Influenza is an acute infection of the respiratory tract caused by an influenza virus. The virus is easily passed from person to person by breathing aerosol droplets containing the virus produced when an infected person coughs or sneezes. It can also be spread through hand-face contact after touching a surface contaminated with the virus.

The most common symptoms are sore throat, fever, coughs, chills, severe headache, muscle pains, general discomfort and fatigue. In severe cases, influenza can cause serious illness or death due to pneumonia and other life-threatening complications.

Influenza pandemics occur when a new strain of influenza emerges, for which people have little or no immunity, and the virus is able to spread easily between people. There were three pandemics in the 20th century: The most serious was in 1918–19 (Spanish flu), which killed millions of people worldwide, and smaller pandemics occurred in 1957–58 (Asian flu) and 1968–69 (Hong Kong flu). Fortunately, the 2009 pandemic (swine flu) has caused fewer deaths than previous pandemics.

The virus

The three types of influenza virus (A, B and C) are similar in structure. The central core of the virus contains the viral RNA genome and proteins that package and protect it. The central core is surrounded by a lipid envelope that bears on its surface two types of glycoproteins — haemagglutinin (HA) and neuraminidase (NA) — and the M2 protein that acts as an ion channel through the envelope. The genome consists of seven or eight pieces of RNA, each piece containing one or two genes that encode for viral proteins (structural, surface and replication proteins, including an RNA polymerase). Influenza A viruses are classified into subtypes (eg, H1N1) based on antibody responses to HA and NA.

Infection of a cell in the respiratory tract of the host with influenza is a multi-step process. The virus has to bind to the host cell, enter the cell, deliver its genome to the cell nucleus, where new copies of the viral proteins and RNA can be produced, then assemble new viral particles and, finally, release the new viral particles from the host cell to allow further infections to occur. The viral proteins mentioned above are involved in important steps in the infection process. HA binds the virus to the host cell. The M2 protein allows protons (H+ ions) to move through the viral envelope and acidify the core, leading to the freeing of its contents from the envelope. NA is an enzyme that helps to release the newly assembled virus particles, allowing them to leave the host cell.

Errors occur during replication of the viral RNA, which causes small changes in the viral surface proteins (antigenic drift). The separation of the genome into separate pieces of RNA allows mixing (reassortment) of viral RNA when more than one virus infects the host cell, which can cause large changes in the viral surface proteins (antigenic shift). The changes that occur in the surface antigens prevent the development of long-term immunity to influenza.

Current treatments

Two treatment strategies are currently recommended for influenza: vaccination and the use of antiviral drugs. In the UK, the Department of Health recommends that people at risk of serious illness if they contract influenza (young children, the elderly and people who are immuno-suppressed or have underlying diseases, such as chronic heart disease), carers of “at risk” people, healthcare and other essential workers, and poultry
workers should be vaccinated at the beginning of each winter. The influenza strains active in the community change each year. The World Health Organization monitors influenza and recommends the vaccine composition for the upcoming influenza season.

**Vaccines**

There are two types of vaccine. For each type, the selected viruses are grown almost exclusively in fertilised chicken eggs. The most common type is made from inactivated viruses (typically, the vaccine is a trivalent influenza vaccine that contains purified and inactivated material from two influenza A virus subtypes and one influenza B strain) and is given as an intramuscular injection. The other type is a live virus vaccine that contains live viruses that have been attenuated (weakened) and is administered as a nasal spray.

**Antivirals**

Influenza antivirals can be used either to prevent people from contracting influenza or to treat them after they have become infected. Since the lag time between virus identification and vaccine distribution exceeds six months, antiviral therapy is vital to control the spread of influenza when a vaccine is not yet available. To be effective, treatment with the antiviral compounds should normally be started within 48 hours of the first symptoms. Two classes of drugs are currently available to treat influenza: M2 ion channel blockers (amantadine and rimantadine) and NA inhibitors (oseltamivir and zanamivir). M2 ion channel blockers inhibit viral replication by preventing the uncoating of the virus core within the host cell. NA inhibitors interrupt the release of new virus particles from the host cell.

The anti-influenza drugs that are currently recommended are oseltamivir, which is taken orally as capsules or as a syrup, and zanamivir, which is administered by inhalation. Resistance to oseltamivir has emerged in some strains of influenza. With the development of strains of influenza resistant to current influenza antiviral drugs, a wider range of antiviral compounds is clearly needed.

**Current research**

There are several developments in vaccines and drug treatments for influenza.

**Vaccine development**

Researchers are looking to improve methods of vaccine production to increase capacity, and make it quicker and more affordable. Established mammalian cell-culture lines have started to be adopted, for example, Optaflu is made using Madin-Darby canine kidney (MDCK) cell-based technology, and this trend looks set to continue. Non-egg-based vaccine technology brings a number of advantages: it is more scalable and avoids the problems associated with the use of eggs, such as potential shortages in egg supply, allergic reactions and incompatibility with avian influenza strains.

Another area of development is dose-sparing technology. An antigen can be added to a vaccine to enhance the recipient’s immune response to the supplied antigen, thus reducing the quantity of antigen required per dose.

For example, Pandemrix, a vaccine that has been approved in the UK for use against the current swine flu strain, contains the adjuvant AS03 composed of squalene, DL-α-tocopherol and polysorbate 80. A variety of approaches may prove useful in the long-term. These include DNA vaccines and vaccines based on an antigen that is highly conserved, such as the M2 protein, with the aim of producing a “universal” vaccine that would not need annual reformulation.

**Antiviral development**

Two promising new NA inhibitors, peramivir and lanaminavir, are being evaluated in phase III clinical trials. Peramivir has been developed in an injectable form and has a resistance profile and efficacy similar to oseltamivir. The US Food and Drug Administration issued an emergency use authorisation to allow the use of intravenous peramivir to treat certain adult and paediatric patients admitted to hospital with suspected or laboratory confirmed 2009 H1N1 virus infection during the 2009 pandemic.

Lanaminavir (CS-8958) is a long-acting NA inhibitor. In trials, a single intracheal dose of lanaminavir was shown to be as effective as oseltamivir taken orally twice daily for five days. It has been found to inhibit NA activity in oseltamivir-resistant influenza A H1N1 and H3N2 and influenza B viruses.6 Favipiravir and Fludase are two new antivirals that have different modes of action to the approved anti-influenza drugs. Favipiravir is undergoing phase III clinical trials and Fludase is in phase II development. The orally administered drug favipiravir (T-705) interferes with the replication of influenza viral RNA by inhibiting influenza RNA polymerase activity. In a mouse model, it prevented death to an extent comparable to oseltamivir. In another study, it effectively protected mice from lethal infection with oseltamivir-resistant highly pathogenic H5N1 viruses.7

Fludase (DAS181) is a recombinant fusion protein composed of the catalytic domain of *Actinomyces viscosus* sialidase and the epithelial anchoring domain of human amphilagin. Cell-surface sialic acids are the host cell receptors for influenza viruses. The sialidase removes sialic acids from mucosal membranes, preventing attachment of the virus via its HA glycoprotein. In mouse models with a control group death rate of 57 per cent, Fludase given by inhalation 48 hours after infection was 100 per cent effective at preventing death. It has shown activity against influenza A 2009 H1N1 and H5N1 viruses and retained activity against oseltamivir-resistant viruses.10,11

**Conclusion**

Without complications, patients can recover from influenza without treatment, but may experience substantial discomfort. With complications such as viral pneumonia, influenza can cause serious illness or death. Vaccine production is currently based predominantly on old egg-based technology, but modern methods are being introduced that should allow increased capacity and shorten the production cycle. New antiviral drugs are being developed to address the problem of resistance in strains of influenza to current drugs.

**References**