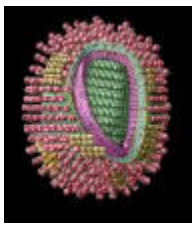
INFLUENZA A & B VIRUSES
General Information

1. BACKGROUND



Influenza, commonly called "the flu" is a respiratory illness associated with infection by influenza virus type A or B.
Symptoms include headache, fever, cough, sore throat, aching muscles and joints. There is a wide spectrum of illness ranging from minor symptoms through to pneumonia and death.

The name "Influenza" refers to the ancient belief that it was caused by a malign and supernatural influence.
In Florence, during the time of Renaissance, astrologers linked a curious juxtaposition of stars with an outbreak of infection in the city and attributed it to the "influence" of the stars, hence influenza.
Known in the sixteenth century as "the new Acquayntance", influenza still causes major outbreaks of acute respiratory infection. It has indeed been described as "the last great uncontrolled plague of manking."

Richard SHOPE isolated the agent responsible for Influenza in pigs in 1931.
The human Influenza virus was first identified by a team of the *National Institute for Medical Research* in London (W. Smith, C.H. Andrewes and P.P. Laidlaw) in 1933.
True influenza is caused by the small family of the Orthomyxoviridae.
MYXO derives from Greek for mucus and refers to the ability of these viruses to attach to mucoproteins on the cell surfaces; ORTHO means true or regular, as in orthodox, and distinguishes these viruses from the paramyxovirus.

Influenza type A is most common and causes the most serious epidemics and pandemics. Influenza type B may cause epidemics, but usually causes milder illness than type A. Type C is not known to cause large epidemics; it causes mild illness, mainly in children between 1 and 4 years of age. It represents less than 1 % of viruses in children with respiratory infections.

Outbreaks of influenza occur annually during winter. The virus infects the columnar epithelial cells of the upper respiratory tract, and gives rise to pharyngitis and myalgia. Less frequently, virus spreads to the lower respiratory tract, causing tracheobronchitis and pneumonia. However, pneumonia associated with influenza virus infection is generally due to secondary bacterial infection.

Influenza usually spreads from person to person when an infected person coughs, sneezes leading to virus spread into the air. Unlike many other viral

respiratory infections, such as the common cold, the flu causes severe illness and life-threatening complications in many people.

2. CLINICAL FEATURES

A. The virus

Influenza virus has 2 surface antigens that are used for subtyping Influenza A viruses: hemagglutinin (H) and neuraminidase (N). Subtypes are classified by H and N antigen types: H1N1, H2N2, H3N2 and H5N1 are the primary influenza A subtypes known to have caused disease in humans since 1918.
The known changing antigenicity of Influenza viruses could results from mutations in the gene segment of HA or NA and is called ***antigenic drift***. Emergence of epidemiological important drift is observed every 2 to 3 years. Aside of these minor changes, occur marked changes in HA with or without changes in NA and called ***antigenic shift***. It occurs during gene reassortments in cells infected by both human and animal viruses or by interspecific transmissions. It leads to the so-called pandemics (worldwide epidemics) in the past century, 3 pandemics have been observed.
Antigenic drift can occur for both types A and B. Changes in the influenza virus due to drift are classified by designating prototype viruses.
Antigenic shift is a major change in the subtypes and occurs only in influenza type A. The result of a shift is a new strain to which there is little or no previous immunity. Subsequently, a pandemic usually results with high attack rates occurring in all age groups.

B. Clinical presentation

Most people with influenza recover in a few days, but the infection can lead to complications that may require hospitalisation for certain patients.
Rapid spread leads to epidemics complications and tends to occur in the young, elderly, and persons with chronic cardio-pulmonary diseases.
Overall death rates increase in times of influenza epidemics.
Characteristically, the patient is prostrated and has to take to bed.
The temperature rises rapidly to around 39°C. Influenza is not characterized by runny noses or sore throats at the beginning, as are common cold infections.
Fortunately, influenza is usually short-lived in younger persons. In older people and the “at-risk” group, however, recovery may take much longer, with persistent weakness and lassitude sometimes for 3-6 months. In general, the severity of influenza is proportional to age.

- *High-risk patients*

The fatality rate from influenza begins to rise in midlife and is higher in those who have chronic medical conditions, such as chronic obstructive lung disease, cardiovascular disease, and diabetes mellitus, particularly in elderly.
Older persons make up the population with the highest age-specific case fatality rate from influenza and account for 80 to 90% or more of associated deaths, due in part to a high rate of chronic medical conditions.
However, influenza has a higher case fatality rate in middle-aged persons with chronic medical conditions than persons older than 65 years who are well.
Hospitalisation rates for influenza and pneumonia are highest in persons with high-risk medical conditions, infants, and the elderly.

Data from 1997 National Health Interview Survey show that persons of 65 years and older account for 35% to 46% of hospitalisations for influenza-like illness (ILI), although they account for only 9% to 10% of doctor visits for ILI.
24% to 32% of those aged 50 through 64 years have an underlying medical condition that places them at high risk for complications from influenza.

Patients most likely to be infected by influenza:

- people aged 65 or older (because they often have underlying diseases)
- nursing home and other chronic-care facility residents
- adults and children with chronic disorders of the pulmonary and cardiovascular systems, including asthma
- adults and children who require regular medical follow-up for HIV
- children and teenagers aged 6 months to 18 years who receive long-term aspirin therapy
- the young who have not developed immunity to the virus
- women who will be in the second or third trimester of pregnancy during the influenza season

- *Complications*

Influenza proves fatal most often in newborns, the elderly, the immunocompromised, and the chronically ill. The small airways of infants and very young children make them susceptible to severe case of influenza.
Infants younger than 1 year old have the most serious complications of influenza and the highest rates of hospitalisation. An estimated 80% of influenza complications occur in elderly patients, however. Serious complications, such as

high fever, dyspnea, crepitation, and rhonchi on chest examination – especially among young children and debilitated elderly patients who may be unable to communicate systemic symptoms. Most mortality is attributable to lower respiratory problems and up to two-third of the excess deaths is related to cardiovascular diseases.

The complications of influenza are secondary bacterial pneumonia, worsening of chronic respiratory and cardiac diseases, sinusitis, otitis media, primary viral pneumonia (uncommon), and Reye syndrome (rare), which is associated with salicylate use concomitant with influenza type A or B infection in children.

- *Symptoms*

The symptoms vary greatly according to age.

Primary symptoms of influenza in children :

- cough
- fever
- rhinorrhea
- croup

Symptoms in adults :

- cough
- fever
- myalgia
- headache
- sore throat

In the elderly :

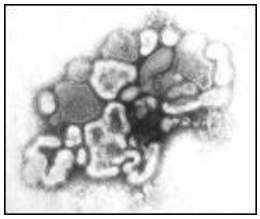
- cough alone or cough with headache
- fever

There is usually a very abrupt onset with shivering, malaise, headache, and aching in the limbs and back.

Influenza illness can also include fever, muscle aches, lack of energy, dry cough, sore throat, and possibly runny nose.

During the influenza season hospitalisations increase because of pneumonia, acute bronchitis, chronic respiratory disease, and congestive heart failure.

→Influenza is an acute, usually self-limited febrile illness caused by infection with influenza viruses. Inflammation of the nasal mucosa, pharynx, conjunctiva, and respiratory tract commonly occurs.

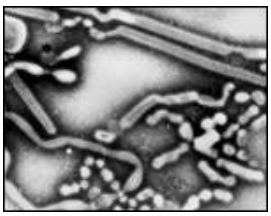


3. EPIDEMIOLOGY

Influenza A is essentially an avian virus that has "recently" crossed into mammals. Birds have the greatest number and range of influenza strains. Avian haemagglutinins sometimes appear in pig, human and horse influenza strains. Every now and then a major new pandemic strain appears in man, with a totally new HA and sometimes a new NA as well (antigenic shift). Over the subsequent years this strain undergoes minor changes (antigenic drift) every two to three years, probably driven by selective antibody pressure in the populations of humans infected.

Influenza makes people feel worse than an ordinary cold. For most people influenza infection is just a nasty experience, but for some it can lead to illnesses that are more serious. The most common complications of influenza are bronchitis and secondary bacterial pneumonia. These illnesses may require treatment in hospital and can be life threatening especially in the elderly, asthmatics and those in poor health. The influenza virus does not necessarily cause high mortality, but for old sick people it may speed up their death. During a pandemic, though, influenza can cause serious illness in young healthy individuals.

Influenza occurs most often in the winter months and usually peaks between December and March in the northern hemisphere, and between May and October in the southern hemisphere. Illnesses resembling influenza may occur in the summer months but they are usually due to other viruses.



In temperate climates influenza strikes from late autumn through spring, although technically influenza is not bound by seasons, and can occur all year round in tropical climates. A possible explanation for the high influenza virus activity in the wintertime is that people congregating indoor during winter facilitates the transmission of the virus or that more humid air indoors may help the viruses survive longer.

When influenza spreads through a community, physician's practices typically experience upsurge in visits by patients with fever and respiratory symptoms. One influenza season can result in 192 million bed days and 75 million lost work days in the United States, placing a substantial burden on physicians to prevent, diagnose, and treat influenza and its complications as early as possible.

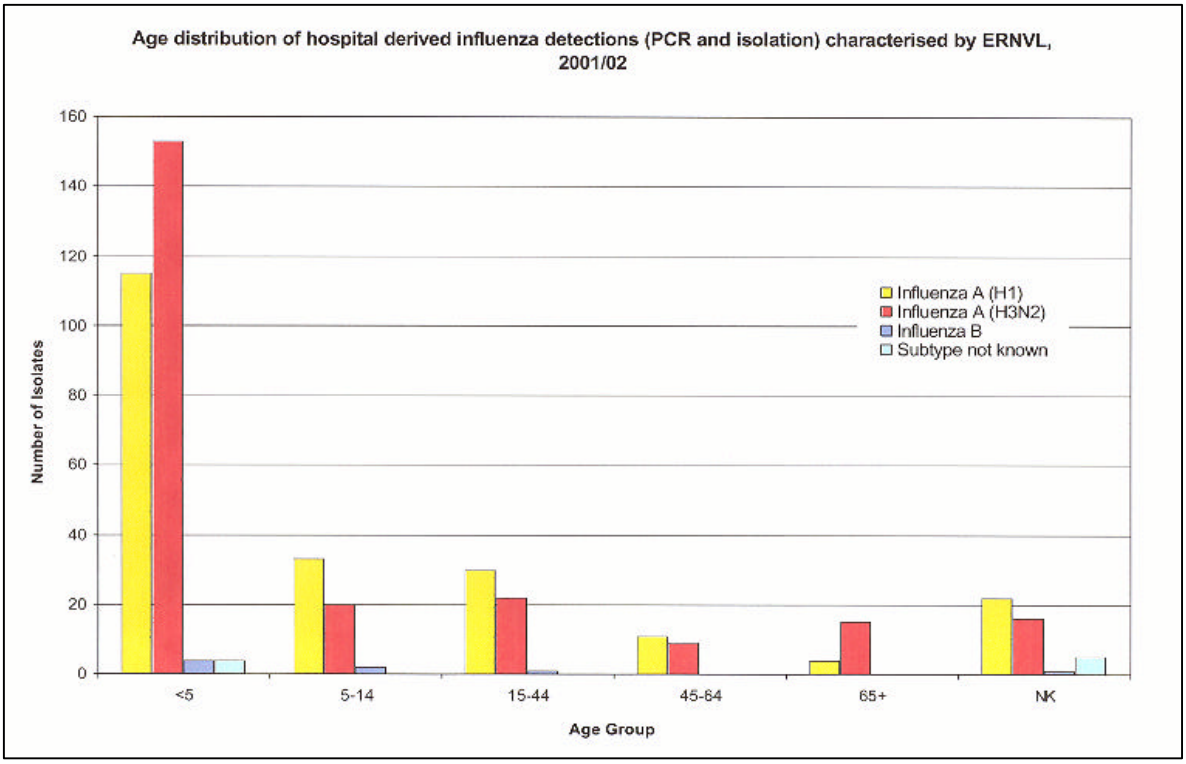
Influenza and pneumonia together are the sixth leading cause of death in the United States and the fifth leading cause in elderly. Influenza outbreaks of varying severity occur every winter. Each year influenza causes approximately 20,000 deaths ; the figure climbs to 40,000 or more deaths in selected epidemics. Also, each year, there is an average of approximately 114,000 influenza-related hospitalisations ; this figure climbs to more than 300,000 in selected epidemics. The economic cost of influenza is estimated at $3 to $5 billion annually.

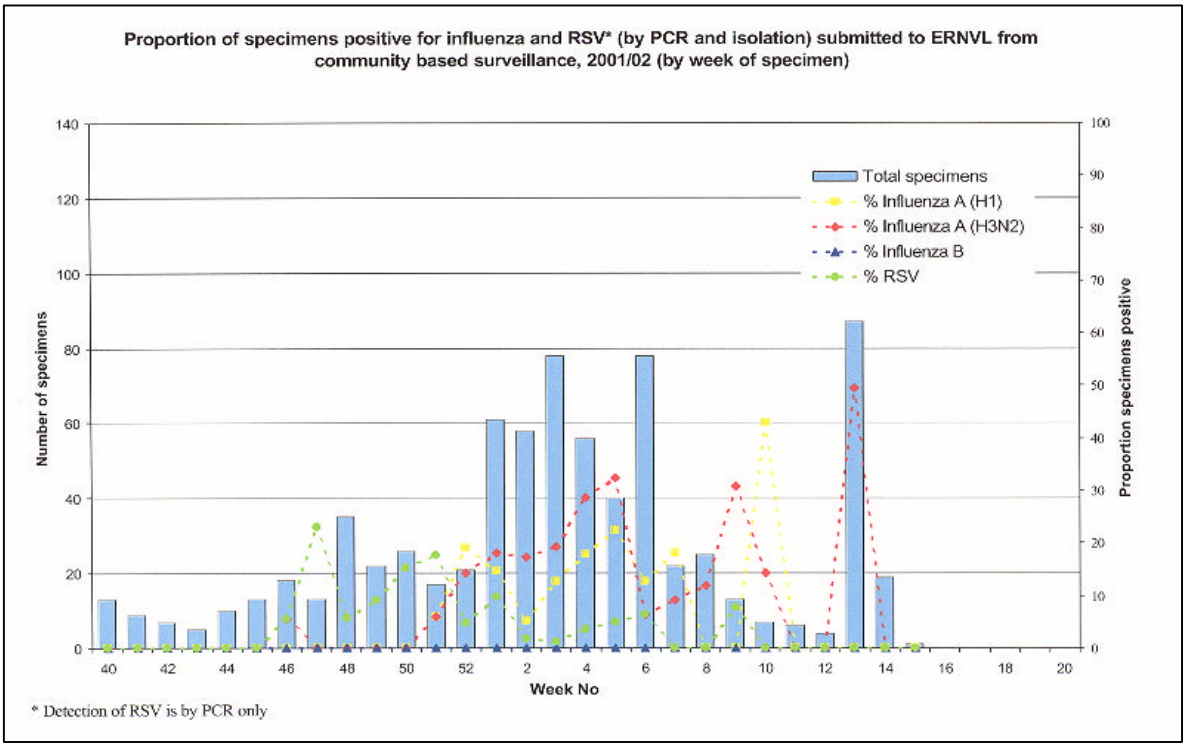
Transmission in schools plays a major role in propagating influenza outbreaks, as seen by the rapid rise student cases following holiday recesses.
Children frequently infect their families, as suggested by the increase in absenteeism just before a noted increase in absenteeism amongst manufacturing employees and by the higher risk of infection for families with children than those without.

→ Outbreaks occur nearly every year during the winter months and significantly increase morbidity and mortality from all causes, especially cardiovascular and pulmonary diseases, and certain metabolic conditions.

→ Influenza causes about 20,000 deaths per year in the United States. The hardest hit are the elderly and patients who have underlying medical conditions.

→ Fatality rates are higher in persons who have chronic medical conditions such as chronic obstructive lung disease and diabetes mellitus, particularly if they are elderly.


Age distribution of hospital derived influenza detections (PCR and isolation) characterised by ERNVL, 2001/02
Number of Isolates
160
140
120
100
80
60
40
20
0
Influenza A (H1)
Influenza A (H3N2)
Influenza B
Subtype not known
<5
5-14
15-44
45-64
65+
NK
Age Group


Proportion of specimens positive for influenza and RSV* (by PCR and isolation) submitted to ERNVL from community based surveillance, 2001/02 (by week of specimen)
Number of specimens
Proportion specimens positive
Total specimens
% Influenza A (H1)
% Influenza A (H3N2)
% Influenza B
% RSV
Week No
40
42
44
46
48
50
52
2
4
6
8
10
12
14
16
18
20
* Detection of RSV is by PCR only

4. TRANSMISSION

Influenza viruses are highly contagious and are usually transmitted when a person who has the flu coughs, sneezes, or speaks, and sends the flu virus into the air to be inhalated by another person.

Flu may, less often, be spread when a person touches a surface that has flu viruses on it (a door handle, for instance) and then touches his or her nose or mouth.
The virus enters the nose, throat, or lungs of a person and begins to multiply, causing symptoms of the flu.

Adults can continue to pass the flu virus to others for another 3-7 days after symptoms start. Children can pass the virus for longer than 7 days. Symptoms start 1-4 days after the virus enters the body. Some persons can be infected with the flu virus but have no symptoms. During this time, those persons can still spread the virus to others.

Persons in semi-closed or crowded environments, such as students, prisoners and residents of nursing homes, are at high risk for exposure.

5. PANDEMIC INFLUENZA

A pandemic is a worldwide epidemic of a disease. When a new subtype of flu virus appears after antigenic shift and when the new virus can cause illness in people and can be spread easily from person to person, an influenza pandemic can occur.

Epidemic influenza remains the biggest and unconquered acute threat to human health, inflicting damage and death far beyond familiar notification data.
The impact of influenza A is particularly severe during periodic pandemics owing to novel antigenic variants which override immunity from experience of earlier subtypes.

The great pandemic of Spanish influenza in 1918 was especially terrible and caused the highest number of known flu deaths : more than 500,000 people died in the United States, and 20-50 million people may have died worldwide. Many died within the first few days after infection and others died of complications soon thereafter. Half of the people who died were young, healthy adults.

An influenza pandemic occurred nearly 30 years later in 1957 in China and caused 70,000 deaths in the United States. This Asian flu was first identified in late February, 1957 in China and spread to the United States by June, 1957.

In 1968 there was another pandemic, again originating in the Far East ; the virus, first isolated in Hong Kong in early 1968, had now undergone a partial shift that affected only the HA and not the NA.

In 1976 there was considerable alarm in the USA: influenza A virus appeared in a military barracks.
This was a drifted variant related to the 1918 virus.

A virus re-emerged in China in 1977 and is still spreading round the world.

→ Origin of pandemic or shifted strains of influenza A

Pandemic strains of influenza A seem to originate in southern China due to the close association of humans with domestic animals and birds.
Largely unremarked except by farmers and veterinarians, influenza A viruses are constantly circulating in pigs, horses, and birds, including poultry ; and it is a reasonable assumption that, in areas of very intensive small-scale farming, the chances of interchange of viruses between humans and other species are considerable.
Another factor that may be important is the very high population density in that area, in which lives half the world's population.
Another possible explanation of the origin of these pandemic strains is that influenza A viruses continually recycle in humans and "new" pandemic viruses are really old viruses re-emerging from a previously infected individual.

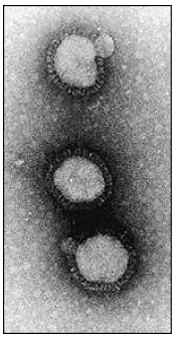
6. DIAGNOSIS

Influenza can be difficult to diagnose based on clinical symptoms alone because the initial symptoms of influenza can be similar to those caused by other infections agents including, but not limited to, *Mycoplasma pneumonia*, Adenovirus, Respiratory Syncytial Virus, Rhinovirus, Parainfluenza viruses, and *Legionella spp*.

Appropriate samples for influenza testing can include a nasopharyngeal or throat swab, nasal wash, or nasal aspirates, depending on which type of test is used.
Samples should be collected within the first 4 days of illness.

The available tests for diagnosing influenza include viral culture, serology, ELISA and rapid antigen testings, and immunofluorescence. Viral culture is generally the most sensitive method for serotype-specific diagnosis of influenza. However, culture and other tests, such as the use of fluorescent labelled antibodies and the polymerase chain reaction, are not as rapid or widely available as would be needed to be clinically useful in guiding antiviral therapy.
To be effective, antiviral therapy should be initiated within 2 days of the onset of influenza symptoms.

Rapid influenza tests provide results within 24 hours ; viral culture provides results in 3-10 days. Most of the rapid tests that can be done in a physician's office are approximately > 70% sensitive for detecting influenza and approximately > 90% specific. Thus, as many as 30% of samples that would be positive for influenza by viral culture may give a negative rapid test result. And, some rapid test results may indicate influenza when a person is not infected with influenza.



Serum samples also can be tested for influenza antibody to diagnose recent infections. Two samples should be collected per person: one sample within the first week of illness and a second sample 2-4 weeks later. If antibody levels increase from the first to the second sample, influenza infection likely occurred. Because of the length of time needed for a diagnosis of influenza by serologic testing, other diagnostic testing should be used if a more rapid diagnosis is needed.

If isolation of influenza virus in culture for further examination is not essential, it can be identified rapidly by immunofluorescence staining of cells in nasopharyngeal aspirates, a useful method in hospital practice.
However, this method is likely to be replaced by rapid ELISA-type tests, which can be carried out at the bedside in 30 minutes.
Four antiviral drugs are licensed in the United States for the treatment of influenza : amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine are active only against influenza A, while zanamivir and oseltamivir are active against both influenza A and B.

Rapid diagnostic tests for influenza, including direct enzyme immunoassay for influenza A and an endogenous viral-encoded enzyme assay for influenza A or B, have recently been developed and are widely available. These tests are easy to perform and provide results quickly enough to facilitate antiviral therapy.

Techniques used to detect influenza

Procedure	Influenza Types Detected	Acceptable Specimens	Time for Results	Point-of-care market
Viral culture	A and B	• NP swab • throat swab • nasal wash • bronchial wash • nasal aspirate • sputum	5-10 days	No
Immunofluorescence	A and B	• NP swab • nasal wash • bronchial wash • nasal aspirate • sputum	2-4 hours	No
Influenza Enzyme Immuno Assay (EIA)	A and B	• NP swab • throat swab • nasal wash • bronchial wash	2 hours	No
Directigen Flu A (Becton-Dickinson)	A	• NP swab • throat swab • nasal wash • nasal aspirate	<30 minutes	Yes
Directigen Flu A + B (Becton-Dickinson)	A and B	• NP swab • throat swab • nasal wash • nasal aspirate • bronchial wash	<30 minutes	Yes
OIA (Biostar)	A and B	• NP swab • throat swab • nasal aspirate • sputum	<30 minutes	Yes
ICT (Coris BioConcept, Quidel)	A and B	• NP swab • Nasal wash • nasal aspirate	<30 minutes	Yes
Zstat Flu (ZymeTx)	A and B	• Throat swab	<30 minutes	Yes
RT-PCR	A and B	• NP swab • throat swab • nasal wash • bronchial wash • nasal aspirate • sputum	1-2 days	No
Serology	A and B	Paired acute and convalescent serum samples	>2 weeks	No

List of commercial kits

BRAND	MANUFACTURER	*MECHANISM*	*TIME*
Directigen Flu A + B	Becton Dickinson & Co., Cockeysville, Md	ELISA	< 30 minutes
Directigen Flu A	Becton Dickinson & Co., Cockeysville, Md	ELISA	< 30 minutes
BioStar AB FLU OIA	BioStar, Inc., Boulder, Colo.	OIA	< 30 minutes
Quick Vue Influenza A/B Test	Quidel Corp., San Diego, Calif.	Lateral ELISA	10 minutes
ZstatFlu Test for Influenza A & B Virus	Zyme Tx, Inc. Oklahoma City, Okla	Neuraminidase detection	< 30 minutes
Roche Diagnostics Influenza A/B Rapid Test	Roche Diagnostics Corp., Indianapolis, Ind.	Gold-labelled immunoassay	
Influ-A Respi-Strip	**Coris BioConcept**	**Rapid Membrane Test**	**15 minutes**
Influ-A & B Respi-Strip	**Coris BioConcept**	**Rapid Membrane Test**	**15 minutes**

7. TREATMENT

The best treatment is to rest, drink plenty of fluids and take analgesics.
It is best to treat the infection at home until the person is well enough to return to normal activities.
Aspirin is contraindicated for symptom relief in children because it can cause a rare but serious illness called Reye syndrome.

When using in the treatment of influenza A, amantadine and rimantadine can reduce the duration of uncomplicated Influenza A illness. However, these drugs must be administrated within 2 days of the start of the illness to be effective.
Treatment should continue until 24 to 48 hours after the symptoms disappear.
Because of renal clearance, the daily dosage of amantadine and rimantadine in persons older than 65 years should not exceed 100mg per day for treatment or prophylaxis.

Anytime a nursing home resident presents with influenza-like symptoms or another respiratory illness, the possibility of an influenza outbreak should be considered. An outbreak should be defined clinically and by laboratory testing.
Once an outbreak is clinically suspected, several laboratory tests and viral cultures can be used to confirm the outbreak and distinguish influenza from other etiologies. These tests generally have sensitivities as high as 90%. If an

outbreak of influenza is confirmed, several measures, including vaccination of unvaccinated residents and employees as well as limitations on resident movement and visits, should be implemented by nursing home staff and physicians to prevent further transmission and reduce susceptibility.

Most national authorities immunize about 10% of the population annually: these are the "at-risk" group who has a much-increased chance of serious complications after an attack of influenza.

8. PREVENTION

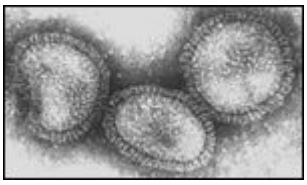
Keeping away from crowded places can reduce the risk of becoming infected and spreading it to others.
It is also considered sensible to immunize groups in community service, such as healthcare staff and police, who may need protection against wholesale sickness at times of major epidemics.

Antibiotics are often prescribed. They have no effect on virus but may prevent or cure bacterial superinfection. The drug Amantadine may prevent influenza if taken continuously by high-risk persons at the time of an epidemic, but is not used widely.

The effectiveness of an influenza vaccine ranges from 70% to 90% in healthy young adults. In elderly patients with chronic lung disease, hospitalisation rates for pneumonia and influenza may be reduced by more than 50%; mortality risk may be lowered by 70%. Immunization can also result in fewer outpatient visits for pneumonia and influenza.
It is recommended to all persons aged 50 years and older receiving annual influenza vaccination to reduce the severity of symptoms and risk of complications. Reasons for lowering the recommended age for routine vaccination from 65 years to 50 years include reductions in office visits, hospitalisations, time taken off work, and costs. Persons younger than 50 years who have medical conditions that place them at risk for complications should also be vaccinated.
A previous flu infection or vaccination will not necessarily provide protection against further infections because the virus is continually changing genetically and different subtypes circulate each winter.
Routine vaccination offers the best protection and people who are at high risk of infection should be vaccinated. It is difficult to avoid infection if there is an epidemic.

Vaccination in October and November is considered optimal for many target groups because optimal antibody responses appear in about 2 weeks in most people, and peak infection rates for influenza typically occur from late December to early March. However, it may be reasonable to vaccinate certain high-risk patients, such as those who see a provider for routine care or are hospitalised, in September (if the influenza vaccine is available). Administration of vaccine in facilities such as nursing homes before October should generally be avoided because antibody levels often begin to decline within several months after vaccination.

Many studies have shown that vaccination of nursing homes residents and staff can significantly decrease rates of hospitalisation, pneumonia, and related mortality.



Two doses are needed in the first year that a child younger than 9 years of age is vaccinated against influenza. Many young children would not normally have a visit for well childcare that coincided with the influenza vaccination season.
The feasibility issues need to be addressed before a recommendation can be further considered.
Because of the high rate of hospitalisations of young infants because of influenza disease and its complications, experts are beginning to consider whether infants should be vaccinated routinely. The vaccine is safe and effective in infants of 6 months and older.

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