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# Influenza

## General

**Influenza is an infection caused by respiratory viruses, known as Influenza viruses.** These viruses are enveloped by a membrane comprising two surface proteins, haemagglutinin (HA) and neuraminidase (NA). HA enables the viruses to enter host cells while NA enables the viruses to leave cells. In addition, these proteins are the reason for the type A virus classification. Another membrane protein, M2protein, which is found only in Type A viruses is the target of the first antivirals developed: amantadine and rimantadine. The genotype is a single-strand RNA, consisting of eight gene segments, each being responsible for the synthesis of one or two proteins.
One of the main characteristics of influenza viruses is their ability to mutate.

### Several types of Influenza viruses

Three types of influenza virus can infect humans: A, B and C. Type C viruses do not give rise to epidemics, rarely result in sporadic infections and most frequently cause rhinitis rather than flu. The A and B viruses are the cause of epidemics every winter in temperate countries. Type A viruses comprise individual viral subtypes: the two subtypes currently in circulation in humans are H1N1 and H3N2 (viruses introduced from an avian reservoir). In exceptional cases, some subjects have been infected by the H5N1 virus (in Egypt and Indonesia).

### Influenza: a viral infection with respiratory transmission

The virus is spread via droplets of saliva and small airborne particles that are projected by coughing or sneezing. The virus enters the body via the nose, mouth and eyes. Eight hours after an influenza virus has entered a cell, 1000 to 3000 new viruses leave it. Transmission is highly effective: a non-immunised subject located within a 2 metre radius of an infected subject for more than one hour will be contaminated.

### Antigenic variability of influenza viruses

In spite of an effective immune response (humoral +++ and cellular), influenza epidemics occur every winter. This is due to the antigenic variability of the viruses, a modification of the surface proteins that gives them an ability to escape pre-existing antibodies. Viral epitope changes occur (antigenic drift) every winter. Another mechanism may occur: antigenic shift, causing the emergence of a pandemic virus.

## Clinical aspects of influenza

Influenza is an upper, and sometimes lower, respiratory tract infection (it is a potential cause of pneumonia). As the signs are generally non-specific, Influenza diagnosis should take into account season and epidemic conditions. More than 75 % of patients with influenza display the combination of three factors: abrupt onset, dry cough, fever. The type A/H3N2 virus produces more severe symptoms than H1N1, which is in turn more severe than type B viruses. Type C occurs only in exceptional cases.

**The "typical" form of influenza** is, by far, the most frequent. In adults, there is an abrupt onset of fever, usually occurring in two stages (influenza virus). After rising to 39-39.5 °C on day one, the temperature of an infected subject falls to 38 °C on day two and then rises again before disappearing on day five. It is accompanied by respiratory signs (coughing, sneezing, clear running nose, etc.) and sometimes by very marked systemic signs, frequently resulting in confinement to bed (headaches, muscle pains, joint pains, abdominal pains) for a total of 5 to 7 days (fatigue and muscle pains may last longer). In children over 5 years of age, the clinical profile is similar to that of adults, and sometimes more violent. In children under 5 years, simple or unexpected forms occur (no fever, potential hypothermia). More than one third of children under 1 year of age infected with the virus are completely asymptomatic. NB: the subjects are contagious for 24 to 48 hrs before clinical signs appear, and especially on the first day of symptoms. An influenza epidemic lasts for 10 weeks on average. Groups at a high risk of mortality have been identified: subjects over 65 years of age, subjects suffering from heart or lung failure, asthma, immunocompromised subjects, subjects receiving a long-term treatment with aspirin or institutionalised subjects. These subjects should be vaccinated. The indication for vaccination was extended in 2007 to patients with chronic bronchitis.

**Complicated forms of influenza** are observed particularly in pregnant women and infants. They are generally associated with the appearance of a bacterial superinfection with Haemophilus influenzae, Staphylococcus aureus or Streptococcus pneumoniae. In exceptional cases, specific forms

occur: myocarditis (particularly in pregnant women, and potentially life-threatening), glomerulonephritis (purely viral or associated with a superinfection), and Guillain Barré syndrome.

**The severe form of influenza or "malignant influenza"** is very rare. It starts normally and is followed by acute respiratory failure on the second day with dyspnoea, polypnoea, cyanosis, hypoxia, hypercapnia, acute pulmonary oedema, right-sided heart failure, hepatic cytolysis and renal failure. It is solely associated with the consequences of the infection and the inflammatory response (60 % mortality) and tends to be more frequent in young adults (15 to 25 years of age). Five to six cases are reported each winter in France.

## Biological diagnosis

The purpose of the biological diagnosis of influenza is epidemiological monitoring, to update the vaccine composition (for this purpose, it is necessary to isolate the viruses in circulation and thus place a number of samples in culture) and implement a curative or prophylactic treatment. Curative treatment (anti-neuraminidases) is effective if it is given within 24 hours following the appearance of symptoms (ineffective after 48 hours). In this case, it reduces the duration of symptoms by 1 day. If it is administered in the first 6 hours, it reduces the symptoms by 4 days.

**NB:** administering an influenza treatment to a subject not suffering from influenza has no effect (no resistant mutant selection occurs).

### Direct diagnosis

Respiratory samples are taken: nasal swabs (one nostril is sufficient: the swab is introduced parallel with the floor of the palate, and turned by a quarter-turn), nasopharyngeal aspiration or lavage. Samples must be taken as early as possible and, in all cases, within 3 days following the onset of clinical signs. In children, nasopharyngeal lavage is preferable as it enables rapid diagnosis of RSV (respiratory syncitial virus) infection. In adults, a swab sample is sufficient. It is advisable to use a sampling kit specially designed for the viruses (swabs including a storage medium enabling storage for 48 hours). Nasopharyngeal lavage samples must be sent to a laboratory and analysed within 4 hours. Unlike antibiotic therapy, the set-up of an antiviral treatment does not affect the likelihood of detecting the virus.

The virus can be detected using a rapid immunological technique (Rapid Diagnostic Test or RDT) in the form of a unit bedside test or unit laboratory test. Other techniques – immunofluorescence (IF), ELISA or immunochromatography – must be used in the laboratory. IF is highly sensitive, but requires reading expertise; in effect, almost all laboratories currently use RDTs, which are simple, economical, sensitive (sensitivity of approximately 80 %), specific (95-96 %) and rapid (results in 3 hours).

The other direct diagnostic methods consist of RT-PCR viral genome detection (development of real-time PCR tests in hospital laboratories: response in 1 hour and superior sensitivity to RDTs) and virus isolation and identification in cell culture (a few specialised laboratories). After inoculation on cells, the multiplication of the virus is detected by the appearance of a cytopathogenic effect. The virus is identified by haemadsorption or haemagglutination inhibition. The benefit of isolation essentially lies in the antigenic study of the viral strains.

### Indirect diagnosis

This is performed on two sera, the first sampled in the acute phase (in the first 5 days of infection), the second in the convalescence phase (10 to 14 days after the first). Both sera must be analysed in the same serological reaction. The most commonly used techniques are the complement fixation reaction and the haemagglutination reaction.

Serology represents no diagnostic interest. It is of interest for epidemiological or post-vaccination purposes.

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