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Agent

Avian influenza is caused by influenza A virus. More information about avian influenza in bird populations can be found in the document "Avian Influenza (Bird Flu): Agricultural and Wildlife Considerations" on this site.

- Family: Orthomyxoviridae
 - Enveloped virions are 80 to 120 nm in diameter and 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.
 - All past influenza pandemics have been caused by influenza A viruses.
 - 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 transcriptases (PB2, PB1, and PA), surface glycoproteins (hemagglutinin [HA] and neuraminidase [NA]), nonstructural proteins (NS1 and NS2), matrix proteins (M1 and M2), and a nucleocapsid protein (NP).
 - 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).
- Species: Influenza A
 - Divided into subtypes based on 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 known subtypes of influenza A can be found in birds, and feral aquatic birds are the major reservoir for influenza A viruses. Severe disease from influenza generally does not develop in feral birds.
 - Influenza A viruses have traditionally been known to also cause disease in horses, pigs, whales, and seals; however, the range of several influenza A subtypes is expanding to different mammalian species. H5N1 influenza A recently has been shown to infect cats, leopards, tigers, and civets (see [References: Keawcharoen 2004; Kuiken 2004; Aug 26, 2005, CIDRAP News story](#)). An H3N8 strain,

genetically and antigenically similar to equine influenza viruses, recently was identified in racing greyhounds in Iowa and elsewhere (see [References](#): Yoon 2005; Sep 27, 2005, [CIDRAP News story](#)).

- Subtypes are further divided into strains. 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 A/Hong Kong/03/68[H3N2], A/swine/Iowa/15/30[H1N1].)
- Avian influenza
 - All 16 HA types and 9 NA types of influenza A virus have been identified in birds (see [References](#): Fouchier 2004).
 - The term "avian influenza" is used to describe influenza A subtypes that primarily affect chickens, turkeys, guinea fowl, migratory waterfowl, and other avian species.
 - As with other influenza A subtypes, standard nomenclature is used to define strains (for example: A/Chicken/HK/5/98 [H5N1]).
 - Avian influenza is divided into highly pathogenic avian influenza (HPAI, also known as fowl plague) and low-pathogenic avian influenza (LPAI) as defined by in vivo tests.
 - HPAI strains have caused severe outbreaks of disease in domestic bird populations.
 - HPAI infections are notifiable, and virus-containing materials are classified as select agents under regulations from the US Department of Agriculture (USDA) (see [Biosafety and Biosecurity](#), below).
 - Currently, all HPAI strains are H5 and H7 subtypes; LPAI strains may be of any H subtype.
 - Evidence that HPAI strains arise from LPAI strains has led the World Organization for Animal Health (OIE) to classify all H5 and H7 strains as notifiable (see [References](#): Alexander 2003, Capua 2004, OIE 2004).
 - The 1918 influenza pandemic strain (H1N1) appears to be of avian origin (see [References](#): CDC: Information about pandemic influenza viruses).
- H5 subtypes
 - H5 subtypes include both HPAI and LPAI strains.
 - H5N1 strains circulate among birds worldwide and are responsible for the current outbreak in Asian among poultry and other birds.
 - H5N1 appears to be expanding its host range, has caused a number of human deaths (see below), and the possibility that H5N1 could mutate into a human pandemic strain is causing worldwide concern (see [References](#): WHO: Epidemic and pandemic alert and response).

- H5N1 has been differentiated into genetic clades on the basis of sequence data. Clade 1 includes human and bird isolates from Vietnam, Thailand, and Cambodia and bird isolates from Laos and Malaysia. Clade 2 viruses have been identified in bird isolates from China, Indonesia, Japan, and South Korea (see [References](#): WHO Global Influenza Program Surveillance Network).
- H7, H9, H10 subtypes
 - H7 includes HPAI and LPAI strains.
 - H9 is only known to include LPAI strains.
 - These subtypes have caused infections in humans on rare occasions (see [References](#): CDC: Avian influenza A viruses; NIAID: Timeline of human pandemics).

Environmental Survival of Avian Influenza Viruses

Influenza A virus remains viable at moderate temperatures for long periods in the environment and can survive indefinitely in frozen material. It can survive for 4 days in water at 22°C and for over 30 days at 0°C (see [References](#): PHS).

Recent data from studies of H5N1 in domestic ducks have shown that H5N1 can survive in the environment for 6 days at 37°C (see [References](#): WHO: Laboratory study of H5N1 viruses in domestic ducks).

Inactivation of the virus occurs under the following conditions (see [References](#): OIE 2002, PHS):

- Temperatures of 56°C for 3 hours or 60°C or more for 30 minutes
- Acidic pH conditions
- Presence of oxidizing agents such as sodium dodecyl sulfate, lipid solvents, and B-propiolactone
- Exposure to disinfectants: formalin, iodine compounds

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Laboratory Testing for Influenza in Humans

General Considerations

- Tests for influenza include: viral culture, polymerase chain reaction (PCR), rapid antigen testing, and immunofluorescence.
- Laboratory tests are widely used to identify influenza virus at the genus level (influenza A/B) or at the H-type level (H1, H3, and H5).

- H subtype–specific tests must be used to identify potential avian strains, including H5N1.
- The World Health Organization (WHO) recommends forwarding all H5, H7, and H9-positive isolates to a designated influenza reference laboratory for confirmation and N-typing (see [References](#): WHO: Guidelines for global surveillance of influenza A/H5; WHO: Recommended laboratory tests to identify avian influenza A virus in specimens from patients with an influenza-like illness).
- In vivo tests are used to identify HPAI and LPAI strains.
- Serologic tests have been used to diagnose infection retrospectively.
- 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.
- The sensitivity and specificity of laboratory tests appears to vary with the involved strain, which has implications for avian influenza and other emerging influenza variants (see [References](#): Weinberg 2005).
- Laboratory tests are required for specific identification of avian influenza. The most likely ways that an avian influenza strain would be detected in the human population are:
 - Outbreak investigations or investigation of unexplained death in a previously healthy individual
 - Influenza surveillance with laboratory testing
 - Investigation of unusual laboratory findings

Specimen Collection

- Appropriate specimens for testing include: (1) nasal wash, (2) nasal aspirates, (3) nasopharyngeal swab, and (4) throat swab; these should be collected within 4 days after illness onset. Some rapid test kits require specific specimen types and storage/transport requirements. Nasopharyngeal swabs, nasal washes, and aspirates are considered to be more sensitive for culture than throat swabs. Viral transport media should be used 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 (see [References](#): CDC: Lab diagnosis; Hayden 2002; Treanor 2005).
- Pharyngeal swabs taken 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/H5 2005).
- Specimen collection for animals with suspected H5N1 disease is described in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, updated May 2005 (see [References](#)).

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) early in 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 avian influenza A[H5N1] and SARS).
 - Culture of influenza subtypes H1-4, H6, and H8-15 (with exceptions noted below) requires biosafety level 2 (BSL-2) containment and practices (BSL-2 Animal for animal models).
 - Culture of noncontemporary influenza strains (H2N2) or research involving reverse genetics of the 1918 Spanish flu strain (H1N1) require BSL-3 containment with additional specific engineering and practice enhancements.
 - Culture in patients suspected of having avian influenza or SARS coronavirus requires enhanced BSL-3 containment (also see Biosecurity just below).
- 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 USDA classifies 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 an 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](#)).

Virus Isolation by Cell Culture

- Virus isolation is considered the "gold standard" of influenza testing (see [References: Hayden 2002, Treanor 2005](#)).
- Culture of specimens from suspect cases of avian influenza requires special containment facilities, procedures, and registration (see above). Samples from cases without specific risk factors may be cultured using standard facilities and procedures.
- Unlike antigen or nucleic acid-based tests, a positive result is considered definitive for the diagnosis.
- 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.
- 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 and mumps virus, may also cause haemadsorption. The lack of HAd 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 HAd-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 an 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
 - RT-PCR assays use conserved targets such as the matrix (M) protein for genus-level identification. Hemagglutinin and neuraminidase targets are used for specific identification of avian subtypes. PCR generally is not used for strain-level identification, which is based on serologic markers.
 - 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, and H5 (see [References](#): Arizona Department of Health Services). H5 primers allow for specific detection of avian influenza strains.
 - Multiplex realtime RT-PCR assays have been developed for specific detection of H5N1 (See [References](#): Kessler 2004, Ng 2005, Payungporn 2005).
 - 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 normal precautions.
 - The likelihood that a RT-PCR assay will detect new pandemic strains increases when more conserved target sequences are used.
 - The development of portable real-time platforms has made possible the use of PCR assays in the field (see [References](#): Perdue 2003).
- Immunofluorescence
 - Under the general heading of immunofluorescence are tests for antigen or antibody, and direct or indirect methods.

- Indirect immunofluorescence (IFA) methods can be used either directly on patient material or on cell cultures; they use either genus-specific (influenza A/B) or H-specific detection antibody (see [References: WHO: Recommended laboratory tests to identify avian influenza A virus in specimens from humans](#)).
- 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 "Rapid direct tests" just below).
- **Rapid direct tests (see [References: Call 2005; CDC: Interim guidance for influenza diagnostic testing during the 2004-05 influenza season; Treanor 2005; 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.
 - Reported sensitivities range from 40% to 80%.
 - Sensitivity is generally greater in children than adults.
 - Sensitivity is greater early in the course of illness.
 - 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 positive predictive value of a positive test decreases; therefore, disease prevalence should be considered before making the decision to use rapid tests.
 - 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.
 - Sensitivity of rapid assays for detection of emerging strains (including pandemic strains) is mostly unknown. Only 4 of 11 (36%) 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](#)).
 - 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.

Serology

- Serologic testing can be used for retrospective diagnosis of infection but is rarely useful for patient management (see [References](#): Hayden 2002, Treanor 2005).
- 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 EIA. A variety of other methods such as neutralization, microneutralization, single radial hemolysis, radial immunodiffusion, and western blotting 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.
- A fourfold rise in titer between acute and convalescent sera is generally considered necessary for confirmation of influenza infection.
- HAI enzyme immunoassays (EIA) measure antibody to hemagglutinin. These tests are more sensitive than CF, but their increased specificity could 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.
- 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 avian influenza strains.

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 or suspected to be 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).

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)
 - Zanamivir: There is currently no evidence of current resistance.
 - Oseltamivir: 0.4% to 1% resistance in adults; 4% to 8% in pediatric patients. An oseltamivir-resistant H5N1 strain was recently identified in a Vietnamese child who received prophylactic treatment with the drug (see [References](#): Le 2005).
- Current antiviral agents appear effective against a reconstructed 1918 (H1N1) pandemic strain (see [References](#): Tumpey 2002).

Laboratory Values Which That 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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Avian Influenza in Humans

In the past several years, it has become clear that avian influenza viruses can infect humans. Situations where avian influenza viruses have been recognized in humans include the following:

Human Cases of Avian Influenza				
Year	Subtype	No. of Cases	Location	Comments
1997	H5N1	18 (6 deaths)	Hong Kong	Cases were linked to an outbreak of H5N1 in poultry. Sustained person-to-person transmission did not occur and the outbreak stopped when all birds in the Hong Kong commercial poultry industry (about 1.4 million) were slaughtered (see References: Yuen 1998).
1999	H9N2	2 (children ages 4 yr, 13 mo)	Hong Kong	Both case-patients had been hospitalized with influenza-like illness and both recovered uneventfully (see References: Peiris 1999, Uyeki 2002). No additional cases of person-to-person transmission occurred. Further investigation demonstrated that H9N2 strains were circulating in poultry in Hong Kong and China, although the viruses were not highly pathogenic for birds.
2002	H7N2	1	United States (Virginia)	Evidence of infection was found in one person in Virginia following a poultry outbreak.
2003	H5N1	2 (1 death)	Hong Kong	The 2 case-patients were family members who had recently traveled to China (see References: CDC: Avian influenza infection in humans). A third family member died while in China of an undiagnosed respiratory illness). No direct link between these cases and H5N1 infection in poultry was identified.
2003	H7N7	89 (1 death)	The Netherlands	During an outbreak of H7N7 avian influenza in poultry, infection spread to poultry workers and their families in the area (see References: Fouchier 2004; Koopmans 2004). Most patients had conjunctivitis and several complained of influenza-like illness. The death occurred in a 57-year-old veterinarian. Subsequent serologic testing demonstrated that additional case-patients had asymptomatic infection.
2003	H7N2	1	New York	The source of exposure was not determined (see References: NIAID: Timeline of human pandemics).
2003	H9N2	1 (child)	Hong Kong	The source of infection remains unknown (see References: NIAID: Timeline of human pandemics).
2003-2005	H5N1	Over 130, with a	Vietnam,	Human cases are associated with an

(ongoing)		case-fatality rate of about 50%, according to official WHO numbers	Thailand, Cambodia, Indonesia, China	ongoing extensive outbreak of avian influenza in poultry (see References: WHO: Cumulative number of confirmed human cases of avian influenza A (H5N1) since 28 January 2004). More information on this situation can be found in the section below.
2004	H7N3	2	Canada (British Columbia)	Poultry workers became ill during an outbreak of H7N3 avian influenza in poultry (see References: Health Canada 2004).
2004	H10N7	2 (infants)	Egypt	One child's father was a poultry merchant (see References: NIAID: Timeline of human pandemics).

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The 2003-2005 Outbreak of H5N1

An outbreak of HPAI caused by a strain of H5N1 avian influenza started in Asia in the fall of 2003 and spread in domestic poultry farms at an historically unprecedented rate. The outbreak tapered off in spring 2004 but in summer re-emerged in several areas and is still of great concern. In October 2005 H5N1 was discovered to have spread to Europe. The strain causing the outbreak is genetically distinct from the one isolated from humans in Hong Kong in 2003. Areas affected by H5N1 avian influenza in poultry or migratory birds are shown in the following table.

Countries Affected by H5N1 in Poultry	
East Asia	Europe, Siberia, Central Asia
Cambodia	Croatia
China	Kazakhstan
Hong Kong	Romania
Indonesia	Russia (Siberia and European Russia)
Japan	Turkey
Laos	
Malaysia	
Mongolia	
South Korea	
Thailand	
Vietnam	

From WHO: H5N1 avian influenza: Timeline (see [References](#)).

WHO has officially recognized almost 140 human cases of H5N1 influenza; cases have been reported from Vietnam, Thailand, Cambodia, Indonesia, and China (see [References: WHO: Cumulative number of confirmed human cases of avian influenza A \[H5N1\]; WHO: Situation updates](#)). The case-fatality rate is about 50%.

Low perceived risk and high population exposures to live chickens appear to be factors that are contributing to the spread of H5N1 in Asia (see [References: Fielding 2005](#)). For example, a survey of households in an area of rural Thailand affected by avian influenza found that 74% of households surveyed owned live poultry (see [References: Olsen 2005: Poultry-handling practices during avian influenza outbreak](#),

Thailand). Most recognized human cases have involved direct contact with poultry (see [References](#): WHO Writing Committee of the WHO Consultation on Human Influenza A/H5). Types of exposures that have been identified to date include:

- Plucking and preparing diseased birds
- Handling fighting cocks
- Playing with poultry (particularly asymptomatic ducks)
- Consumption of duck blood and possibly undercooked poultry

Sustained person-to-person transmission has not occurred to date, although it has been suggested in several household clusters and in one case of apparent child-to-mother transmission in Thailand (see [References](#): Olsen 2005: Family clustering of avian influenza A (H5N1); Ungchusak 2005; WHO Writing Committee of the WHO Consultation on Human Influenza A/H5). Intensified surveillance in northern Vietnam suggests that the local strains are adapting to humans. These efforts have identified mild cases, more infections in older adults, and more family clusters that suggest person-to-person spread (see [References](#): WHO Writing Committee of the WHO Consultation on Human Influenza A/H5).

In addition, the H5N1 virus has jumped the species barrier to other mammalian species in recent years, including cats, pigs, tigers, leopards, and civets. A 2004 study showed that the virus was causing increasingly severe disease when injected into laboratory mice (see [References](#): Chen 2004).

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Clinical and Treatment Considerations

The incubation period for most patients with H5N1 influenza is 2 to 4 days; however, the range appears to be as long as 8 days. A recent report summarized the clinical presentations for different groups of patients in Asia; the information is presented in the table below (see [References](#): WHO Writing Committee of the WHO Consultation on Human Influenza A/H5).

Clinical Presentation for Different Groups of Patients in Asia					
	Hong Kong (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Outcome or Measure	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)
Fever (>38°C)	17/18 (94)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Headache	4/18 (22)	NS	NS	1/10 (10)	4/4 (100)
Myalgia	2/18 (11)	9/17 (53)	0	2/10 (20)	NS

Diarrhea	3/18 (17)	7/17 (41)	7/10 (70)	NS	2/4 (50)
Abdominal pain	3/18 (17)	4/17 (24)	NS	NS	2/4 (50)
Vomiting	6/18 (33)	4/17 (24)	NS	1/10 (10)	0
Cough	12/18 (67)	16/17 (94)	10/10 (70)	10/10 (100)	4/4 (100)
Sputum	NS	13/17 (76)	5/10 (50)	3/10 (30)	NS
Sore throat	4/12 (33)	12/17 (71)	0	0	1/4 (25)
Rhinorrhea	7/12 (58)	9/17 (53)	0	0	NS
Shortness of breath	1/18 (6)	13/17 (76)	10/10 (100)	10/10 (100)	NS
Pulmonary infiltrates	11/18 (61)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Lymphopenia	11/18 (61)	7/12 (58)	NS	8/10 (80)	1/2 (50)
Thrombocytopenia	NS	4/12 (33)	NS	8/10 (80)	1/2 (50)
Increased aminotransferase levels	11/18 (61)	8/12 (67)	5/6 (83)	7/10 (70)	NS
Development of respiratory failure (usually with ARDS)*	8/19 (44)	13/17 (76)	9/10 (90)	7/10 (70)	4/4 (100)

Abbreviations: ARDS: Acute respiratory distress syndrome; NS: Not stated.

*High levels of inflammatory mediators may contribute to ARDS and multiorgan failure.

Data were obtained from a recent WHO report and are derived primarily from several separate studies (see References: WHO Writing Committee of the WHO Consultation on Human Influenza A/H5; Chan 2002; Chotpitayasunondh 2004, Tran 2004, Yuen 1998).

Overall, the case-fatality rate for H5N1 influenza is about 50%. 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.

Some patients have presented with primarily gastrointestinal symptoms. In addition, a recent case report of a 4-year-old Vietnamese child with H5N1 avian influenza who presented in 2004 with encephalitis demonstrated the following features (see [References: De Jong 2005](#)):

- The child presented with a 2-day history of fever, headache, vomiting, and severe diarrhea (approximately 10 episodes per day). The stools were watery without blood or mucus.
- Laboratory tests on admission were unremarkable and chest x-ray was normal.
- On the third day following initial presentation, the child had a generalized convulsion and became comatose. He developed respiratory failure and died

- on the fifth day after initial presentation. Acute encephalitis of unknown origin was reported as the cause of death; no autopsy was performed.
- H5N1 influenza A virus was isolated from cerebrospinal fluid, fecal, throat, and serum specimens.
 - The patient's 9-year-old sister had died 2 weeks earlier from a similar clinical syndrome.

Although antiviral agents have been used in most of the Asian cases, their effectiveness has not been adequately assessed. According to the WHO report cited in the above table, early institution of neuraminidase inhibitors may be beneficial. Resistance to neuraminidase inhibitors is low, although an oseltamivir-resistant H5N1 strain was recently identified in a Vietnamese child who received prophylactic treatment with the drug (see [References: Le 2005](#)).

If H5N1 avian influenza escalates into a pandemic, stockpiles of antiviral agents may be used at the start of the pandemic in an attempt to curtail spread. WHO is in the process of developing a stockpile of oseltamivir through the donation of 3 million treatment courses from Roche, maker of Tamiflu (see [References: WHO: Donation of three million treatments of oseltamivir to WHO to help early response to an emerging influenza pandemic](#)). WHO anticipates having 1 million treatment courses available by early 2006 and the remaining 2 million available later in the year.

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Vaccine Development

Because of concerns about the pandemic potential of H5N1, WHO has been working with laboratories in the WHO 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](#)). On August 6, 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 was 180 mcg versus the 15 mcg given in annual flu shots, which makes the problem of adequate production far more acute. Further testing is ongoing, including trials to determine effectiveness and safety in children and the elderly (see August 8, 2005, [CIDRAP News story](#)).
- In the fall of 2005, Sanofi Pasteur and Chiron were awarded additional contracts from HHS to mass produce their candidate H5N1 vaccines. These doses will be added to a federal stockpile as indicated in the US Pandemic Influenza Plan (see [References](#): HHS: Pandemic influenza plan).

At this point, it is not clear if prototype H5 vaccines will offer protection against an emergent pandemic strain. 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).

- One recent 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.

One way of protecting against all types of influenza, including emerging pandemic strains, would be a universal flu vaccine that would not have to be reengineered each year. The British company Acambis announced in early August 2005 that it is developing such a vaccine and has had successful results in animal testing (see [References: Acambis 2005](#)). The vaccine would focus on the M2 viral protein, which does not change, rather than the surface hemagglutinin and neuraminidase proteins targeted by traditional 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 continuously, since its formulation would not change. Still, such a vaccine is years away from full testing, approval, and use. Other researchers are also working on a universal agent.

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WHO and CDC Travel Recommendations

WHO Recommendations

In November 2005, WHO updated travel recommendations to be consistent with Phase 3 of the WHO six-phase Pandemic Alert (see [References: WHO: Advice to international travelers 2005](#)):

Advice to countries

- WHO does not recommend any restrictions on travel to any areas affected by H5N1 avian influenza.
- WHO does not recommend travel restrictions to areas experiencing outbreaks of highly pathogenic H5N1 avian influenza in birds, including countries which have reported associated cases of human infection.
- WHO does not recommend the screening of travelers coming from H5N1 affected areas.
- WHO does not, at present, recommend the routine screening of travelers coming from affected areas. Local authorities may, however, usefully provide information to travelers on risks, risk avoidance, symptoms, and when and where to report should symptoms develop.

Advice to travelers

- WHO advises travelers to avoid contact with high-risk environments in affected countries.
- Travelers to areas affected by avian influenza in birds are not considered to be at elevated risk of infection unless direct and unprotected exposure to infected birds (including feathers, feces, and undercooked meat and egg products) occurs.
- WHO continues to recommend that travelers to affected areas avoid contact with live animal markets and poultry farms as well as any free-ranging or caged poultry. Large amounts of the virus are known to be excreted in the droppings of infected birds. Populations in affected countries are advised to avoid contact with dead migratory birds or wild birds showing signs of disease.
- Direct contact with infected poultry or with surfaces and objects contaminated by their droppings is considered the main route of human infection. Exposure risk is considered highest during slaughter, defeathering, butchering, and preparation of poultry for cooking. There is no evidence that properly cooked poultry or poultry products can be a source of infection.
- Travelers should contact their local health providers or national health authorities for supplementary information.

CDC Recommendations

CDC also has issued a set of recommendations for travelers to areas affected by H5N1 influenza; these were updated in November 2005 (see [References](#): CDC: Outbreak notice). CDC recommends the following:

Before international travel to an area affected by H5N1 avian influenza

- Visit CDC's Travelers' Health Web site (see [References](#)) to educate yourself and others who may be traveling with you about any disease risks and CDC health recommendations for international travel in areas you plan to visit.
- Be sure you are up-to-date with all your routine vaccinations and see your doctor or healthcare provider, ideally 4-6 weeks before travel, to get any additional vaccination medications or information you may need.
- Assemble a travel health kit containing basic first aid and medical supplies. Be sure to include a thermometer and alcohol-based hand gel for hand hygiene. See [References](#): CDC: Travelers' health kit).
- Identify in-country healthcare resources in advance of your trip.
- Check your health insurance plan or get additional insurance that covers medical evacuation in case you become sick. Information about medical

evacuation services is provided on the US Department of State website (see [References: US Department of State](#)).

During travel to an affected area

- Avoid all direct contact with poultry, including touching well-appearing, sick, or dead chickens and ducks. Avoid places such as poultry farms and bird markets where live poultry are raised or kept, and avoid handling surfaces contaminated with poultry feces or secretions.
- As with other infectious illnesses, one of the most important preventive practices is careful and frequent handwashing. Cleaning your hands often with soap and water removes potentially infectious material from your skin and helps prevent disease transmission. Waterless alcohol-based hand gels may be used when soap is not available and hands are not visibly soiled.
- Influenza viruses are destroyed by heat; therefore, as a precaution, all foods from poultry, including eggs and poultry blood, should be thoroughly cooked.
- If you become sick with symptoms such as a fever accompanied by a cough, sore throat, or difficulty breathing or if you develop any illness that requires prompt medical attention, a US consular officer can assist you in locating medical services and informing your family or friends. The book *Health Information for International Travel* provides information about what to do if you become ill while abroad (see [References: CDC: Seeking health care abroad](#)). You should defer further travel until you are free of symptoms, unless your travel is health-related. Inform your healthcare provider of any possible exposures to avian influenza.

After your return

- Monitor your health for 10 days.
- If you become ill with a fever plus cough, sore throat, or trouble breathing during this 10-day period, consult a healthcare provider. Important: Before you visit a healthcare setting, tell the provider the following: (1) your symptoms, (2) where you traveled, and (3) if you have had direct contact with poultry or close contact with a severely ill person.
- Do not travel while ill, unless you are seeking medical care. Limiting contact with others as much as possible can help prevent the spread of an infectious illness.

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Use of Seasonal Influenza Vaccine in Humans at Risk for H5N1 Infections

On January 30, 2004, WHO released guidelines for the use of seasonal influenza vaccine among persons at risk for H5N1 influenza (see [References](#): WHO: Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection). WHO is recommending targeted use of seasonal influenza vaccine to reduce the potential for humans to be infected with H5N1 at the same time that they are harboring a human influenza strain. This will decrease the opportunity for genetic reassortment of the avian H5N1 strain with genes from a human (H1 or H3) strain and thereby reduce the likelihood that a novel pandemic strain will emerge from the current situation in Asia.

Groups recommended for vaccination include:

- All persons who expected to be in contact with poultry or poultry farms suspected or known to be affected with avian influenza (H5N1), especially:
 - Cullers involved in destruction of poultry
 - People living and working on poultry farms where H5N1 has been reported or is suspected or where culling takes place
- Healthcare workers involved in the daily care of known or confirmed human cases of influenza H5N1
- Healthcare workers in emergency care facilities in areas where there is confirmed occurrence of influenza H5N1 in birds (provided that sufficient supplies of vaccine are available)

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Surveillance Considerations

Guidelines regarding reporting have been issued from WHO and CDC (see [References](#): WHO: Avian influenza surveillance; CDC: Outbreaks of avian influenza A (H5N1) in Asia and interim recommendations for evaluation and reporting of suspected cases, United States, 2004).

According to current recommendations from CDC, testing for H5N1 of patients hospitalized in the United States is indicated for patients who have both of the following conditions:

- Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternative diagnosis has not been established

- A history of travel within 10 days of symptom onset to a country with documented H5N1 avian influenza infection in poultry or humans

Testing for influenza A (H5N1) also should be considered for patients with all of the following:

- Documented temperature of over 100.4°F (38°C)
- Cough, sore throat, or shortness of breath
- History of contact with poultry or domestic birds (eg, visited a poultry farm, a household raising poultry, or a bird market) or a known or suspected patient with influenza A (H5N1) in an H5N1-affected country within 10 days of symptom onset)

CDC recommends the following for laboratory testing of clinical specimens from patients with suspected H5N1 influenza A:

- Virus isolation studies on respiratory specimens should not be performed unless all biosafety level 3 (BSL-3) laboratory conditions are met.
- Clinical specimens can be tested by polymerase chain reaction (PCR) assays by using standard BSL-2 work practices in a Class II biological safety cabinet.
- Commercially available antigen-detection tests can be used under BSL-2 levels to test for influenza.
- Specimens from suspected cases should be sent to CDC if they test positive for influenza A either by PCR or antigen-detection testing, or if PCR assays for influenza are not locally available.

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Influenza Pandemic Considerations

Past influenza pandemics occurring during the 20th century apparently all arose from the Eurasian avian lineage of viruses. These strains underwent genetic reassortment, most likely in pigs, before spreading widely among humans. It is unclear whether reassortment in another animal host is necessary or whether an avian strain could directly cause a global pandemic in humans (see [References](#): Webster 1997).

Of the avian influenza subtypes, H5N1 is of concern for the following reasons (see [References](#): WHO: Avian influenza: assessing the pandemic threat):

- The subtype mutates rapidly.
- It has shown a propensity to acquire genes from viruses infecting other animal species.

- It causes severe disease in humans, with a high case-fatality rate.
- The virus has spread rapidly throughout poultry flocks in Asia, increasing the likelihood of infecting humans or pigs, where genetic reassortment with human strains could occur, leading to a new pandemic strain.

The current H5N1 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 been shown to be easily transmitted between humans, and sustained person-to-person transmission has not yet occurred. If the virus continues to circulate widely among poultry, it has a greater potential to infect humans and other animals (such as pigs), where genetic reassortment could take place and create a new pandemic strain. A WHO consultation held May 6-7, 2005, in Manila suggested that the pandemic potential of H5N1 is continuing to evolve (see [References: WHO: Inter-country consultation on influenza A/H5N1 in humans in Asia](#)). However, WHO stated June 30, 2005, that a team of experts sent to Vietnam found no laboratory evidence that the virus had changed appreciably (see [References: WHO: Situation updates: avian flu \[click update 24\]](#)).

More information can be found in the [Pandemic Influenza](#) section of this Web site.

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Infection Control

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 2004](#)). Summaries from CDC and WHO of recommended isolation precautions 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
Standard Precautions —Pay careful attention to hand hygiene before and after all patient contact or contact with items potentially contaminated with respiratory secretions.
Contact Precautions —Use gloves and gown during all patient contact. —Use dedicated equipment such as stethoscopes, disposable blood pressure cuffs, and disposable thermometers.
Eye protection (ie, goggles or face shields)

—Wear when within 3 ft of patient.

Airborne Precautions

—Place patient in an AIR. Such rooms should have monitored negative air pressure in relation to corridor, with 6 to 12 ACH, and should 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 ACH.

—Use a fit-tested respirator, at least as protective as a NIOSH-approved N95 filtering facepiece (ie, disposable) respirator, when entering room.

WHO Recommendations

Standard Precautions

Droplet Precautions

Contact Precautions

Airborne Precautions (including use of high-efficiency masks and negative-pressure rooms when available)

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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Food Safety Issues

In November 2005, WHO issued a statement on food safety issues (see [References: WHO/INFOSAN 2004](#)). This statement includes the following information:

- The H5N1 avian influenza virus is not transmitted to humans through properly cooked food. The virus is sensitive to heat and normal temperatures used for cooking (so that food reaches 70oC in all parts) will kill the virus.
- To date, no evidence indicates that any person has become infected with the H5N1 virus following the consumption of properly cooked poultry or poultry products, even in cases where the food item contained the virus prior to cooking. However, several cases have involved consumption of raw poultry ingredients, uncooked duck blood.
- Poultry and poultry products from areas free of the disease can be prepared and consumed as usual, with no fear of acquiring H5N1 infection.
- Most strains of avian influenza virus are found only in the respiratory and gastrointestinal tracts of infected birds, not in meat. However, available studies indicate that highly pathogenic viruses, including the H5N1 virus, spread to virtually all parts of an infected bird, including meat. For this reason, proper handling of poultry and poultry products during food preparation and proper cooking are extremely important in areas experiencing outbreaks of H5N1 avian influenza in poultry.
- Consumers in areas with outbreaks need to be aware of the risks of cross-contamination between raw poultry and other foods that will not be cooked prior to their consumption. Juices from raw poultry or poultry products should never be allowed during food preparation to touch or mix with items eaten raw. When handling raw poultry or raw poultry products, persons involved in food preparation should wash their hands thoroughly and clean and disinfect

surfaces in contact with the poultry products. Soap and hot water are sufficient for this purpose.

- In countries with outbreaks, thorough cooking is imperative. Consumers need to be sure that all parts of the poultry are fully cooked (no "pink" parts) and that eggs, too, are properly cooked (no "runny" yolks).
- The H5N1 virus can survive for at least 1 month at low temperatures. For this reason, common food preservation measures, such as freezing and refrigeration, will not substantially reduce the concentration of virus in contaminated meat or kill the virus. In countries with outbreaks, poultry stored under refrigeration or frozen should be handled and prepared with the same precautions as fresh products.
- In countries with outbreaks, eggs may contain virus both on the outside (shell) and inside (white and yolk). Eggs from areas with outbreaks should not be consumed raw or partially cooked. Raw eggs should not be used in foods that will not be treated by heat high enough to kill the virus (70°C).
- To date, a large number of human infections with the H5N1 virus have been linked to the home slaughter and subsequent handling of diseased or dead birds prior to cooking. These practices represent the highest risk of human infection and are the most important to avoid. Proper handling and cooking of poultry and poultry products can further lower the risk of human infections.

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