

when the child ingests fleas that, in their larval stage, have eaten eggs from proglottids. In 3–4 weeks the tapeworm becomes mature. Infection is prevented by keeping dogs and cats free of fleas and worms; treatment as for *H. nana*.



INFLUENZA

ICD-9 487; ICD-10 J09, J10, J11

I. SEASONAL INFLUENZA ICD-9 487; ICD-10 J10, J11
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1. Identification—An acute viral disease of the respiratory tract characterized by fever, cough (usually dry), headache, myalgia, prostration, coryza, and sore throat. Cough is often severe and can last 2 or more weeks; fever and other symptoms generally resolve in 5–7 days. In temperate climates, recognition is commonly based on clinical presentation during winter months with a syndrome consistent with influenza. Diagnosis improves when influenza surveillance information is available to indicate influenza viruses are in circulation. Influenza may be clinically indistinguishable from disease caused by other respiratory viruses, such as rhinovirus, RSV, parainfluenza, adenovirus and other pathogens. Syndromes consistent with influenza include acute upper respiratory illness, croup, bronchiolitis, febrile seizures, and pneumonia. In children, GI tract manifestations (nausea, vomiting, diarrhea) may accompany the respiratory phase, and have been reported in up to 25% of children in school outbreaks of influenza B and A (H1N1). GI manifestations are uncommon in adults. Infants may present with a sepsis-like syndrome. Older adults with influenza can present with worsening of underlying conditions such as congestive heart failure, and may not have an elevated temperature.

Point-of-care rapid testing is increasingly available to assist with diagnosis. Such tests are useful especially in rapidly establishing influenza as the basis for out-of-season outbreaks or outbreaks in remote areas where specimen transportation takes time. Such information can enable timely implementation of control measures. Commercially available point-of-care tests are generally 70% or less sensitive, but approximately 95% specific. Thus, particularly in the setting of a known influenza epidemic, negative results from patients with symptoms consistent with influenza must be interpreted cautiously. If excluding a false-negative result is important, then more sensitive testing should be considered, including viral culture and RT-PCR testing.

Yearly seasonal influenza epidemics impose a substantial health burden on all age groups, but the highest risk of complications occur among children less than 2 years, adults older than 64 years, and persons of any age with certain medical conditions, including chronic cardiovascular,

pulmonary, renal, hepatic, hematologic or metabolic disorders (e.g. diabetes); immunosuppression; pregnancy; and neurologic/neuromuscular conditions that can compromise respiratory function or handling of respiratory secretions. Secondary complications of influenza include bacterial pneumonia, including co-infection with MRSA and *S. pneumoniae*; viral pneumonia; worsening of underlying conditions; sinusitis; otitis media; febrile seizures; encephalitis/encephalopathy; myositis; and Reye syndrome in association with use of salicylates. Although seasonal influenza deaths can occur in any age group, over 90% of influenza deaths occur among those aged 65 years and older. Annual epidemics of influenza can be explosive and overwhelm health care services.

Most studies of the epidemiology of influenza have been conducted in developed countries in temperate climates, but more information is now being obtained from developing and tropical countries that have found higher risk of influenza complications and death among children less than 5 years, the elderly, and those with chronic diseases. Reports of influenza outbreak investigations in Africa and Indonesia suggest malnutrition and poor access to health care are likely to contribute to higher rates of complications and death.

Laboratory confirmation of influenza infection can be done by isolation of viruses from throat, nasal, and nasopharyngeal secretions or tracheal aspirate or washings using cell culture or in embryonated eggs; direct identification of viral antigens in nasopharyngeal cells and fluids (FA test or ELISA); rapid diagnostic tests; or viral RNA amplification. Demonstration of a 4-fold or greater rise in specific antibody titer between acute and convalescent sera can also be used to confirm acute infection. Single serological specimens cannot be used to diagnose an acute infection. Ideally, respiratory specimens should be collected as early in the illness as possible. Virus shedding starts to wane by the 3rd day of symptoms, and in most cases virus is not detected after 5 days in adults, though virus shedding can occur longer in children.

2. Infectious agents—Three types of seasonal influenza virus are recognized: A, B and C. The antigenic properties of the two relatively stable internal structural proteins, the nucleoprotein and the matrix protein, determine virus type. Influenza A viruses are further divided into subtypes based on two viral surface glycoproteins: the hemagglutinin (H) and the neuraminidase (N). There are 16 different hemagglutinin subtypes and 9 different neuraminidase subtypes. The current subtypes of influenza A viruses circulating widely among humans are A (H1N1) and A (H3N2). Aquatic birds are the primary reservoir for influenza A viruses and all subtypes of influenza A have been found among birds. Influenza A viruses also circulate among other animals, including pigs, horses, seals, and other animals. Influenza B viruses are not divided into subtypes, but two antigenically distinct lineages of B viruses currently circulate among humans. Humans are the primary reservoir for influenza B. Both influenza A and B viruses can be further classified into strains, and can cause seasonal

outbreaks of influenza. Only the emergence and spread of influenza A viruses bearing an H or H/N combination to which most persons have never been exposed are known to cause pandemics. Type C influenza is associated with sporadic cases and minor localized outbreaks and imposes much less of a disease burden than influenza A and B. Only influenza A and influenza B viruses are included in seasonal influenza vaccines.

Levels of antibody against the hemagglutinin are the most important predictor of protection against infection by human influenza viruses. Antibody against the neuraminidase can reduce the severity of illness. Genes encoding these surface glycoproteins are constantly changing through mutations, a process termed "drift" that occurs during virus replication. The constant emergence of new influenza strains through drift requires the annual review and periodic replacement of vaccine strains. Usually, one or more strains are replaced in each year's vaccine. The constant emergence of new strains is the virologic basis for yearly epidemics of seasonal influenza and one of the main reasons why multiple influenza infections can occur in an individual over their lifetime. Influenza virus strains are named based on their type, geographic site of isolation, laboratory number, year of isolation, and subtype (for A viruses only). Examples are A/New Caledonia/20/99(H1N1); A/Brisbane/10/2007 (H3N2); and B/Malaysia/2506/2004.

3. Occurrence—Seasonal influenza results in yearly epidemics of varying severity, with sporadic cases or outbreaks of human disease occurring outside of typical seasonal patterns, and, rarely, as a pandemic. Clinical attack rates during annual epidemics can range from 5% to 20% in the general community to more than 50% in closed populations (e.g. nursing homes, schools). During yearly epidemics in industrialized countries, influenza illness often appears earliest among school-age children. The highest illness rates generally occur in children, with accompanying increases in school absences, physician visits, and pediatric hospital admissions. Influenza illness among adults is associated with increases in workplace absenteeism, adult hospital admissions, and mortality, especially among the elderly. In North America, epidemics generally last from 8–10 weeks. One or more strains, subtypes and/or types of influenza can circulate within a single influenza season in the same area. In temperate zones, epidemics tend to occur in winter months. In some tropical countries, influenza can occur year-round with 2 peaks per year consistent with peak activity in Northern and Southern Hemisphere temperate zones, and/or peaks during the rainy season.

4. Reservoir—Humans are normally infected by human influenza viruses (H3N2, H1N1 and B), and form the primary reservoir for these human viruses. With some notable exceptions, seasonal influenza usually is not a zoonotic disease.

5. Mode of transmission—The relative contribution of large droplet, droplet nuclei (i.e. airborne spread), and contact transmission (direct and

indirect) in the spread of seasonal influenza is unknown, although large droplet spread is believed to be the primary means of transmission, through coughing and sneezing by infected persons. Human influenza virus may persist for hours on solid surfaces, particularly in lower temperatures and lower humidity.

6. Incubation period—Average 2 days (range 1-4) for seasonal influenza.

7. Period of communicability—In adults, viral shedding and probable communicability is greatest in the first 3-5 days of illness. In young children, virus shedding can occur for longer, 7-10 days, and may be even longer in severely immunocompromised persons.

8. Susceptibility—The size and relative impact of epidemics and pandemics depend upon several factors, including natural or vaccine-induced levels of protective immunity in the population, the age and condition of the population, strain virulence, and the extent of antigenic variation of new viruses. Infection induces immunity to the infecting virus and antigenically similar viruses. The duration and breadth of immunity depend, in part, upon the degree of antigenic similarity between viruses causing immunity and those causing disease. During seasonal epidemics, much of the population has partial protection, because of earlier infections from related viruses. Vaccines produce serological responses specific for the influenza vaccine virus strains, but can also provide cross-protection against related strains.

Age-specific attack rates during seasonal influenza epidemics reflect persisting immunity from past experience with variant viruses related to the epidemic subtype, so that the incidence of infection is often highest in children who have fewer prior influenza infections and less pre-existing antibody.

9. Methods of control—Detailed recommendations for the prevention and control of annual seasonal influenza epidemics are issued annually by national health agencies and WHO.

A. Preventive measures:

- 1) Educate the public and health care personnel in basic personal hygiene, including hand hygiene and cough etiquette, and especially transmission via unprotected coughs and sneezes, and from hand to mucous membranes.
- 2) Immunization with available inactivated influenza vaccines (IIV) and live virus vaccines may provide 70%-90% protection against infection in healthy young adults when the vaccine antigen closely matches the circulating strains of virus. Live attenuated influenza vaccines (LAIV), used in Russia for many years, are now also licensed in other industrialized countries for intranasal application in healthy

individuals aged 2–49. In the elderly, although immunization may be less effective in preventing illness, inactivated vaccines may reduce severity of disease and incidence of complications by 50%–60%, and deaths by approximately 80%. Influenza immunization should preferably be coupled with immunization against pneumococcal pneumonia for groups recommended to receive both vaccines (see *Pneumonia*).

A single dose suffices for those with prior exposures to influenza A and B viruses; 2 doses at least 4 weeks apart are essential for children less than 9 years old who have not previously been vaccinated against influenza. Routine immunization programs should focus efforts on vaccinating those at greatest risk of serious complications or death from influenza (see Identification, above) and those who might spread influenza (health care personnel and household contacts of high-risk persons) to high-risk persons. Immunization of children on long-term aspirin treatment is also recommended to prevent development of Reye syndrome after influenza infection.

The vaccine should be given each year before influenza is expected in the community; the timing of immunization should be based on a country's seasonal patterns of influenza circulation (i.e. winter months in temperate zones, often rainy season in tropical regions). Biannual recommendations for vaccine strain are based on the viral strains currently circulating, as determined by WHO through global surveillance.

Contraindications: Allergic hypersensitivity to egg protein or other vaccine components is a contraindication. During the swine influenza vaccine program in 1976, the USA reported an increased risk of developing Guillain-Barré syndrome (GBS) within 6 weeks after vaccination. Subsequent vaccines produced from other virus strains in other years have not been clearly associated with an increased risk of GBS. However, prior GBS is a contraindication for receiving an LAIV. The development of GBS within the 6 weeks following a dose of IIV is considered a precaution for future IIV use.

- 3) There are two classes of antiviral agents that are available for prophylaxis and treatment of influenza infections. Antiviral agents are supplemental to vaccine when immediate maximal protection is desired. The use of antiviral agents should be considered in persons at high risk for complications due to influenza, persons hospitalized with influenza, and during facility outbreaks. Antiviral agents are effective at reducing inter-facility transmission during outbreaks, such as among residents of nursing homes for the elderly. The drugs will not

interfere with the response to inactivated influenza vaccine, and should ideally be continued throughout the period of likely exposure to influenza. However, antivirals ideally should not be administered for 2 weeks after receipt of LAIV, and should be stopped for 2 days prior to LAIV vaccination. Treatment with antiviral agents within 48 hours of influenza symptom onset reduces the duration and severity of symptoms, and may reduce complications and deaths associated with influenza infections.

Inhibitors of influenza neuraminidase (oseltamivir and zanamivir) have been shown to be safe and effective for both prophylaxis and treatment of influenza A and B. Oseltamivir is an orally administered medicine; zanamivir is a powder administered via an inhaler. Oseltamivir may be used for persons 1 year and zanamivir is approved for treatment of persons 7 years and for prophylaxis for persons 5 years. Dosing is twice a day for 5 days for treatment and once a day for prophylaxis, with dosing for oseltamivir adjusted by body weight for children. Post-exposure prophylaxis should be continued for 7–10 days after a known exposure to influenza; however, prophylaxis used to prevent exposures throughout an influenza season would extend through the season. Few data, however, are available on the use of antiviral prophylaxis for more than 6 weeks. Reports of resistance to neuraminidase inhibitors have been rare until recently. In 2008, a significant increase in the number of oseltamivir-resistant influenza A (H1N1) viruses was detected in many countries. The proportion of viruses resistant to oseltamivir was variable among countries, and studies to characterize transmission and illness due to these viruses are underway. Resistance to zanamivir is rare. Serious cases of bronchospasm have been reported with zanamivir use in patients with and without underlying airways disease. Zanamivir use should be avoided in patients with underlying lung disease or reactive airway disease.

The adamantanes, amantadine and rimantadine, are effective for prophylaxis and treatment of influenza type A infection, but not influenza type B. Both adamantane agents may be used in persons 1 year of age. During treatment, 15–30% of patients develop resistance to adamantanes and resistant viruses are fully transmissible. Globally, adamantane resistance among influenza type A viruses is high. Therefore, routine use of adamantanes is not recommended. CNS side-effects are reported in 5%–10% of recipients of amantadine, and may be more severe in the elderly or those with impaired kidney function—the latter should receive reduced dosages that reflect the degree of renal impairment. Fewer CNS side

effects have been reported with rimantadine use compared with amantadine.

B. Control of patient, contacts and the immediate environment:

- 1) Report to local health authority: Reporting outbreaks or laboratory-confirmed cases assists disease surveillance. Report identity of the infectious agent as determined by laboratory testing if possible, Class 1 (see *Reporting*). Untypable or new subtypes of influenza infections should be further tested by qualified laboratories, and public health authorities should be rapidly notified.
- 2) Isolation: Ideally, all persons admitted to a hospital with a respiratory illness, including suspected influenza, should be placed in single patient rooms or, if this is not possible, placed in a room with patients with similar illness (cohorting). When cohorting is used, adequate spacing between beds should be provided for droplet precautions. For influenza, isolation should continue for the initial 5–7 days of illness, and possibly longer for patients who are severely immunocompromised who may be infectious for longer periods. Both standard and droplet precautions are recommended.
- 3) Concurrent disinfection: Not applicable for seasonal influenza.
- 4) Quarantine: Not applicable for seasonal influenza.
- 5) Protection of contacts: A specific role has been shown for antiviral chemoprophylaxis (see 9A3). Clinicians should take local antiviral susceptibility information into account when prescribing antivirals.
- 6) Investigation of contacts and source of infection: Of no practical value during annual seasonal influenza epidemics.
- 7) Specific treatment: Antiviral agents begun within 48 hours of symptom onset reduce illness duration and may reduce complications associated with influenza (see 9A3).

Patients should be watched for bacterial complications, including co-infection with MRSA, and antibiotics prescribed accordingly. Because of the association with Reye syndrome, avoid salicylates in children with suspected influenza infection.

C. Epidemic measures:

- 1) The severe and often disruptive effects of epidemic seasonal influenza on community activities may be reduced in part by effective health planning and education, particularly locally organized immunization programs for high-risk patients, their close contacts, and health care providers. Community

surveillance for influenza, use of outbreak control measures, adherence to infection control recommendations, and reporting of surveillance and outbreak findings to the community are all important.

- 2) Closure of individual schools has not been proven to be an effective measure to reduce the impact of seasonal influenza in a community, possibly because such measures are generally applied late in the course of an epidemic, due to high staff and student absenteeism rather than as an outbreak control measure.
- 3) Hospital administrators should anticipate increased demand for medical care during epidemic periods and possible absenteeism of health care personnel as a result of influenza. Health care personnel should be immunized annually to minimize absenteeism and transmission of seasonal influenza from health care personnel to patients.
- 4) Maintaining adequate supplies of appropriate antiviral drugs would be desirable to treat high-risk patients, persons hospitalized with influenza, and essential personnel in the event of the emergence of a new pandemic strain for which no suitable vaccine is available in time for the initial wave.

D. Disaster implications: Aggregations of people in emergency shelters will favor outbreaks of influenza if the virus is introduced.

E. International measures: A disease under surveillance by WHO. The following are recommended:

- 1) Report regularly on epidemiological situations within each given country to WHO/GISN (<http://www.who.int/flunet>).
- 2) Respiratory specimens, throat and nasal swabs, nasopharyngeal swabs or aspirates, and paired blood samples may be sent to any WHO-recognized National Influenza Center (<http://www.who.int/csr/disease/influenza/centres/en/index.html>). Identify the causative virus in reports, and submit prototype strains to one of the WHO Centers for Reference and Research on Influenza in Atlanta, London, Melbourne or Tokyo (<http://www.who.int/influenza>).
- 3) Conduct epidemiological studies; promptly identify and report viruses to national and international health agencies.
- 4) Ensure sufficient commercial and/or governmental facilities to provide rapid production of adequate quantities of vaccine and antiviral drugs, and maintain programs for vaccine and antiviral drug administration to high-risk persons and essential personnel.

II. INFLUENZA VIRUS INFECTION OF AVIAN AND OTHER ANIMAL ORIGIN

ICD-10 J09

1. Identification—Occasionally, a new subtype of influenza A emerges that is infectious for humans (a process termed shift). If such a virus is able to transmit from person to person efficiently enough to cause community outbreaks, then such a virus has the potential to cause a pandemic. Although most human infections with novel influenza A viruses probably result in sporadic cases or very limited human-to-human transmission, all human cases of novel influenza A infection must be considered a potential pandemic infection and should be investigated to assess the risk of human-to-human transmission. The first laboratory clue of a novel influenza A infection is the inability of available tests to subtype influenza A viruses. Suspicion is heightened if illness has occurred after exposure to birds, pigs or other animals that may be infected with influenza or exposure to their environments. Animal influenza A virus subtypes that have infected humans include H5N1, H7N2, H7N3, H7N7, H9N2, H10N7 and swine and avian H1 viruses, which are antigenically distinct from human H1 viruses. The current situation of widespread outbreaks of highly pathogenic avian influenza (HPAI) A(H5N1) virus infection among poultry is of a great concern because H5N1 virus is now endemic in poultry in some countries, causes high rates of death among infected poultry, and has resulted in a 60% case-fatality ratio among infected humans. Although human-to-human transmission of this H5N1 virus is currently limited and unsustainable, continued vigilance is needed to detect changes in H5N1 viruses that might signal a pandemic. H5N1 viruses are dealt with in a separate section on influenza virus infection of avian and other animal origin, below.

New subtypes of influenza A can emerge among humans through direct transmission of an animal influenza virus to humans, or through reassortment of genes derived from an animal influenza virus and a human influenza virus. Such genetic reassortment can create a new virus that combines human and animal influenza properties. The 1918 pandemic virus is hypothesized to have developed from an avian influenza virus that adapted to humans. The 1957 and 1968 pandemic viruses were the result of genetic reassortment between avian and human influenza viruses. Pandemic viruses in the past have spread globally within 4 months of detection; modern air travel may further hasten the spread of a new pandemic virus, leaving little time for vaccine development, manufacturing or administration to the world's population. Planning for responses to pandemics ahead of actual pandemics is therefore critical for preparedness.

Human infections with avian H7 influenza virus have been reported, resulting in subclinical infections, conjunctivitis, and respiratory tract symptoms. In 2003, there were 89 human cases of avian influenza A

(H7N7) virus infection, including 1 death and limited human-to-human transmission in the Netherlands. In 2007, there were 4 cases of human infection with avian influenza A (H7N2) virus in the United Kingdom. In addition, four cases of avian influenza A (H9N2) illness in children in Hong Kong, SAR, China, were reported from 1999-2007. Swine influenza viruses have also caused illness in humans. Earlier, in 1976, the A/New Jersey/76 (Hsw1N1) influenza virus of swine origin caused severe respiratory illness in 13 soldiers, including one death, at Fort Dix, New Jersey, but did not spread beyond Fort Dix. Other human infections with swine influenza viruses have been sporadically identified, including 5 cases of human infection with a swine influenza A (H1N1) virus containing swine, avian, and human influenza virus genes (i.e. a triple reassortant) during 2007 in the United States. In most non-H5N1 cases, including swine influenza, symptoms associated with animal influenza virus infections have been similar to those for seasonal influenza infections. Conjunctivitis has been prominent in many cases of H7N7 and H7N2 infection. Of the animal influenza virus infections of humans, H5N1 has been the most studied and has the most advanced prevention guidance developed; thus this chapter will focus mostly on H5N1.

Diagnosis of animal influenza viruses often requires specialized laboratories, since these viruses cannot be typed by reagents used for seasonal influenza viruses. Detection of viral RNA in respiratory and other clinical specimens by means of conventional or real-time reverse-transcriptase polymerase chain reaction remains the best method for the initial diagnosis. Infection can be also confirmed by documenting seroconversion based upon a rise in antibody titer between an acute and a convalescent serum specimen. Otherwise, point-of-care rapid testing (also sometimes called "rapid tests") used for human influenza viruses have been insensitive for animal influenza viruses, and generally not useful. If an animal influenza virus infection is suspected, a negative test result by a point-of-care test does not exclude the presence of the virus infection.

Avian influenza A(H5N1) virus infection in humans: In 1997, the first avian influenza A(H5N1) outbreak among humans occurred in Hong Kong, SAR, China; since 2003, there has been a resurgence of H5N1 outbreaks, first among poultry in southeast Asia, with subsequent rapid spread to other parts of the world. In association with this panzootic in poultry, sporadic cases and clusters of human infection have been reported. Human H5N1 illness typically manifests as severe pneumonia, and the case fatality has been high (60%). Common initial symptoms are fever (usually higher than 38°C) and cough, plus signs and symptoms of lower respiratory tract involvement including dyspnea. Upper respiratory tract symptoms such as sore throat and coryza are present only sometimes. Gastrointestinal symptoms were frequently reported in cases in Thailand and Vietnam in 2004, but less frequently since 2005, suggesting that clinical presentations may differ depending on the virus (see II.2 for different virus clades). Severe lower respiratory tract manifestations often develop early in the course of illness, and clinically apparent pneumonia

with radiological changes has usually been found at presentation. The disease progresses rapidly, and often progresses to an acute respiratory distress syndrome. Median times of 4 days from the onset of illness to presentation at a health care facility and 9 to 10 days until death in fatal cases has been reported. Atypical presentations have included fever and diarrhea without pneumonia, and fever with diarrhea and seizures progressing to coma. Common laboratory findings include leukopenia, lymphopenia, mild-to-moderate thrombocytopenia, and elevated levels of aminotransferases. Lymphopenia and increased levels of lactate dehydrogenase at presentation have been associated with a poor prognosis. Other reported abnormalities include elevated levels of creatine phosphokinase, hypoalbuminemia, and increased D-dimer levels and changes indicative of disseminated intravascular coagulopathy. Of six infected pregnant women, four have died, and the two survivors had spontaneous abortion. Mild illnesses such as upper respiratory illnesses without clinical or radiological signs of pneumonia have been reported more frequently recently in children. Limited seroepidemiologic studies conducted since 2004 suggest that subclinical infection appears uncommon.

2. Infectious agents—(See II.2). The first outbreak of highly pathogenic avian influenza (HPAI) A(H5N1) virus infections in humans—in Hong Kong, SAR, China, in 1997—was coincident with local outbreaks in poultry. In the intervening years, reports of limited H5N1 infections among birds in southeast Asia were reported, but starting in 2003, H5N1 infections led to large and recurring outbreaks in poultry. The viruses have spread, and are now entrenched among poultry populations in parts of Eurasia, Africa and the Middle East. In the summer of 2005, outbreaks in migratory birds in China preceded rapid spread of H5N1 through Mongolia and Russia to many European, Middle Eastern and African countries. A(H5N1) virus infections have been associated with high levels of mortality among poultry and substantial economic losses. Based on evolution of the hemagglutinin gene, H5N1 viruses can now be divided into 10 phylogenetically distinct clades that are antigenically distinguishable, and additional subclades; however, only 3 clades have caused human illness since 1997. The influenza A(H5N1) viruses that have infected humans so far have contained only avian influenza virus genes, and generally have been similar to strains circulating among poultry and wild birds in the same general location. Although migratory birds may sometimes spread A(H5N1) viruses to new geographic regions, their importance as a vector for spread is uncertain. Gene sequencing of some viruses isolated from infected humans showed mutations that may reflect some adaptation in humans.

3. Occurrence—

Epidemiology of Human infection with HPAI A(H5N1) virus: By the end of February 2008, over 360 cases of Human infection with HPAI

A(H5N1) virus in humans had been reported from Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Lao People's Democratic Republic, Myanmar, Nigeria, Pakistan, Thailand, Turkey and Viet Nam, with an overall case fatality of 64%. Regular updates on case counts are available at:

https://www.who.int/csr/disease/avian_influenza/country/en/index.html

Reasons for national differences in mortality are uncertain, but in all countries, mortality has been high. Potential differences could be differences in patient behaviors, types of viral exposure, time before case recognition, access to health care and/or clinical management, or differences in surveillance. The case fatality is highest among persons 10 to 19 years of age and lowest among persons 50 years of age or older. The median age of patients is approximately 18 years with 90% of patients 40 years of age or younger. In comparison to estimated numbers of poultry infections and human exposures to infected birds, human infections by an influenza A(H5N1) virus remain relatively rare. During situations in which there was close, prolonged and unprotected contact between a severely ill patient and a susceptible person, and most often a family member acting as a care giver, instances of non-sustained human-to-human transmission are thought to have occurred.

4. Reservoir—Aquatic birds are natural reservoirs of influenza A subtypes. For some avian influenza viruses, and particularly H5N1, the range of mammals that can be infected from aquatic birds (pigs, whales, seals, horses, ferrets, cats, dogs, tigers, etc.) has been wide. Domestic poultry are also infected, and are the main source of human infections. Swine influenza viruses are endemic in pigs. Influenza infections are also known to occur in other animals besides birds and pigs, including horses and dogs, but with the exception of pigs, influenza viruses have not been shown to transmit from these mammals to humans.

5. Mode of transmission—Most human infections by animal influenza viruses are thought to result from direct contact with infected animals. For H5N1 virus infection, the exact mode and sites of the virus entry are incompletely understood, but possibilities include inhalation of small particles to the lower respiratory tract, contamination of facial mucus membranes by self-inoculation or by droplet contact, or ingestion. In about one quarter of patients with influenza A(H5N1) virus infection, the source of exposure is unclear, and infection from exposure to contaminated environments remains possible. Visiting live-poultry markets is a recognized risk factor. Human-to-human transmission is thought to have occurred in some instances when there has been very close and prolonged contact between a very sick patient and care givers who have usually been family members. This observation suggests near-distance aerosol, droplet or direct contact may have been routes of transmission. However, the potential contribution of each route has not been demonstrated. No evidence to support long-distance airborne transmission has

been reported to date. For swine influenza virus infections in humans, close proximity to ill pigs or visiting a place where pigs are exhibited has been reported for most cases, but some human-to-human transmission, such as among soldiers in the 1976 Fort Dix outbreak and transmission to health care workers from an infected pregnant woman, has also occurred. Serologic studies show increased prevalence of swine influenza antibody among persons occupationally exposed to pigs compared to controls.

6. Incubation period—For H5N1 disease associated with poultry exposure, 7 days or less, and often 2–5 days. For swine influenza, 2–7 days has been reported.

7. Period of communicability—For H5N1 disease, limited data suggest that patients may remain infectious as long as 3 weeks, and perhaps even longer in immunosuppressed patients (e.g. those using corticosteroids). The longest documented period has been 27 days after the onset of illness, based upon detection of virus antigen in a patient's respiratory specimens.

8. Susceptibility—H5N1 illness occurs in all age groups, and limited serological studies demonstrate negligible pre-existing immunity in the subjects. Duration of protection from immunity generated by previous infection or immunization by an H5N1 vaccine is unknown. The role of host factors other than acquired immunity is uncertain.

9. Methods of control—

A. Preventive measures:

- 1) Preventing human exposure to infected animals or contaminated environments and controlling spread of infection among domesticated animal populations are critical elements for protecting humans from animal influenza virus infections. Guidelines for controlling outbreaks in domesticated animals have been issued by relevant national and international agencies (e.g. the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health).
- 2) Rapid information sharing between animal and/or agricultural sectors and human health authorities is essential for timely implementation of public health actions. Social mobilization and risk communication targeting high-risk populations in affected areas are important measures for raising disease awareness and initiating protective behavioral changes.
- 3) Use of appropriate personal protective equipment (PPEs) and proper training is recommended for groups considered to be at high risk of exposure to infected birds (e.g. poultry workers, persons involved in mass culling operations, outbreak investigators, etc.). Following a probable exposure,

asymptomatic persons should be followed for signs of illness for at least one week, while symptomatic persons should be tested for infection, administered antiviral medicines, and monitored closely.

- 4) Immunization: Inactivated H5N1 vaccines for human use have been developed based on WHO recommended strains and licensed in several countries, but are not yet generally available, although this situation is expected to change. Some countries are stockpiling these vaccines as part of pandemic preparedness measures. Although immunogenic, the effectiveness of these vaccines in preventing the H5N1 infection or reducing disease severity is unknown. Use of seasonal influenza vaccination in certain high-risk animal exposure occupational groups is recommended in some countries for reducing influenza-like illness caused by seasonal influenza viruses. Such vaccines will not provide direct protection against animal influenza virus infections, but may prevent seasonal and animal influenza co-infections.

B. Control of patient, contacts and the immediate environment:

- 1) Report to local health authority: Laboratory-confirmed human infection with a novel subtype of influenza A virus, or influenza A infection where the virus cannot be subtyped, should be reported immediately to the national authority and then to WHO. Reporting to WHO is mandatory under the International Health Regulations (2005).
- 2) Isolation: When possible, suspected or confirmed cases with H5N1 and other non-human influenza virus infections should be treated using well-ventilated single isolation rooms with implementation of Standard and Droplet Precautions. Use of higher-level precautions such as airborne precautions may be considered when aerosol-generating procedures (e.g. sampling respiratory specimens, suction, use of nebulizers, intubation and mechanical ventilation) are to be performed.
- 3) Concurrent disinfection: Regular surface cleaning and disinfection with a commonly used detergent or hospital disinfectant is desirable during hospitalization and after removal of a patient from the room. Environmental disinfection should follow guidelines published by relevant agencies (e.g. Food and Agriculture Organization of the United Nations, World Organization for Animal Health).
- 4) Quarantine: Hospital isolation is recommended for symptomatic patients infected with novel influenza A viruses, including H5N1. In large-scale outbreak settings, voluntary home quarantine of contacts may be used. Symptomatic contacts

with mild illness that do not require hospitalization should be placed in isolation and provided with antiviral treatment.

- 5) Protection of contacts: A neuraminidase inhibitor drug (oseltamivir or zanamivir) should be administered as chemoprophylaxis for 7-10 days to close contacts (such as household or family members) after the last exposure to a person strongly suspected or confirmed to have a H5N1 infection. This includes pregnant women. Where neuraminidase inhibitors are not available, amantadine or rimantadine might be used for chemoprophylaxis of high-risk exposure groups if the virus is known or likely to be susceptible to these drugs. However, these drugs should not be used as chemoprophylaxis in pregnant women.
- 6) Investigation of contacts and source of infection: When an influenza infection with H5N1 is suspected, clinical samples (e.g. throat swab and other respiratory specimens) should be collected and tested to confirm infection. Virus isolation or PCR testing will allow further genetic characterization of the virus. When concomitant animal outbreaks are ongoing, co-ordination with the animal and/or agricultural sectors is essential. Epidemiological field investigations should identify the source of infection, identify situation-specific control measures, and determine whether human-to-human transmission has occurred. If a novel influenza virus is associated with efficient spread among people, then rapid containment, using antivirals and vaccines, may be indicated to try and prevent pandemic spread. The WHO protocol for such operation is available, and can be found at:

<http://www.who.int/csr/disease/avian_influenza/guidelines/RapidContProtOct15.pdf>

- 7) Specific treatment: The efficacy of antiviral drugs for treating non-seasonal influenza infections is uncertain, due to limited opportunities for documentation. For H5N1 disease, early treatment with oseltamivir is recommended, using the standard regimen indicated for treatment of seasonal influenza. Data from uncontrolled clinical studies suggest this improves survival, although the optimal dose and duration of therapy are uncertain and no data from controlled trials are available. Based on in vitro and animal studies suggesting improved outcomes, physicians may consider using higher doses of oseltamivir therapy, longer durations of treatment, or combination therapy (oseltamivir + amantadine). Clade 1 H5N1 viruses and most clade 2 subclade 1 H5N1 viruses from Indonesia are fully resistant to M2 inhibitors, whereas clade 2 subclade 2 H5N1 viruses from the lineages in other parts of

Eurasia and Africa and clade 2 subclade 3 H5N1 viruses from China are usually susceptible. During oseltamivir therapy, the emergence of highly resistant H5N1 variants was observed in Vietnamese patients, with fatal outcomes. Infection by viruses partially resistant to oseltamivir, before treatment, was reported in two Egyptian patients who died. Treatment of H5N1-associated ARDS should follow published national guidelines. In principle, early intervention by intermittent positive pressure ventilation (IPPV) using low tidal volumes and low pressure ventilation may help, and is recommended. Corticosteroid therapy has not been shown to be effective in patients with influenza A(H5N1) virus infection, and it has not been determined whether other immunomodulators and serotherapy are useful.

C. Epidemic measures:

- 1) Clinicians and local public health officers should be aware that human infections may occur in countries with outbreaks of influenza A(H5N1) among poultry. The clinical presentation of influenza A(H5N1) disease is nonspecific, and has often resulted in an initial misdiagnosis, especially in circumstances in tropical countries where endemic acute febrile diseases are common. Influenza A(H5N1) virus infection should be considered in the differential diagnosis for patients who present with fever, rapidly progressing atypical pneumonia and epidemiologic risk factors.
- 2) Develop or use a case definition and undertake active surveillance in the appropriate epidemiological setting for early detection of human cases. If an infection occurs or is strongly suspected, family members and household contacts should be placed under medical observation and provided with antiviral chemoprophylaxis or treatment according to national guidelines.
- 3) Establish a mechanism for rapidly obtaining reliable laboratory testing results. Characterization of the virus and its susceptibility to antivirals are important factors for disease control.
- 4) Provide information about the disease and preventive measures to at-risk population. Social mobilization including sensitization campaigns may be required for effective message penetration. Timely provision of information to the public is essential.
- 5) Collect epidemiological, clinical and other information to assess the situation. If efficient human-to-human transmission is observed, a large-scale containment operation should be considered to stop further spread of the infection (see 9B6).

D. Disaster implications: The emergence of an animal virus with the capacity to transmit and spread easily among humans could result in a global pandemic.

E. International measures: Human influenza caused by a new subtype is subject to notification to WHO under IHR (2005), Class 1 (see *Reporting*).

- 1) Any specimen from a patient suspected of novel influenza A virus infection, including H5N1, should be immediately tested and forwarded to a national reference laboratory or WHO Collaborating Centre/Reference Laboratories for confirmatory testing. WHO Collaborating Centres provide support as required—more information on the Centres can be found at:

<<http://www.who.int/collaboratingcentres/database/en/>>

- 2) Under the 2005 International health regulations, human influenza caused by a new subtype is considered as an event that may constitute a public health emergency of international concern.
- 3) Continued viral and disease surveillance is critical for identifying human infections caused by influenza viruses of animal origin, including H5N1, and determining their ability to transmit efficiently among humans.

Pandemic Influenza: The response to an influenza pandemic must be planned at the local, national and international levels; guidance is provided on the WHO website:

<http://www.who.int/csr/disease/avian_influenza/en/>

Similar information is available on the websites of many governments, including that of the USA at:

<www.pandemicflu.gov>



KAWASAKI SYNDROME ICD-9 446.1; ICD-10 M30.3
 (Kawasaki disease, Mucocutaneous lymph node syndrome,
 Acute febrile mucocutaneous lymph node syndrome)
 [CDDM19: Editorial Board]
 [CCDM18: H. Yanagawa]

1. Identification—An acute febrile, self-limited, systemic vasculitis of early childhood, presumably of infectious or toxic origin. Clinically characterized by a high, spiking fever, unresponsive to antibiotics, associated