INFLUENZA

1. Identification—An acute viral disease of the respiratory tract characterized by fever, headache, myalgia, prostration, coryza, sore throat and cough. Cough is often severe and protracted; other manifestations are self-limited in most patients, with recovery in 2–7 days. Recognition is commonly by epidemiological characteristics (current quick tests lack sensitivity); only laboratory procedures can reliably identify sporadic cases. Influenza may be clinically indistinguishable from disease caused by other respiratory viruses, such as common cold, croup, bronchiolitis, viral pneumonia and undifferentiated acute respiratory disease. GI tract manifestations (nausea, vomiting, diarrhea) are uncommon, but may accompany the respiratory phase in children, and have been reported in up to 25% of children in school outbreaks of influenza B and A (H1N1).

Influenza derives its importance from the rapidity with which epidemics evolve, the widespread morbidity and the seriousness of complications, notably viral and bacterial pneumonias. In addition, emergence among humans of influenza viruses with new surface proteins can cause pandemics ranking as global health emergencies (e.g. 1918, 1957, 1968) with millions of deaths (≥40 million in 1918). Severe illness and death during annual influenza epidemics occur primarily among the elderly and those debilitated by chronic cardiac, pulmonary, renal or metabolic disease, anemia or immunosuppression. The proportion of total deaths associated with pneumonia and influenza in excess of that expected for the time of year (excess mortality) varies and depends on the prevalent virus type. The annual global death toll is estimated to reach up to 1 million. In most epidemics, 80%–90% of deaths occur in persons over 65; in the 1918 pandemic, young adults showed the highest mortality rates. Reye syndrome, involving the CNS and liver, is a rare complication following virus infections in children who have ingested salicylates.

While the epidemiology of influenza is well understood in industrialized countries, information on influenza in developing countries is minimal.

During the early febrile stage, laboratory confirmation is through isolation of influenza viruses from pharyngeal or nasal secretions or washings on cell culture or in embryonated eggs; direct identification of viral antigens in nasopharyngeal cells and fluids (FA test or ELISA); rapid diagnostic tests (these differ in the influenza viruses they detect); or viral RNA amplification. Demonstration of a specific serological response between acute and convalescent sera may also confirm infection.

2. Infectious agents—Three types of influenza virus are recognized: A, B and C. Type A includes 15 subtypes of which only 2 (H1 and H3) are associated with widespread epidemics; type B is infrequently associated with regional or widespread epidemics; type C with sporadic cases and minor localized outbreaks. The antigenic properties of the 2 relatively stable internal structural proteins, the nucleoprotein and the matrix protein, determine virus type.
Influenza A subtypes are classified by the antigenic properties of surface glycoproteins, hemagglutinin (H) and neuraminidase (N). Frequent mutation of the genes encoding surface glycoproteins of influenza A and influenza B viruses results in emergence of variants that are described by geographic site of isolation, year of isolation and culture number. Examples are A/New Caledonia/20/99(H1N1), A/Moscow/10/99(H3N2)-like virus, B/Hong Kong/330/2001.

Emergence of completely new subtypes—at irregular intervals and only for type A viruses—results from antigenic shift in HA gene or unpredictable recombination of human and mammalian or avian antigens, and leads to pandemics. The relatively minor antigenic changes (antigenic drift) of A and B viruses responsible for frequent epidemics and regional outbreaks occur constantly and require annual reformulation of influenza vaccine.

3. Occurrence—As pandemics (rare), epidemics (almost annual), localized outbreaks and sporadic cases. Clinical attack rates during epidemics range from 10% to 20% in the general community to more than 50% in closed populations (e.g. nursing homes, schools). During the initial phase of epidemics in industrialized countries, infection and illness appear predominantly in school-age children, with a sharp rise in school absences, physician visits, and pediatric hospital admissions. Schoolchildren infect family members, other children and adults. During a subsequent phase, infection and illness occur in adults, with industrial absenteeism, adult hospital admissions, and an increase in mortality from influenza-related pneumonia. Epidemics generally last 3–6 weeks, although the virus is present in the community for a variable number of weeks before and after the epidemic. The highest attack rates during type A epidemics occur among children aged 5–9, although the rate is also high in preschool children and adults.

Epidemics of influenza occur almost every year, caused primarily by type A viruses, occasionally influenza B viruses or both. In temperate zones, epidemics tend to occur in winter; in the tropics, they often occur in the rainy season, but outbreaks or sporadic cases may occur in any month.

Influenza viral infections with different antigenic subtypes also occur naturally in swine, horses, mink and seals, and in many other domestic species in many parts of the world. Aquatic birds are a natural reservoir and carrier for all influenza virus subtypes. Interspecies transmission (mainly transitory) and reassortment of influenza A viruses have been reported among swine, humans and some wild and domestic fowl.

Since 1997 influenza avian infections of the A(H3N1) type have been identified in isolated human groups, with high fatality. Transmission gradually increased among poultry; in the first half of 2004, poultry outbreaks of influenza A(H3N1) were occurring in several Asian countries, with transmission to humans in Thailand and Viet Nam. The cases fatality was high in human infections; there are no records of person-to-person transmission.
4. **Reservoir**—Humans are the primary reservoir for human infections; birds and mammalian reservoirs such as swine are likely sources of new human subtypes thought to emerge through genetic reassortment.

5. **Mode of transmission**—Airborne spread predominates among crowded populations in enclosed spaces; the influenza virus may persist for hours, particularly in the cold and in low humidity, and transmission may also occur through direct contact. New subtypes may be transmitted globally within 3–6 months.

6. **Incubation period**—Short, usually 1–3 days.

7. **Period of communicability**—Probably 3–5 days from clinical onset in adults; up to 7 days in young children.

8. **Susceptibility**—Size and relative impact of epidemics and pandemics depend upon level of protective immunity in the population, strain virulence, extent of antigenic variation of new viruses and number of previous infections. Infection produces immunity to the specific antigenic variant of the infecting virus; duration and breadth of immunity depend on the degree of antigenic similarity between viruses causing immunity.

   Pandemics (emergence of a new subtype): Total population immunologically naive; children and adults equally susceptible, except for those who have lived through earlier pandemics caused by the same or an antigenically similar subtype.

   Epidemics: Population partially protected because of earlier infections. Vaccines produce serological responses specific for the subtype viruses included and elicit booster responses to related strains with which the individual had prior experience.

   Age-specific attack rates during an epidemic reflect persisting immunity from past experience with strains related to the epidemic subtype, so that incidence of infection is often highest in school-age children.

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

   **A. Preventive measures:**

   1) Educate the public and health care personnel in basic personal hygiene, especially transmission via unprotected coughs and sneezes, and from hand to mucous membrane.

   2) Immunization with available inactivated and live virus vaccines may provide 70%–80% protection against infection in healthy young adults when the vaccine antigen closely matches the circulating strains of virus. Live vaccines, used in the Russian Federation for many years, have recently been licensed in the USA: registered for intranasal application in healthy individuals aged 5–49. 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 (see Pneumonia).

A single dose suffices for those with recent exposure to influenza A and B viruses; 2 doses more than 1 month apart are essential for children under 9. Routine immunization programs should be directed primarily towards those at greatest risk of serious complications or death (see Identification) and those who might spread infection (health care personnel and household contacts of 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; timing of immunization should be based on the seasonal patterns of influenza in different parts of the world (April to September in the southern hemisphere and rainy season in the tropics). Biannual recommendations for vaccine components 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 within 6 weeks after vaccination. Subsequent vaccines produced from other virus strains have not been clearly associated with an increased risk of Guillain-Barré.

3) Amantadine hydrochloride or rimantadine hydrochloride is effective in the chemoprophylaxis of influenza A, but not influenza type B. The CNS side-effects associated with amantadine in 5%–10% of recipients 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. Rimantadine is reported to cause fewer CNS side-effects. The use of these drugs should be considered in nonimmunized persons or groups at high risk of complications, such as residents of institutions or nursing homes for the elderly, when an appropriate vaccine is not available or as a supplement to vaccine when immediate maximal protection is desired against influenza A infection. The drug will not interfere with the response to influenza vaccine and should be continued throughout the epidemic. Inhibitors of influenza neuraminidase (oseltamivir) have
been shown to be safe and effective for both prophylaxis and treatment of influenza A and B, although not yet approved in many countries for this use.

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 examination if possible, Class 1 (see Reporting).

2) Isolation: Impractical under most circumstances because of the delay in diagnosis, unless rapid tests are available. In epidemics, because of increased patient load, it would be desirable to isolate patients (especially infants and young children) believed to have influenza by placing them in the same room (cohorting) during the initial 5–7 days of illness.

3) Concurrent disinfection: Not applicable.

4) Quarantine: Not applicable.

5) Protection of contacts: A specific role has been shown for antiviral chemoprophylaxis with amantadine or rimantadine against type A strains (see 9A3). Neuraminidase inhibitors may also be considered for influenza A and B.

6) Investigation of contacts and source of infection: Of no practical value.

7) Specific treatment: Amantadine or rimantadine started within 48 hours of onset of influenza A illness and given for approximately 3–5 days reduces symptoms and virus titres in respiratory secretions. Dosages are 5 mg/kg/day in 2 divided doses for ages 1–9, 100 mg twice a day above 9 years (if weight less than 45 kg, 5 mg/kg/day in 2 doses) for 2–5 days. Doses should be reduced for those over 65 or with decreased hepatic or renal function. Neuraminidase inhibitors may also be considered for the treatment of influenza A and B.

During treatment with either drug, drug-resistant viruses may emerge late in the course of treatment and be transmitted to others; cohorting people on antiviral therapy should be considered, especially in closed populations with many high-risk individuals. Patients should be watched for bacterial complications and only then should antibiotics be administered. Because of the association with Reye syndrome, avoid salicylates in children.

C. Epidemic measures:

1) The severe and often disruptive effects of epidemic influenza on community activities may be reduced in part by effective health planning and education, particularly locally
organized immunization programs for high-risk patients and their care providers. Surveillance by health authorities of the extent and progress of outbreaks and reporting of findings to the community are important.

The response to influenza pandemic must be planned at national level.

2) Closure of individual schools has not proven to be an effective control measure; it is generally applied too late and only because of high staff and students absenteeism.

3) Hospital administrators must anticipate the increased demand for medical care during epidemic periods and possible absenteeism of health care personnel as a result of influenza. To prevent this, health care personnel should be immunized annually.

4) Maintaining adequate supplies of antiviral drugs would be desirable to treat high-risk patients 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 disease if the virus is introduced.

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

1) Regularly report on epidemiological situation within a country to WHO (http://www.who.int/flu).n
2) Identify the causative virus in reports, and submit prototype strains to one of the WHO Centres for Reference and Research on Influenza in Atlanta, London, Melbourne and Tokyo (http://www.who.int/influenza). Throat secretion specimens, nasopharyngeal aspirates and paired blood samples may be sent to any WHO-recognized national influenza center.

3) Conduct epidemiological studies and promptly identify viruses to the national health agencies.

4) Ensure sufficient commercial and/or governmental facilities to provide rapid production of adequate quantities of vaccine and antiviral drugs; maintain programs for vaccine and antiviral drug administration to high-risk persons and essential personnel.

Further information also on http://www.oms.b3c.jussieu.fr/flu/.

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