results should be confirmed by culture or RT-PCR. When influenza is known to be circulating, the negative predictive value is lower and clinicians should consider confirming negative tests with viral culture or other tests.

- Rapid test predictive value and diagnostic indications: Rapid tests increase the diagnostic predictive value when used for confirmation of influenza (when symptoms are strongly suggestive) and for ruling out influenza (when symptoms suggest illness other than influenza). When symptoms are not strongly suggestive in either direction, the utility of rapid testing becomes questionable.
- While the sensitivity and specificity of rapid tests has been evaluated for circulating strains, these measures are largely unknown for detection of emerging strains (including pandemic strains) (see [References](#): FDA: Cautions in using rapid tests for detecting influenza A viruses). Only 4 (36%) of 11 culture-positive H5N1 influenza A specimens from patients in Thailand were positive by rapid antigen tests (see [References](#): WHO Writing Committee of WHO Consultation on Human Influenza A/H5 2005).
- WHO, in their Checklist for Influenza Pandemic Preparedness Planning, recommends against routine use of commercial rapid antigen detection kits and suggests they be used for outbreak investigation only when no other options exist (see [References](#): WHO Writing Committee of WHO Consultation on Human Influenza A/H5 2005).
- During a pandemic, rapid tests may be useful for distinguishing influenza from other respiratory illnesses (see [References](#): HHS: Pandemic influenza plan).

Serology

- Serologic testing can be used for retrospective diagnosis of infection but is rarely useful for patient management and is not widely available. However, serology may be useful for investigation of novel viruses (see [References](#): Hayden 2002; Treanor 2005; HHS: Pandemic influenza plan).
- Acute-phase sera should be collected within 1 week after illness onset, and convalescent sera should be collected 2 to 3 weeks later.
- The most common serologic methods are complement fixation (CF), HAI, and enzyme immunoassays (EIA). A variety of other methods, such as neutralization, microneutralization, single radial hemolysis, radial immunodiffusion, and Western blot, have been reported (see [References](#): Hayden 2002, Rowe 1999).
- IgG, IgA, and IgM antibodies appear simultaneously about 2 weeks after initial infection. Antibodies appear more quickly with subsequent infections. Tests for IgM and IgA are less useful than IgG for routine clinical use, as most infections are reinfections (see [References](#): Australian Government Department of Health and Ageing; Hayden 2002)
- Peak antibody response occurs 4 to 7 weeks after infection.

- Since most people are repeatedly exposed to influenza viruses, a fourfold rise in titer between acute and convalescent sera is generally considered necessary for confirmation of influenza infection.
- While paired sera are optimal, single convalescent specimens may be useful in investigations involving novel viruses. Antibody test results have been compared with results from age-matched persons in the acute phase of illness or from non-ill controls. The geometric mean titers between the two groups to a single influenza virus type or subtype can be compared (see References: HHS: Pandemic influenza plan)
- HAI EIAs measure antibody to hemagglutinin. These tests are more sensitive than CF, but their increased specificity appears to limit their ability to detect new strains.
- HAI titers of at least 1:40 or serum neutralizing titers of 1:8 or greater are associated with protection.
- HAI titers in human avian influenza cases have been low or undetectable (see References: HHS: Pandemic influenza plan).
- CF measures antibody response to nucleoprotein, which is conserved among influenza A strains. This feature could be an advantage for diagnosis of infection with novel pandemic strains.
- The microneutralization assay can sensitively and specifically detect H5N1 antibody in patients with H5N1 influenza. Since the test uses infectious organisms, HPAI strains should be tested under enhanced BSL-3 containment. As with other tests, paired sera are preferable to single specimens (see References: HHS: Pandemic influenza plan).

Susceptibility Testing

- Susceptibility testing generally is conducted at specialized laboratories as part of surveillance or research and is considered an integral component of pandemic influenza response.
- Plaque reduction assay (see [References](#): Hayden 1980, McKimm-Breschkin 2003)
 - The traditional influenza susceptibility testing method for the M2 ion channel inhibitors (amantadine, rimantadine)
 - Can detect a wide range of resistance phenotypes
 - Limited utility for neuraminidase inhibitors
- Enzyme inhibition assays (see [References](#): McKimm-Breschkin 2003, Wetherall 2003)
 - Useful for assay of neuraminidase inhibitors
 - Chemiluminescent or fluorescent substrates
- Sequence analysis (see [References](#): McKimm-Breschkin 2003, Wetherall 2003)
 - Used to detect mutations in genes known to be or suspected of being responsible for resistance
 - Neuraminidase gene sequences from strains isolated prior to introduction of the drugs can be used to evaluate current strain sequences
 - Mutations in the M2 can be used to detect amantadine resistance (see [References](#): Pachucki 2004)
- The Neuraminidase Inhibitor Susceptibility Network (NISN) was established to monitor susceptibility of clinical isolates to zanamivir and oseltamivir. The

chemiluminescent neuraminidase enzyme assay was chosen by the NISN as the method of choice for testing neuraminidase inhibitors (see [References](#): Wetherall 2003).

Laboratory Values That May Trigger Concern for Human Pandemic Influenza

- Positive test for influenza from a patient with risk factors for avian influenza
- Culture: CPE positive or negative; HA positive; HI titer low or negative and no other hemagglutinating viruses identified
- RT-PCR positive for H5 or H7
- RT-PCR positive for influenza A from a conserved target, such as matrix protein, and negative for H1-H3
- A four-fold rise in H5-specific antibody titer (acute and convalescent serum samples)

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General Considerations

Cross-Immunity

In general, the degree of immunity induced by one strain of influenza virus to a second challenge with another influenza virus is related to the taxonomic distance between the two strains (see [References](#): Epstein 2003). Several terms that characterize the type of immunity are identified below.

- *Heterologous immunity*: Immunization with one type of influenza virus (eg, A, B, or C) does not offer protection from challenge with a different type.
- *Heterosubtypic immunity (also referred to as "heterotypic immunity")*: Immunization with one influenza A virus subtype (eg, H1N1) may offer some protection from challenge with a second influenza A subtype (eg, H5N2). The degree of protection, or lack of protection, is important to the discussion of pandemic influenza and vaccine development.
- *Homosubtypic immunity*: Immunization with one strain within a subtype (eg, A/Hong Kong/03/68[H3N2]) will frequently offer some protection against challenge with a second strain within the same subtype (eg, A/Fujian/447/2003[H3N2]).
- *Homologous immunity*: Immunization with one strain of influenza A virus (eg, A/Fujian/447/2003[H3N2]) offers protection from a second challenge with the same strain.

Antigenic Drift vs Antigenic Shift

- "Antigenic drift" refers to the process of small genetic changes that influenza viruses continuously undergo from year to year, which necessitates the development of new vaccines annually. Partial immunologic cross-reactivity between new strains and those they are replacing (ie, homosubtypic immunity) limits morbidity, mortality, and spread in the population.

- "Antigenic shift" refers to substantial genetic changes caused by the process of genetic reassortment. Relatively few lineages of influenza A are circulating among humans at any one time, which reduces the likelihood of significant genetic reassortments. However, antigenic shift can occur between human and animal strains, which is what happened with the pandemic strains of 1957 and 1968. It is important to note that not all pandemic strains arise from genetic reassortment. For example, the 1918 pandemic strain apparently did not originate through a reassortment event; rather, it is likely that an avian strain initially infected humans and then adapted gradually to the human population over time to become a pandemic strain (see [References](#): Taubenberger 2005).

Features of Pandemic Strains

Pandemics occur when a novel influenza strain emerges that has the following features:

- Highly pathogenic for humans
- Easily transmitted between humans
- Genetically unique (ie, lack of preexisting immunity in the human population)

Pandemic Phases

In reviewing the public health implications of a pandemic, it is useful to understand the various phases that a pandemic will likely go through. These are outlined in the following table. (Note: In 1999, WHO developed a set of pandemic phases; these were revised in the new WHO Global Influenza Preparedness Plan that was released in April 2005. The phases identified below are from the 2005 Plan [see [References](#): WHO: WHO global influenza preparedness plan 2005].) The current pandemic phase for H5N1 is Phase 3.

WHO Pandemic Phases		
Phase	Characteristics of Phase	Rationale
Phase 1	No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present in animals, the risk of human infection or disease is considered to be low.	It is likely that influenza subtypes that have caused human infection and/or disease will always be present in wild birds or other animal species. Lack of recognized animal or human infections does not mean that no action is needed. Preparedness requires planning and action in advance.
Phase 2	No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.	The presence of animal infection caused by a virus of known human pathogenicity may pose a substantial risk to human health and justify public health measures to protect persons at risk.
<i>Pandemic Alert Period</i>		
Phase 3	Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of	The occurrence of cases of human disease increases the chance that the virus may adapt or reassort to become transmissible from

	spread to a close contact.	human to human, especially if coinciding with a seasonal outbreak of influenza. Measures are needed to detect and prevent spread of disease. Rare instances of transmission to a close contact—for example, in a household or healthcare setting—may occur but do not alter the main attribute of this phase (ie, that the virus is essentially not transmissible from human to human).
Phase 4	Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.	Virus has increased human-to-human transmissibility but is not well adapted to humans and remains highly localized, so that its spread may possibly be delayed or contained.
Phase 5	Larger cluster(s) but human-to-human spread is still localized, suggesting that the virus is becoming increasingly better adapted to humans but may not yet be fully transmissible (substantial pandemic risk).	Virus is more adapted to humans and therefore more easily transmissible among humans. It has spread in larger clusters, but spread is localized. This is likely to be the last chance for massive coordinated global intervention, targeted to one or more foci, to delay or contain spread. In view of possible delays in documenting spread of infection during pandemic Phase 4, it is anticipated that there would be a low threshold for progressing to Phase 5.
<i>Pandemic Period</i>		
Phase 6	Increased and sustained transmission among general population.	Major change in global surveillance and response strategy, since pandemic risk is imminent for all countries. The national response is determined primarily by the disease impact within the country.
<i>From WHO: WHO global influenza preparedness plan 2005 (see References).</i>		

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Historical Perspective

Earliest reports of influenza epidemics date back to 412 BC and were recorded by Hippocrates. A number of epidemics that likely were influenza were described in the Middle Ages, and one that was probably a true pandemic took place in 1510 (see [References](#): Beveridge 1978). Other key historical facts include the following:

- One of the earliest recorded pandemics occurred in 1580. Like the 1918 pandemic, this one was particularly severe. It started in Asia and spread to Africa, Europe, and the Americas. In 6 weeks it afflicted all of Europe. Death rates were high; 9,000 of

80,000 people died in Rome, and some Spanish cities were described as "nearly entirely depopulated" by the disease (see [References](#): Beveridge 1978).

- Ten pandemics have been recorded in the past 300 years. During this time, 10 to 49 years has occurred between pandemic with an average of 24 years.
- During the 17th century, localized epidemics were reported, and in the 18th century at least three pandemics occurred (1729-30, 1732-33, and 1781-82).
- Three influenza pandemics occurred during the 19th century (1830-31, 1833-34, and 1889-90). The 1889 pandemic known as the Russian Flu began in Russia and spread rapidly throughout Europe. It reached North America in December 1889 and spread to Latin America and Asia in February 1890. About 1 million people died in this pandemic.

Global influenza surveillance was established in 1947 by WHO to better understand the epidemiology of influenza and to obtain isolates in a systematic fashion for annual vaccine development (see [References](#): Hampson 1997).

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Pandemics of the 20th Century

Three pandemics occurred during the 20th century, caused by an H1, an H2, and an H3 strain. These are outlined in the table below and then briefly summarized. Currently, H1 and H3 influenza strains are circulating in the human population. Scientists have raised concern about the possibility of H2N2 reemerging (also referred to as recycling) in humans, particularly through accidental release of a laboratory strain (see [References](#): Dowdle 2006).

Influenza Pandemics of the 20th Century: Impact in the United States*			
Date	Strain	Estimated No. of Deaths in US	Comments
1918-19 (Spanish Flu)	H1N1	500,000	Global mortality may have been as high as 100 million. The virus likely originated in the US and then spread to Europe.
1957-58 (Asian Flu)	H2N2	60,000	The virus was first identified in China; approximately 1 million people died globally during this pandemic.
1968-69 (Hong Kong Flu)	H3N2	40,000	The death rate from this pandemic may have been lower because the strain had a shift in the hemagglutinin (H) antigen only and not in the neuraminidase (N) antigen.
*All three pandemics were characterized by a shift in age distribution of deaths to younger population under age 65 (at least initially); shift was particularly dramatic during 1918 pandemic (see References : NIAID: Focus on the flu; HHS: Influenza pandemics; Kilbourne 2005; Simonsen 2004; Webster 1997).			

1918-19 (Spanish Flu)

This pandemic was caused by an influenza A (H1N1) strain. Worldwide, about one third of the world's population was infected and had clinically apparent illness (about 500 million people) and an estimated 50 to 100 million died (see [References](#): Johnson 2002, Taubenberger 2006). Earlier estimates implied that the death toll was 20 to 40 million, but more recent evidence supports the higher figures. Adjusting for today's population, a similar pandemic would yield a modern death toll of 175 to 350 million.

- The pandemic began with a relatively mild "herald" wave in the spring of 1918. During that time, outbreaks were reported in Europe and in the United States (particularly in military training camps for new recruits headed to the war in Europe) (see [References](#): Reid 2001, Glezen 1996).
- Many investigators believe that the strain originated in the United States (perhaps in rural Kansas) and then migrated initially to France before spreading throughout Europe (see [References](#): Barry 2004). However, others believe that the strain may have been circulating in the Mid-Atlantic States as early as February of 1918 (see [References](#): Simonsen 2004). Furthermore, an outbreak of severe respiratory disease occurred in an army camp in France in 1916-17 (see [References](#): Oxford 2000). A significant clinical feature of the disease was cyanosis, which also was a predominant finding among those who acquired the pandemic strain of influenza. It is possible that this outbreak represented H1N1 infection and was an early precursor to the pandemic. At any rate, it is clear that the 1918-19 pandemic did not begin in Asia, although the origin of the implicated H1N1 strain still remains a mystery.
- This first wave was followed by two additional waves in the fall and winter of 1918-19 that were much more severe (see [References](#): Taubenberger 2006). The second highly virulent wave spread rapidly around the world in the fall of 1918; it took only 2 months for the pandemic to circle the globe at that time.
- Recorded case-fatality rates varied around the globe. In the US military, death rates ranged from 5% to 10% (see [References](#): Barry 2004). Higher rates were reported in some areas.
- Additional waves that were not as severe occurred in 1919 and 1920.

An unusual feature of the pandemic was the age-related mortality; the pandemic strain killed a disproportionate number of healthy young adults. This led to the observation of a "W" shaped age-related mortality curve in the United States, with high rates of mortality among very young children, persons 15 to 45 years of age, and the elderly (see [References](#): Reid 2001; Glezen 1996). Usually the curve associated with influenza mortality follows a "U" shape, with excess deaths occurring only among the very young and the elderly. One striking feature of the pandemic was its impact on pregnant women; a summary of 13 studies involving pregnant women demonstrated that case-fatality rates ranged from 23% to 71% (see [References](#): Barry 2004).

In October 2005, CDC reported that scientists had reconstructed the 1918 pandemic H1N1 strain and tested it in mice (see [References](#): Tumpey 2005). They found that mice infected with the 1918 strain died in as little as 3 days, and mice that survived as long as 4 days had 39,000 times as many virus particles in their lungs as did mice infected with a

control flu virus, a Texas strain of H1N1 from 1991. All the mice infected with the 1918 virus died, while those exposed to the Texas strain survived. Further, the 1918 virus was at least 100 times as lethal as an engineered virus that contained five 1918 genes and three genes from the Texas H1N1 strain. The researchers found that the mice had severe inflammation in their lungs and bronchial passages—findings very similar to those in people who died of the 1918 virus.

Earlier studies in mice using genetically engineered influenza strains similar to the H1N1 1918 pandemic strain suggest that macrophage activation with high levels of cytokine production may have been a key factor in lung damage caused by the pandemic strain (see [References](#): Kobasa 2004). It is possible that an overly robust immune response inducing a "cytokine storm" may have contributed to the high case-fatality rates seen in younger populations during the 1918 pandemic.

Recent genetic sequencing of the 1918 strain indicates that the strain was of avian origin and that the strain did not reassort with a human strain (unlike later pandemics), but rather adapted to humans until it could be efficiently transmitted person to person (see [References](#): Taubenberger 2005). It now appears that the 1918 virus was an avian-like virus derived in toto from an unknown source (see [References](#): Taubenberger 2006).

1957-58 (Asian Flu)

The Asian flu was caused by an H2N2 strain and originated in China. The virus was initially isolated in Singapore in February 1957 and in Hong Kong in April of that year. The pandemic spread to the Southern Hemisphere during the summer of 1957 and reached the United States in June 1957 (see [References](#): Glezen 1996). The pandemic strain acquired three genes from the avian influenza gene pool in wild ducks by genetic reassortment and obtained five other genes from the then-circulating human strain.

About 69,800 people in the United States died and mortality was spread over three seasons. Overall, the highest mortality rates occurred among the elderly; however, during the initial season in 1957, nearly 40% of the influenza deaths occurred among persons less than 65 years of age (see [References](#): Simonsen 2004). The high case-fatality rate in this age-group declined in subsequent years. Globally, approximately 1 million people died during this pandemic.

1968-69 (Hong Kong Flu)

The Hong Kong flu was caused by an H3N2 strain. The strain acquired two genes from the duck reservoir by reassortment and kept six genes from the virus circulating at the time in humans.

During the pandemic, about 33,800 people died in the United States. The death rate from this pandemic may have been lower because the strain had a shift in the hemagglutinin (H) antigen only and not in the neuraminidase (N) antigen. Although antibodies to neuraminidase antigen do not prevent infection, they may modify the severity of disease

(see [References](#): Glezen 1996). Also, an H3 strain had apparently circulated in the United States around the turn of the century, so very old persons may have had some protective antibody from past exposure to an H3 strain (see [References](#): Simonsen 2004). This could have caused a lower fatality rate in the elderly.

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Lessons from Past Pandemics

In a recent report issued in January 2005, WHO officials identified key lessons from the three pandemics of the past century (see [References](#): WHO: Avian influenza: assessing the pandemic threat). These lessons are summarized as follows.

- Pandemics behave as unpredictably as the viruses that cause them. During the previous century, great variations were seen in mortality, severity of illness, and patterns of spread.
- One consistent feature important for preparedness planning is the rapid surge in the number of cases and their exponential increase over a very brief time, often measured in weeks.
- Apart from the inherent lethality of the virus, its capacity to cause severe disease in non-traditional age groups, namely young adults, is a major determinant of a pandemic's overall impact.
- The epidemiologic potential of a virus tends to unfold in waves. Subsequent waves have tended to be more severe.
- Virologic surveillance, as conducted by the WHO Laboratory Network, has performed a vital function in rapidly confirming the onset of pandemics.
- Most pandemics have originated in parts of Asia where dense populations of humans live in close proximity to ducks and pigs.
- Some public health interventions may have delayed the international spread of past pandemics, but could not stop them.
- Delaying spread is desirable, as it can flatten the epidemiological peak, thus distributing cases over a longer period of time.
- The impact of vaccines on a pandemic, though potentially great, remains to be demonstrated. In 1957 and 1968, vaccine manufacturers responded rapidly, but limited production capacity resulted in the arrival of inadequate quantities too late to have an impact.
- Countries with domestic manufacturing capacity will be the first to receive vaccines.
- The tendency of pandemics to be most severe in later waves may extend the time before large supplies of vaccine are needed to prevent severe disease in high-risk populations.
- In the best-case scenario, a pandemic will cause excess mortality at the extremes of the lifespan and in persons with underlying chronic disease. Countries with good programs for yearly influenza vaccinations will have experience with the logistics of vaccinations for these populations.

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The Current H5N1 Threat

According to WHO, at this time the pandemic alert level for H5N1 influenza is at Phase 3: a new viral subtype is causing disease in humans but is not yet spreading efficiently and sustainably (see [References](#): WHO: Current WHO phase of pandemic alert).

Detailed information about H5N1 influenza in bird populations can be found in the document on this Web site "Avian Influenza (Bird Flu): Agricultural and Wildlife Considerations" and in human populations in the document "Avian Influenza (Bird Flu): Implications for Human Disease."

Of the avian influenza subtypes, currently the H5N1 subtype is of greatest pandemic concern for the following reasons (see [References](#): WHO: Avian influenza fact sheet; WHO: Influenza pandemic preparedness and response):

- The virus has spread rapidly throughout poultry flocks in Asia over the past 2 years and now appears to be endemic in eastern Asia (see [References](#): Kaye 2005, Li 2004). In October 2005, H5N1 spread to Europe and was identified in Turkey, Romania, European Russia, and Croatia. The virus is expanding its mammalian host range.
- It causes severe disease in humans, with a high case-fatality rate (reportedly at about 50%, although adequate surveillance data are lacking to accurately define the rate).
- The potential of exposure and infection of humans is likely to be ongoing in rural Asia, where many households keep free-ranging poultry flocks for income and food (see [References](#): Stohr 2005).

Since January 2002, the predominant avian H5N1 strain in southern China has been genotype Z. Since its emergence, this strain has replaced other genotypes and has become the predominant genotype circulating in aquatic and terrestrial poultry in the region (see [References](#): Li 2004). This strain circulating in Asia appears to be highly pathogenic for humans, and immunity in the human population is generally lacking. However, the strain has not yet been shown to be easily transmitted between humans, and sustained person-to-person transmission has not occurred. Reassortment with human strain(s) would be necessary for the current virus to acquire this attribute.

If H5N1 continues to circulate widely among poultry, the potential for emergence of a pandemic strain remains high. For example, H5N1 viruses have been found in pigs in southern China, and human H3N2 influenza viruses are endemic in pigs in that area. H5N1 has recently been reported in pigs in Indonesia as well (see [References](#): Cyranoski 2005). Thus, the conditions exist for exchange of genetic material between the different viruses in the pig host (see [References](#): Li 2004; WHO: Avian influenza: update: implications of H5N1 infections in pigs in China). Some scientists believe that reassortment between an avian and a human strain could occur in the human population without an intermediary host; if this proves true, as more humans become exposed and infected, the potential for reassortment with a human strain may also increase. It is also possible that a pandemic strain could emerge following a more gradual process of

adaptive mutation (see [References](#): WHO: Influenza pandemic preparedness and response 2005).

Human cases of H5N1 influenza have been reported in Vietnam, Thailand, Cambodia, Indonesia, China, and Turkey. WHO has officially recognized over 140 cases (see [References](#): WHO: Cumulative number of confirmed human cases of avian influenza), with a case-fatality rate of approximately 50%. To date, sustained person-to-person transmission has not been recognized, although probable person-to-person spread was identified in Thailand involving transmission from an ill child to her mother and aunt (see [References](#): Ungchusak 2005) and several other familial clusters have been recognized (see [References](#): Olsen 2005).

The high case-fatality rate suggests that the pathogenicity of H5N1 may be similar to the 1918 H1N1 pandemic strain. Researchers have hypothesized that cytokine storm (ie, overproduction of cytokines) may have played an important role in the pathogenesis of the 1918 pandemic strain. A laboratory-based study involving H5N1 strains taken from ill humans in Asia (during 1997 and 2004) and an ordinary current H1N1 strain (circulating in Asia in 1998) found that all the H5N1 viruses caused human alveolar cells and bronchial epithelial cells to secrete significantly higher levels of various cytokines and chemokines than did the ordinary virus (see [References](#): Chan 2005). These findings support the role of cytokine storm in the pathogenesis of H5N1, although further work is needed to clarify the clinical implications of these findings.

Public health officials are closely monitoring the ongoing occurrence of H5N1 avian influenza in humans in Southeast Asia and watching for the emergence of a strain capable of causing sustained human-to-human transmission. A WHO consultation held May 6-7, 2005, in Manila determined that the pandemic potential of H5N1 is continuing to evolve (see [References](#): WHO 2005: Inter-country consultation on influenza A/H5N1 in humans in Asia). In June 2005, however, an international team sent to Vietnam found no laboratory evidence that the H5N1 strain is infecting humans with greater frequency or that sustained human-to-human transmission is occurring (see [References](#): WHO: Avian Influenza: Situation Update 24).

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Vaccine Development

Development of an effective vaccine is considered the cornerstone for controlling a global influenza pandemic. In general, if a novel strain occurs without adequate warning, WHO has indicated that it will take at least 4 to 6 months to develop a vaccine (see [References](#): WHO: WHO global influenza preparedness plan 2005). However, there are several major obstacles in producing an adequate vaccine supply during a pandemic:

- Limited production capacity
- Production capability in only a few countries, which will yield an inequitable distribution

- Technological challenges to vaccine development

Limited Production Capacity

For the period 2000 to 2003, global annual influenza vaccine production ranged from approximately 230 million doses of trivalent vaccine (2000) to 291 million doses (see [References](#): Fedson 2004: Pandemic influenza vaccine: obstacles and opportunities; Medema 2004).

- In the "best case scenario," assuming that the pandemic vaccine would be a single-dose monovalent vaccine requiring the same level of antigen per dose (15 mcg HA), the production capacity would be increased to an estimated 750 million doses each year (see [References](#): WHO: Consultation on priority public health interventions before and during an influenza pandemic).
- In the United States, domestic production was estimated at 50 million doses of trivalent vaccine during 2004. This would be equivalent to about 150 million doses of monovalent standard-dose, assuming 15 mcg HA per dose (see [References](#): Fedson 2003).
- Two critical caveats need to be considered with these types of estimates: (1) it is not clear how many micrograms of antigen will be necessary to elicit an immune response to a pandemic strain and (2) two doses of vaccine will likely be needed to confer adequate protection. For example, recent data from a clinical trial of a candidate H5N1 vaccine demonstrated that volunteers required two doses of a 30-mcg vaccine to mount an adequate immune response to H5N1 (see Dec 15, 2005, [CIDRAP News story](#)). If this is the case for a pandemic vaccine, then 60 mcg of antigen would be needed per person, which is four times higher than that needed per dose to confer protection with current annual influenza vaccines. An extrapolation of the current production capacity to this antigen requirement per person suggests that only 37.5 million people in the United States could be vaccinated during the first year of a pandemic (roughly 10% of the country's population).

Production Capability in Only a Few Countries

Most of the world's influenza vaccine is produced in a few countries. These countries are likely to reserve scarce supplies for their own populations during a pandemic, thus leading to an inequitable distribution of vaccine, particularly to developing countries. This issue has relevance for the United States as well, where current domestic vaccine production falls far short of producing adequate vaccine supplies to vaccinate the entire US population. Moreover, the US plan does not address the issue of distributing vaccine to other countries.

Nine companies, located in the following nine developed countries, currently produce influenza vaccine:

- Australia
- Canada
- France

- Germany
- Italy
- The Netherlands
- Switzerland
- The United Kingdom
- The United States

Technological Challenges to Vaccine Development

The manufacture of vaccines derived from pathogenic avian strains poses a number of technological challenges. For example, highly pathogenic avian strains cannot be grown in large quantities in eggs because they are lethal to chick embryos. These strains also pose significant safety issues and would require extensive biocontainment procedures during the manufacturing process.

Several approaches have been suggested to overcome these issues. One approach, use of reverse genetics, has been used for preparing H5N1 seed strains (see [References](#): Webby 2004; WHO: Development of a vaccine effective against avian influenza H5N1 infection in humans). Reverse genetics provides several advantages in influenza vaccine development (see [References](#): Luke 2006, Palese 2006): (1) it allows creation of engineered viruses that are modified to be less virulent, thus eliminating the need for high-level containment, (2) with reverse genetics, a selection system is not needed to derive appropriate reassortant viruses from background parental viruses, (3) it dramatically shortens the timeframe for production of seed strains, (4) it allows for standardization of seed strains to be used in vaccine development, and (5) the process may eliminate the potential for any adventitious agents to enter the manufacturing process. Other approaches include the following (see [References](#): Stephenson 2004).

- Produce inactivated vaccine from wild-type virus
- Select an antigenically related but nonpathogenic surrogate vaccine strain
- Use baculoviruses to express recombinant hemagglutinin
- Develop DNA-based vaccines

It is not yet clear whether new vaccines made from seed strains generated through reverse genetics will be immunogenic in humans, given that candidate vaccines developed against the 1997 H5N1 strain from Hong Kong were poorly immunogenic (see [References](#): Stephenson 2004). It may be that an effective vaccine cannot be developed until a true pandemic strain (reassorted with human influenza viruses) emerges and can be used as the seed virus.

HHS has recently awarded funds for the development of cell-culture technology to make influenza vaccines. Use of this technology will obviate the need to grow the viruses in chicken eggs, which will streamline the manufacturing process. (See Apr 4, 2005, [CIDRAP News story](#).)

Research in this area is a high priority because stockpiling prototype vaccines may be worthwhile if protection against emergent strains can be demonstrated (see [References](#):

Schwartz 2005). Two recent studies using prototype vaccines showed the following findings:

- One study demonstrated good cross-protection against H5N1 in mice following vaccination with an H5 influenza vaccine created through reverse genetics (see [References](#): Lipotov 2005). Protection was achieved despite antigenic differences and incomplete matching between the vaccine strain and the challenge virus. Although these findings are promising, it is not clear if similar protection would occur for humans.
- A second study suggested that use of adjuvanted prototype vaccines may induce antibody capable of neutralizing a pandemic strain until a well-matched vaccine can be made available. In the study, 14 human subjects vaccinated with an adjuvanted influenza A/duck/Singapore 97 (H5N3) vaccine demonstrated higher seroconversion rates to four strains of H5N1 compared with 11 subjects who were vaccinated with a nonadjuvanted vaccine (see [References](#): Stephenson 2005). For those who received the MF59-adjuvanted vaccine, 100% seroconverted to A/HongKong/156/97 and A/HongKong/213/03, 71% to A/Thailand/16/04, and 43% to A/Vietnam/1203/04.

Another option for consideration is development of influenza vaccines based on cell-mediated immunity. Cell-mediated responses generally focus on internal influenza proteins, which are more conserved and less susceptible to antigenic variation (see [References](#): Thomas 2006).

Interpandemic Steps to Facilitate Vaccine Production

During the interpandemic period, a number of steps can be taken to improve vaccine response capability once a pandemic arrives. One set of recommendations includes the following (see [References](#): Fedson 2004: Vaccination for pandemic influenza; a six point agenda for interpandemic years):

- Prepare vaccine seed strains for production. Use of reverse genetics to develop high growth variants can enhance this process.
- Determine the characteristics of a pandemic vaccine and vaccination schedule. This can be done by undertaking clinical trials of pandemic-like candidate vaccines. Such trials should determine the minimal antigenic content per dose needed for an acceptable immune response.
- Consider global registration of pandemic vaccines. A global protocol would allow vaccine produced by any company to be registered in all countries and thereby eliminate regulatory delays on a country-by-country basis.
- Increase the use of influenza vaccines during interpandemic years to bolster manufacturing capacity.
- Document the epidemiology of influenza vaccination. This would help vaccine companies make future plans for vaccine production.
- Address underlying political issues that will affect the global supply of pandemic vaccines. A key issue is the fact that political leaders in vaccine-producing countries will likely prohibit export of domestically produced pandemic vaccine until that

country's vaccine demands are met. International agreements to address this problem should be developed before a pandemic occurs.

Because of concerns about the pandemic potential of H5N1, the World Health Organization (WHO) has been working with laboratories in its influenza network to develop vaccines against this subtype (see [References](#): WHO: Development of a vaccine effective against avian influenza H5N1).

- Candidate vaccines were developed during 2003 by network laboratories in London and in Memphis, Tennessee, for protection against the strain that was isolated from humans in Hong Kong in February of that year. However, the 2004 strain is different from that strain.
- In April 2004, WHO made the prototype seed strain for an H5N1 vaccine available to manufacturers (see [References](#): WHO: Avian influenza: situation in Thailand; status of pandemic vaccine development).
- The National Institute of Allergy and Infectious Diseases (NIAID) awarded two contracts to support the production and clinical testing of an investigational vaccine based on the prototype seed strain made available by WHO (see [References](#): NIAID 2004).
- The contracts were awarded to Aventis Pasteur (now Sanofi Pasteur) of Swiftwater, Pennsylvania, and to Chiron Corporation of Emeryville, California. Each manufacturer is using established techniques in which the virus is grown in eggs and then inactivated and further purified before being formulated into vaccines.
- Clinical trials of candidate H5N1 vaccines are currently under way (see [References](#): WHO: Avian flu: situation in Thailand; status of pandemic vaccine development; Mar 23, 2005 [CIDRAP News story](#)). In August 2005, NIAID announced that the Sanofi Pasteur vaccine was meeting with positive results in the first wave of testing in healthy adults; however, the amount of antigen needed per dose was 180 mcg, versus the 15-mcg dose given in current annual flu shots. A vaccine with this antigen requirement would severely limit production capacity. Further work by Sanofi Pasteur using two doses of a 30-mcg vaccine with alum added (an adjuvant used in many vaccines to boost immune response) elicited an adequate immune response in a group of volunteers (see Dec 15, 2005, [CIDRAP News story](#)). Use of this adjuvanted vaccine could potentially lower the amount of antigen needed per person to 60 mcg. Studies of the adjuvanted vaccine are ongoing.
- The intramural research program of NIAID also has generated live, attenuated, cold-adapted H5N1 and H9N2 vaccine candidates that have been protective in mice (see [References](#): Fauci 2006). Further work on development of live, attenuated pandemic vaccines is ongoing (see [References](#): Luke 2006).
- Researchers have suggested that development and use of an H5N1 vaccine for immunologic priming during the interpandemic period may offset the need for two doses of vaccine once a pandemic begins (assuming the pandemic is caused by H5N1), even if the strain used in the priming vaccine is somewhat different from an emergent pandemic strain (see [References](#): Monto 2006).
- A universal vaccine that would be effective against all types of influenza, including emerging pandemic strains, is being developed by the British company Acambis and is being researched by others as well. Such a vaccine would not have to be

reengineered each year. Acambis announced in early August 2005 that it has had successful results in animal testing (see [References](#): Acambis 2005). The vaccine focuses on the M2 viral protein, which does not change, rather than the surface hemagglutinin and neuraminidase proteins targeted by traditional flu vaccines. The universal vaccine is made through bacterial fermentation technology, which would greatly speed up the rate of production over that possible with culture in chicken eggs, plus the vaccine could be produced constantly, since its formulation would not change. Still, such a vaccine is years away from full testing, approval, and use.

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Use of Antiviral Agents

Two groups of antiviral agents are available for treatment and prophylaxis of influenza—the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors (NIs) (oseltamivir [Tamiflu] and zanamivir [Relenza]). Use of adamantanes during a pandemic is considered to be limited owing to the potential for resistance and high rates of side effects; therefore, the NIs are considered the major class of antiviral agents to be used during a pandemic.

NIs can reduce the duration of illness for both influenza A and B if given early in the clinical course (ie, within 48 hours after illness onset). Oseltamivir is approved for treatment of influenza in adults and children more than 1 year of age and zanamivir is approved for treatment of adults and children more than 7 years of age (see [References](#): Moscona 2005). Oseltamivir also is approved for prevention of influenza in adults and children older than 1 (see Dec 27, 2005, [CIDRAP News Story](#)).

Stockpiling NIs is considered by many experts to be an important strategy for limiting the impact of an influenza pandemic.

- One report, which analyzed several models of different stockpile sizes of NIs, estimated that having a stockpile to cover 20% to 25% of the population would be sufficient to treat most of the clinical cases and could lead to a 50% to 77% reduction in hospitalizations (see [References](#): Gani 2005).
- Two other reports have looked at the cost-benefit of stockpiling oseltamivir in defined geographic locations (Israel and Singapore). The Israeli study suggested that stockpiling oseltamivir could be cost-saving to the economy of Israel in the event of an influenza pandemic (see [References](#): Balicer 2005). In the Singapore study, a decision-based model was used to perform cost-benefit and cost-effectiveness analyses for stockpiling antiviral agents. The model compared three strategies: supportive management, early treatment of clinical influenza with oseltamivir, and prophylaxis in addition to early treatment. The authors found that stockpiles of antiviral agents for 40% of the population would save an estimated 418 lives and \$414 million, at a cost of \$52.6 million per shelf-life cycle of the stockpile. Prophylaxis was found to be economically beneficial in high-risk subpopulations (see [References](#): Lee 2006).

- HHS currently has 4.3 million treatment courses of oseltamivir and is planning on acquiring enough zanamivir to treat 84,300 people. HHS hopes to have a stockpile with enough treatment courses for 20 million people by the fourth quarter of 2006 (see November 2, 2005, [CIDRAP News story](#)). According to the federal pandemic influenza plan, HHS eventually hopes to acquire enough of a stockpile to treat 25% of the US population (see [References](#): HHS: Pandemic influenza plan 2005; Supplement 7).
- According to a recent statement (see [References](#): WHO: Antiviral drugs: their role during a pandemic), WHO intends to "have a dedicated stockpile of antiviral drugs (oseltamivir), sufficient for 3 million treatment courses, by early 2006. These drugs [will be] strictly reserved for use in the first areas affected by an emerging pandemic virus. Recent studies, based on mathematical modeling, suggest that these drugs could be used prophylactically near the start of a pandemic to reduce the risk that a fully transmissible virus will emerge or at least to delay its international spread, thus gaining time to augment vaccine supplies. The drugs will be stored centrally; WHO has considerable experience in the rapid dispatch of medical supplies during emergencies."

Even though antiviral stockpiles are considered to be an important strategy for pandemic preparedness, a number of caveats exist regarding their use during a pandemic.

- First, it is not clear that such agents would be effective against the emergent pandemic strain.
- Second, even if antiviral agents are shown to be effective, the dose and duration of treatment may be dependent on the virulence of the pandemic strain. Current antiviral treatment recommendations for influenza are based on studies using circulating H3N2 strains and not on potentially more virulent pandemic strains. For example, since H5N1 strains can be highly virulent, higher doses of antiviral agents given for a longer period of time may be necessary for effective treatment. This was recently demonstrated in a mouse model using an H5N1 strain from Vietnam (see [References](#): Yen 2005). Early treatment may also be critical for a successful outcome.
- Finally, current production capacity for NIs is limited, although Roche (maker of Tamiflu) is ramping up production and some researchers are claiming to have developed generic forms of the drug, which could be used to augment global supplies (see October 18, 2005, [CIDRAP News story](#)).

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Antiviral Susceptibility

M2 ion-channel inhibitors

- Transmissible amantadine-resistant organisms are shed by about 30% of patients after 2 to 5 days of treatment. Mutations may confer resistance to both amantadine and rimantadine.
- The efficacy of these drugs for prevention of secondary transmission appears to be minimal (see [References](#): Hayden 2004).

Neuraminidase inhibitors (see [References](#): McKimm-Breschkin 2003)

- *Resistance to zanamivir*: No resistance has been detected in previously healthy patients with influenza who have been treated with zanamivir. One influenza B isolate with reduced sensitivity was obtained from an immunocompromised (post–bone marrow transplant) 18-month-old child after 12 days of treatment (see [References](#): Gubareva 1998).
- *Resistance to oseltamivir*: Levels of resistance to oseltamivir for currently circulating influenza strains range from 0.4% to 1% in adults and 4% to 8% in pediatric patients. Oseltamivir-resistant H5N1 strains recently have been isolated from several patients in Vietnam. One was a Vietnamese child who received prophylactic treatment with the drug (see [References](#): Le 2005); another report involved two additional patients, both of whom died of H5N1 influenza (see [References](#): deJong 2005).

Limited data suggest that current antiviral agents may be effective against a reconstructed 1918 H1N1 pandemic strain (see [References](#): Tumpey 2002). Researchers have shown that recombinant viruses possessing the HA and NA genes of the 1918 strain were inhibited effectively in both tissue culture and mice by oseltamivir and zanamivir. A recombinant virus possessing the M segment of the 1918 strains was inhibited effectively both in tissue culture and in vivo by the M2 ion-channel inhibitors amantadine and rimantadine.

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Nonpharmaceutical Interventions

In addition to vaccines and antiviral agents, a number of nonpharmaceutical interventions can be considered, although data assessing the effectiveness of these interventions are limited. Examples of such measures include isolation and quarantine, social distancing, use of masks, handwashing, and respiratory hygiene/cough etiquette. Recently, WHO published two reports on such interventions—one geared toward prevention of transmission internationally and one geared toward the national and local levels. These are briefly addressed below.

International level (see [References](#): WHO Writing Group 2006: Nonpharmaceutical interventions for pandemic influenza, international measures):

- Screening and quarantine of entering travelers have not been shown in previous pandemics to substantially delay virus introduction into countries where such measures were employed.
- Rather than instituting entry screening, WHO recommends providing information to international travelers and possibly conducting exit screening (through health declarations and temperature measurement) for travelers departing from affected areas. It is important to note that exit screening is costly and disruptive and may not detect persons who are asymptomatic or in the pre-clinical stages of infection.

- Conversely, exit screening may decrease transmission on conveyances (such as airplanes) and is a better use of resources than entry screening.
- In general, entry screening is not recommended, although could be considered in the following situations: (1) where exit screening at the traveler's point of embarkation is suboptimal; (2) in geographically isolated areas, such as islands; and (3) when the host country's internal surveillance capacity is limited.

National and community levels (see [References](#): WHO Writing Group 2006: Nonpharmaceutical interventions for pandemic influenza, national and community measures):

- In general, isolation of patients in the community and quarantine of contacts are measures that have not been shown in past pandemics to be effective in preventing transmission outside of closed settings (such as dormitories or military barracks) and are not recommended once a pandemic is well established. However, WHO recommends aggressive measures to detect and isolate cases and quarantine their contacts in situations where human-to-human transmission of a potential pandemic influenza strain is highly localized and limited (ie, during the pandemic alert period [Phases 4 and 5]).
- Social distancing measures, such as closing schools and other public gathering places and canceling sports events, have met with limited success during past pandemics and the impact of such measures remains unclear. Social distancing measures and wearing masks in public apparently decreased influenza and other respiratory infections in Hong Kong during the 2003 SARS epidemic. About 76% of Hong Kong residents wore masks during that period.
- No controlled studies to date have specifically assessed mask use in preventing influenza transmission in community settings.
- Although data on these measures are limited, WHO has made the following recommendations to decrease influenza transmission in community settings during a pandemic (Phase 6).
 - Ill persons should be advised to remain at home as soon as influenza-like symptoms develop.
 - Measures to increase social distance should be considered, depending on the epidemiology of transmission, severity of disease, and risk groups affected.
 - Mask use by the public should be based on risk, including frequency of exposure, and closeness of contact with potentially infectious persons. Routine mask use should be permitted but not required.
 - Handwashing and respiratory hygiene/cough etiquette should be routine for all and strongly encouraged in public messages (although this recommendation is supported on the basis of plausible effectiveness rather than controlled studies or other supporting data).

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Pandemic Preparedness Planning

Although pandemic planning has been ongoing for several years at the global level (through WHO) and in a number of countries, the challenges for preparing for a pandemic are enormous. Even with the best planning efforts, there is no way to adequately prepare for a pandemic given the currently available resources. The challenges include these:

- If an influenza pandemic were to occur in the near future, vaccine for the pandemic strain would not be readily available for a number of months. Even though some developed countries have stockpiles of antiviral agents effective against influenza, supplies of these agents would be extremely limited (see [References](#): Hayden 2004). It is unlikely that they would have a significant effect on curtailing spread of the pandemic unless a mobile stockpile with adequate supplies was created for use in the area where the virus emerges (see [References](#): Monto 2005; WHO: WHO global influenza preparedness plan 2005). Therefore, prevention and treatment options would essentially not be available during the initial wave of the pandemic if a pandemic occurs soon.
- Once a vaccine is available, the current plans do not adequately address how the vaccine will be distributed globally. This is of great concern, since vaccine is only produced by a few countries and those countries are likely to not release vaccine until the needs of their populations are met.
- If the next pandemic strain is highly virulent (such as the 1918 strain) the global death toll could be dramatic. The current plans generally do not address the social, political, or economic issues that would likely be associated with an ongoing influenza pandemic (see [References](#): Osterholm 2005: A weapon the world needs; Osterholm 2005: Preparing for the next pandemic [*N Engl J Med*]; Osterholm 2005: Preparing for the next pandemic [*Foreign Aff*]). It is very possible that substantial disruption of basic services (such as healthcare, food, clothing, provision of utilities [eg, water, electricity], and transportation) will occur. Furthermore, international trade will likely be impacted, which could have serious global economic and societal consequences.

To effectively manage a pandemic, additional information is urgently needed in a number of areas (see [References](#): Stohr 2005); if a pandemic occurs soon, we are unlikely to have answers to these complex issues:

- Case management and hospital infection control
- Immunogenicity of vaccines for pandemic influenza
- Early interventions to slow the spread of emerging pandemic viruses
- The role of various animal and bird species in the epidemiology of influenza viruses with pandemic potential
- Risk assessment

Global Planning

WHO has taken several steps toward global pandemic influenza planning, including development of a pandemic plan in 1999 and an updated plan in 2005 (see [References: WHO: WHO global influenza preparedness plan 2005](#)).

In addition, WHO in November 2005 held an international meeting on avian influenza and human pandemic influenza (see November 9, 2005, [CIDRAP News story](#)). The consultation was attended by more than 600 delegates from over 100 countries. Experts and officials set out key steps that must be taken in response to the threat of the H5N1 influenza virus which is currently circulating in animals in Asia and has been identified in parts of Europe:

Control spread at the source in birds

- Improve veterinary services, emergency preparedness plans, and control campaigns including culling, vaccination, and compensation.
- Assist countries to control avian influenza in animal populations.

Surveillance

- Strengthen early detection and rapid-response systems for animal and human influenza.
- Build and strengthen laboratory capacity.

Rapid containment

- Develop support and training for the investigation of animal and human cases and clusters, and carry out planning and testing of rapid containment activities.

Pandemic preparedness

- Build and test national pandemic preparedness plans.
- Conduct a global pandemic response exercise.
- Strengthen the capacity of health systems and training for clinicians and health managers.

Integrated country plans

- Develop integrated national plans across all sectors to provide the basis for coordinated technical and financial support

Communications

- To support all of the above, factual and transparent communications, in particular risk communication, is vital

The US Pandemic Influenza Plan

HHS issued the final version of the US Pandemic Influenza Plan on November 2, 2005 (see [References](#): HHS: Pandemic influenza plan). The plan includes three main sections: (1) an overview (including executive summary), (2) a strategic plan (part 1), and (3) public health guidance (part 2).

Part 1, Strategic Plan, includes the following:

- The Pandemic Influenza Threat
- Planning Assumptions
- Doctrine for a Pandemic Influenza Response
- Key Pandemic Influenza Response Actions and Key Capabilities for Effective Implementation
- Roles and Responsibilities of HHS Agencies and Offices
- HHS Actions for Pandemic Influenza Preparedness and Response
- Appendices
 - A. National Response Plan
 - B. Pandemic Influenza Background
 - C. WHO Pandemic Phases
 - D. NVAC/ACIP Recommendations on Use of Vaccines and NVAC Recommendations on Pandemic Antiviral Drug Use
 - E. Legal Authorities
 - F. Current Key HHS Activities
 - G. HHS Research Activities
 - H. International Partnership on Avian and Pandemic Influenza
 - I. Acronym List
 - J. Internet Resources on Pandemic Influenza

Part 2, Public Health Guidance for State and Local Partners, includes the following:

- Overview of Planning by State and Local Governments
- Overview of Community-Wide Planning to Support Healthcare Facilities
- Appendix 1: Checklist for Legal Considerations for Pandemic Influenza in Your Community
- Appendix 2: Fact Sheet: Practical Steps for Legal Preparedness
- Public Health Guidance Supplements
 - 1. Pandemic Influenza Surveillance
 - 2. Laboratory Diagnostics
 - 3. Healthcare Planning
 - 4. Infection Control
 - 5. Clinical Guidelines
 - 6. Vaccine Distribution and Use
 - 7. Antiviral Drug Distribution and Use
 - 8. Community Disease Control and Prevention
 - 9. Managing Travel-Related Risk of Disease Transmission

10. Public Health Communications
11. Workforce Support: Psychosocial Considerations and Information Needs

Planning at the Local Level

In addition to the federal plan, pandemic influenza plans have been developed by a number of states. Guidance on pandemic planning for state and local health departments is provided in the federal plan as Part 2. In addition, the Association of State and Territorial Health Officials (ASTHO) has issued a guidance document for pandemic influenza planning (see [References](#): ASTHO).

The Council for State and Territorial Epidemiologists (CSTE) Web site has links to a number of state plans (see [References](#): CSTE), as does the US official government site on pandemic influenza (see [References](#): HHS: PandemicFlu.gov).

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Infection Control Considerations

Infection control guidelines for pandemic influenza are provided in Part 2, Supplement 4 of the HHS Pandemic Influenza Plan (see [References](#): HHS: Pandemic influenza plan 2005).

Modes of Transmission for Influenza Viruses

Recommendations on infection control practices are based on available data regarding the modes of transmission of influenza viruses in general. Modes of transmission for influenza viruses are outlined below.

Droplet transmission

- Influenza viruses are predominantly transmitted by large droplets (ie, >5 mcm).
- Droplets are expelled by coughing and sneezing and generally travel through the air no more than 3 feet from the infected person.
- Transmission via large droplets requires close contact between the source and recipient persons, permitting droplets, which do not remain suspended in the air, to come into direct contact with oral, nasal, or ocular mucosa.
- Special air handling and ventilation systems are not required to prevent droplet transmission.

Direct and indirect contact transmission

- Direct contact transmission involves skin-to-skin contact (such as hand-to-hand) between an infected person and a susceptible person.
- The proportion of influenza virus transmission caused by direct or indirect contact remains unknown; however, transmission by these routes can occur.

- Influenza viruses can live for 24 to 48 hours on nonporous environmental surfaces and less than 12 hours on porous surfaces (see [References](#): Bean 1982), indicating that transmission can occur when hands that touch contaminated surfaces subsequently come into contact with oral, ocular, or nasal mucosa. Fomite transmission appears to be rare.

Airborne transmission

- Airborne transmission of influenza viruses (ie, transmission via droplet nuclei [<5 μm] which remain suspended in the air and have the potential to travel further than several feet) has been suggested in several reports, although evidence to support airborne transmission of influenza virus is limited (see [References](#): Bridges 2003).
 - One report describes the occurrence of an influenza outbreak following exposure to a person with influenza on board a commercial aircraft (see [References](#): Moser 1979). The aircraft was grounded for 3 hours with the ventilation system turned off and passengers on board. After the flight, 39 (72%) of the passengers reported having an influenza-like illness within 72 hours. These findings suggest that airborne transmission via droplet nuclei likely occurred for some passengers and may have been attributed to poor air circulation aboard the aircraft.
 - Another observational study involved comparing rates of influenza among TB patients housed in a TB sanatorium during the 1957-58 influenza pandemic (see [References](#): Riley 1974). TB patients in one building were housed in rooms with ultraviolet (UV) lights on the ceiling, whereas patients in other buildings did not have UV lights in their rooms. During an outbreak of influenza, the illness rate was 19% among those in rooms without UV lights and only 2% among those in rooms with UV lights. The fact that UV lights were protective suggests that airborne transmission of influenza was prevented in rooms with UV lights; however, the potential for exposure may not have been the same between patients in the different buildings and, therefore, no definitive conclusions about airborne transmission can be drawn.
 - Several experimental studies involving humans have shown that influenza viruses can be transmitted via droplet nuclei, although these studies used masks to deliver the aerosols and did not involve person-to-person transmission (see [References](#): Alford 1966, Henle 1946).
- Studies in mice also suggest the possibility of airborne transmission of influenza viruses.
 - In one report, uninfected mice were as likely to become infected when housed in the same cage with infected mice as they were if housed in an adjacent, separate cage that allowed droplet and droplet nuclei transmission between cages but no direct contact (see [References](#): Schulman 1968). In addition, a strong inverse correlation was found between the infection rate and the rate of air exchange, regardless of whether infected and uninfected mice were physically separated. Infectious particles of less than $10 \mu\text{m}$ in diameter produced by infected mice were found by air sampling, suggesting

that airborne transmission occurred between infected and uninfected mice held in separate cages.

- Another report showed that in a nonventilated room with constantly agitated air held at a relative humidity of 17% to 24%, mice could become infected with influenza virus as late as 24 hours after the virus was first aerosolized into the room, although the proportion of animals infected decreased over time (see [References](#): Loosli 1943).
- Aerosol-generating procedures (eg, intubation, bronchoscopy, nebulizer treatments) theoretically could promote dissemination of droplet nuclei from infected patients, although this has not been studied for influenza.
- There is no evidence that droplet nuclei containing influenza viruses can travel through ventilation systems or across long distances, such as can occur with tuberculosis and certain other viral agents.

Recommended Isolation Precautions to Prevent Transmission of Pandemic Influenza

Since large droplets are the major mode of influenza transmission, the US federal plan recommends Droplet Precautions along with Standard Precautions for prevention of transmission in healthcare settings. These recommendations are similar to those provided by WHO for isolation precautions in a pandemic situation (see [References](#): Clarification: Use of masks by health-care workers in pandemic settings). These guidelines assume that adequate PPE (personal protective equipment) supplies such as gloves and masks will be available during a pandemic. It is possible that these items will be in short supply; hospitals and other healthcare settings should consider developing contingency plans that take this possibility into consideration (see [References](#): Osterholm 2005: Avian flu: addressing the global threat).

Patients with pandemic influenza should be placed on Droplet Precautions for a minimum of 5 days from onset of symptoms. Immunocompromised patients should be continued on Droplet Precautions for the duration of their illness. Specific features of Standard and Droplet Precautions as outlined in the federal plan are shown in the table below. These features have been modified slightly from the 1994 CDC Guideline for Isolation Precautions in Hospitals (see [References](#): CDC/HICPAC 1994).

Components of Standard and Droplet Precautions	
Component	Recommendations
Standard Precautions	
Hand Hygiene	Perform hand hygiene after touching blood, body fluids, secretions, excretions, and contaminated items; after removing gloves; and between patient contacts. Hand hygiene includes both handwashing with either plain or antimicrobial soap and water or use of alcohol-based products (gels, rinses, or foams) that contain an emollient and do not require the use of water. If hands are visibly soiled or contaminated with respiratory secretions, they should be washed

	with soap (either nonantimicrobial or antimicrobial) and water. In the absence of visible soiling of hands, approved alcohol-based products for hand disinfection are preferred over soap and water because of the superior microbicidal activity, reduced drying of the skin, and convenience.
PPE: Gloves	Use for touching blood, body fluids, secretions, excretions, and contaminated items; for touching mucous membranes and nonintact skin.
PPE: Gown	Use during procedures and patient-care activities in which contact of clothing/exposed skin containing blood/body fluids, secretions, and excretions is anticipated.
PPE: Face/eye protection (eg, surgical or procedure mask and goggles or face shield)	Use during procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, secretions, or excretions.
Safe work practices	Avoid touching eyes, nose, mouth, or exposed skin with contaminated hands (gloved or ungloved); avoid touching surfaces with contaminated gloves and other PPE that are not directly related to patient care (eg, door knobs, keys, light switches).
Soiled patient care equipment	Handle in a manner that prevents transfer of microorganisms to oneself, others, and environmental surfaces; wear gloves (gown if necessary) when handling and transporting soiled linen and laundry; and perform hand hygiene after handling equipment.
Soiled linen and laundry	Handle in a manner that prevents transfer of microorganisms to oneself, others and environmental surfaces; wear gloves if materials are visibly contaminated; perform hand hygiene after handling.
Needles and other sharps	Use devices with safety features when available; do not recap, bend, break, or hand-manipulate used needles; if recapping is necessary, use a one-handed scoop technique; place used sharps in a puncture-resistant container.
Environmental cleaning and disinfection	Use EPA-registered hospital detergent-disinfectant; follow standard facility procedures for cleaning and disinfection of environmental surfaces; emphasize cleaning/disinfection of frequently touched surfaces (eg, bed rails, phones, lavatory surfaces).
Disposal of solid waste	Contain and dispose of solid waste (medical and nonmedical) in accordance with facility procedures and/or local or state regulations; wear gloves when handling waste and waste containers; perform hand

	hygiene.
Respiratory hygiene/cough etiquette (source control measure for persons with symptoms of a respiratory infection; implement at first point of encounter [eg, triage/reception areas] within a healthcare setting.)	Cover the mouth/nose when sneezing/coughing; use tissues and dispose of in no-touch receptacles; perform hand hygiene after contact with respiratory secretions; wear a mask (procedure or surgical) if tolerated; sit or stand as far away as possible (more than 3 feet) from persons who are not ill.
Droplet Precautions	
Patient placement	—Place patients with influenza in a private room or cohort with other patients with influenza. Keep door closed or slightly ajar, maintain room assignments of patients in nursing homes and other residential settings, and apply Droplet Precautions to all persons in the room. —When a private room is not available and cohorting is not possible, a spatial separation of at least 3 ft should be maintained between the patient and other patients or visitors. (<i>Note:</i> Other sources suggest that contact within 2 m [6.5 ft] can spread the disease.)
PPE	Wear a surgical or procedure mask for entry into patient room; wear other PPE as recommended for Standard Precautions.
Patient transport	Limit patient movement to medically necessary purposes; have patient wear a procedure or surgical mask when outside the room.
Other	Follow Standard Precautions and facility procedures for handling linen and laundry and dishes and eating utensils, and for clearing/disinfection of environmental surfaces and patient care equipment, disposal of solid waste, and postmortem care.
Aerosol-Generating Procedures	
Aerosol-generating Procedures	During procedure that may generate small particles of respiratory secretions (eg, endotracheal intubation, bronchoscopy, nebulizer treatment, suctioning), healthcare personnel should wear gloves, gown, face/eye protection, and a fit-tested N95 respirator or other appropriate particulate respirator.
Abbreviations: EPA, Environmental Protection Agency; PPE, personal protective equipment.	
<i>From: HHS Pandemic Influenza Plan 2005 (see References).</i>	

The US federal plan does not routinely recommend that patients with pandemic influenza be placed on Airborne Precautions (which involve placing patients in airborne isolation rooms [AIRs] and assuring that healthcare personnel caring for infected patients use fit-tested N95 respirators when entering the room). According to the 2003 CDC Guidelines for Preventing Healthcare Associated Pneumonia (see [References](#): CDC/HICPAC 2003), "Airborne transmission of influenza by droplet nuclei has been demonstrated, albeit inconclusively, in some reports; however, this route of transmission is likely less important than large droplet transmission. The added value of placing patients in rooms for airborne isolation (ie, negative air pressure rooms and use of N95 respirators) has not been assessed." Furthermore, use of N95 respirators requires fit-testing for the respirators to be effective and it may not be feasible to fit-test all healthcare workers who would be wearing respirators in the setting of a pandemic. Finally, N95 respirators and isolation rooms may be in short supply during peak pandemic activity.

The approach outlined by CDC and WHO for infection control during a pandemic varies somewhat from current infection control recommendations from CDC and WHO specific to H5N1 influenza, which support placing patients with H5N1 influenza on Airborne Precautions if possible (see [Section below](#)).

Respiratory Hygiene/Cough Etiquette

The federal plan indicates that respiratory hygiene/cough etiquette programs should be in place to decrease transmission of influenza. The CDC Web site outlines steps for implementing these programs (see [References](#): CDC: Respiratory hygiene/cough etiquette in healthcare settings). (*Note*: Although respiratory hygiene seems like a logical approach, its utility in preventing influenza virus transmission has not been scientifically validated.)

- The following measures to contain respiratory secretions are recommended for all individuals with signs and symptoms of a respiratory infection:
 - Cover the nose/mouth when coughing or sneezing.
 - Use tissues to contain respiratory secretions and dispose of them in the nearest waste receptacle after use.
 - Perform hand hygiene (eg, handwashing with nonantimicrobial soap and water, alcohol-based handrub, or antiseptic handwash) after having contact with respiratory secretions and contaminated objects/materials.
- During periods of increased respiratory infection activity in the community (eg, when there is increased absenteeism in schools and work settings and an increased number of medical office visits by persons complaining of respiratory illness), healthcare facilities should offer masks to persons who are coughing.
 - Either procedure masks (ie, with ear loops) or surgical masks (ie, with ties) may be used to contain respiratory secretions.
 - Respirators such as N95 or above are not necessary.
- When space and chair availability permit, coughing persons should be encouraged to sit at least 3 feet away from others in common waiting areas.
- When implementing respiratory hygiene programs, healthcare facilities should:

- Ensure the availability of materials for adhering to respiratory hygiene/cough etiquette in waiting areas for patients and visitors.
- Provide tissues and no-touch receptacles for used tissue disposal.
- Provide conveniently located dispensers of alcohol-based handrub; where sinks are available, ensure that supplies for handwashing (ie, soap, disposable towels) are consistently available.

Additional components of infection control can be found in Part 2, Supplement 4 of the HHS Pandemic Influenza Plan (see [References](#): HHS: Pandemic influenza plan 2005)

Infection Control Guidelines for H5N1 Avian Influenza

In May 2004, CDC and WHO issued infection control guidelines for prevention of transmission of H5N1 influenza in healthcare settings (see [References](#): CDC: Interim recommendations for infection control in health-care facilities caring for patients with known or suspected avian influenza; WHO: Influenza A (H5N1): WHO interim infection control guidelines for healthcare facilities). Summaries of the recommended isolation precautions from CDC and WHO are outlined in the table below. Both agencies recommend that Airborne Precautions be implemented, if possible.

Isolation Precautions for Patients With H5N1 Avian Influenza
CDC Recommendations
<p>Standard Precautions Pay careful attention to hand hygiene before and after all patient contact or contact with items potentially contaminated with respiratory secretions.</p> <p>Contact Precautions —Use gloves and gown for all patient contact. —Use dedicated equipment such as stethoscopes, disposable blood pressure cuffs, disposable thermometers, etc. —Eye protection (ie, goggles or face shields): Wear when within 3 feet of the patient.</p> <p>Airborne Precautions —Place the patient in an AIR. Such rooms should have monitored negative air pressure in relation to corridor, with 6-12 ACH, and exhaust air directly outside or have recirculated air filtered by a HEPA filter. If an AIR is unavailable, contact the healthcare facility engineer to assist or use portable HEPA filters to augment the number of ACH. —Use a fit-tested respirator, at least as protective as a NIOSH-approved N95 filtering facepiece (ie, disposable) respirator, when entering the room.</p>
WHO Recommendations
<p>Standard Precautions</p> <p>Droplet Precautions</p> <p>Contact Precautions</p> <p>Airborne Precautions (including use of high-efficiency masks and negative-pressure rooms when available)</p>
Abbreviations: ACH, air changes per hour; AIR, airborne isolation room; HEPA, high

efficiency particulate air; NIOSH, National Institute of Occupational Safety and Health.

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