Influenza

Influenza is caused by a virus. It affects millions every year – and it can be fatal. The development of vaccines has played a major part in protecting people but as there are changes in virulence continuing research is essential to find new ways of combating this menace.

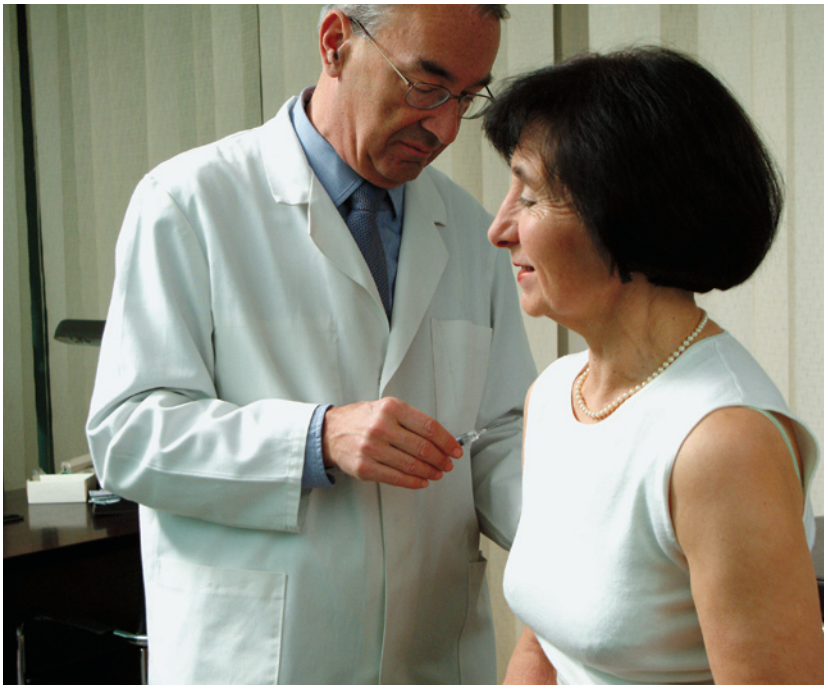
What is influenza?

The influenza virus causes potentially serious infections affecting the nasal passages, throat, larynx and lungs and periodically causes epidemics or even pandemics (worldwide epidemics). It belongs to the group of orthomyxoviruses, a group of viruses which are characterised by possession of an envelope and a viral genome composed of segments of single stranded RNA.

Influenza (flu) is transmitted when an infected person coughs, sneezes, or speaks and sends microscopic drops loaded with influenza virus into the air, which are then inhaled by other people. However, it can also be contracted through contact with flu virus contaminated surfaces. The usual flu season in the northern hemisphere occurs from November to April.

The surface of an influenza virus particle carries haemagglutinin molecules, which enable it to adhere to cells in the respiratory tract of human beings, and the enzyme neuraminidase, which is involved in the release of new virus particles inside the body.

Two major types of influenza cause disease in humans: influenza A and influenza B. Today, we know that influenza A viruses can possess one of 15 different types of haemagglutinin molecules and nine different types of neuraminidase. The possible combinations in the make up of these macromolecules lead to different influenza A subtypes, such as H1N1, H3N2 and H5N1.



Due to the rapid mutation of the viral surface molecules and hence the changing of prevalent strains, a new vaccine is needed each year. To allow for enough time for the manufacturing of tens of millions of doses, each year in early summer, the composition of the new vaccine is determined according to surveillance data collected by a world-wide network of virologists under the aegis of the World Health Organisation.

Who does influenza affect?

Anyone can get influenza. Most people who get the flu will recover in one to two weeks, but some will develop life-threatening complications. Particularly susceptible to develop complications are people aged 65 years and older, people of any age with chronic medical conditions, such as asthma, chest problems, congestive heart failure, malignant diseases and kidney problems, as well as very young children and pregnant women. These people are known as "high risk" and should be immunised. Furthermore, a person can have influenza more than once.

It has been estimated that 120 million people get influenza every year in the USA, Europe and Japan. Every ten years or so, a highly contagious and virulent influenza

virus strain appears and results in a worldwide epidemic, known as a pandemic. The last two pandemics occurred in 1957 and 1968, when more than five million people died. Over 20 million people are estimated to have died worldwide during the great influenza pandemic of 1918/19. It has been cited as the most devastating epidemic in recorded world history.

Present treatments:

The best way to prevent infection with influenza virus is to be vaccinated each autumn, before the start of the flu season. Pregnant women can protect their newborns against influenza infections by getting vaccinated. As infants are particularly vulnerable to the disease because they are too young to get the medicines used to treat influenza, public health officials recommend immunisation for pregnant women.

Since 2008, a flu vaccine produced from mammalian cell cultures has been available in the European Union. The use of cell culture technology enables a faster, more flexible start up of vaccine manufacturing, rather than the earlier method which involved the propagation of the virus in hen's eggs. The approval of the vaccine in 2007 marked the first major innovation in influenza vaccine manufacturing in over 50 years. The vaccine is administered via intramuscular injection like the established, conventional egg-based vaccines.

Children are key flu spreaders. In epidemiological studies, investigators have discovered that in different regions, every one per cent increase in the child population brings a four per cent increase in adult emergency room visits. Therefore, governments in various countries are now recommending that children from age six months to 18 years be vaccinated.

Once influenza has set in, specific antiviral medicines can be taken that stop the virus reproducing and spreading in the body. The neuraminidase inhibitors limit the duration of illness and may limit the spread to others. There are two of this class in current use. One compound is taken orally and absorbed through the digestive system, while the other is inhaled and active in the airways only. These medicines are approved both for the prevention and treatment of influenza Types A and B.

Compounds belonging to the group of cyclic amines are available for the prophylaxis and treatment of flu. They are mainly used in immunocompromised patients or other high risk people, as the benefits are somewhat modest for general use. Cyclic amines are only active against Type A flu viruses, which account for 65 per cent of outbreaks.

Over-the-counter medicines such as mild analgesics and decongestants provide symptomatic relief and reduce fever, but have no effect on the transmission of the virus to others. There are no medicines that cure influenza.

What's in the development pipeline?

Prevention of influenza depends on the rapid production of vaccines tailored to the specific strain at the first signs of an epidemic. Thus, each vaccine is, in effect, a new product each year. However, new types of vaccine are also being explored.

There is an intranasal live attenuated vaccine in Phase 3 trials. It contains influenza virus rendered unable to cause the disease and may make future vaccinations easier and more acceptable to people who wish to avoid injections.

Researchers are testing a recombinant vaccine against influenza virus linked to a Hepatitis B core protein. It targets M2e, a common region of all influenza A strains. This approach could overcome the need for annual vaccine reformulations and, since all

pandemic influenza strains are type A, it could also be a potential vaccine against pandemics. The project is in clinical Phase 2 clinical trials.

Other research groups are studying a proteosomal influenza vaccine. This type of vaccine consists of a small part of the influenza virus's genetic code. Inserting this material into a few cells of the body leads to synthesis of a part of the virus, which in turn stimulates the body to produce high levels of protective antibody.

Following analysis of more than 13,000 isolates of the virus and a particular domain of its haemagglutinin, researchers have been able to determine the ancestry of circulating influenza strains. Travel and trade connections explain the global dissemination on a one-way route out of east and southeast Asia, taking about six to nine months to reach Europe and North America. Several months later, these strains arrive at their evolutionary graveyard in South America. Thus, the antigenic characteristics of circulating viruses in Asia may be crucial to forecasting vaccine needs for the future.

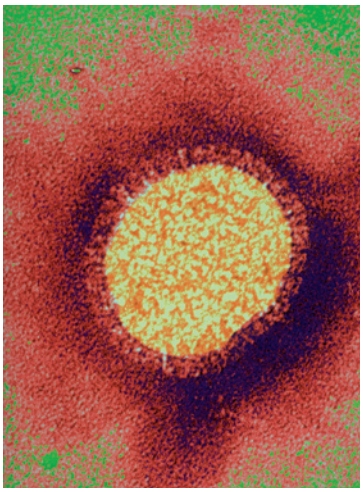


FIGURE 1: **Electron-microscopic picture of the influenza virus**

The longer-term future

Scientists are looking for new medicines to prevent or treat influenza. Long-acting neuraminidase inhibitor products which are expected to show activity with a once-weekly dosing regimen are still at the preclinical stage.

Another avenue to treat flu which is being studied is the application of immunoglobulin fusion proteins. These would act on a receptor molecule found on the surface of influenza-activated white blood cells or T-cells. This approach is thought to be able to attenuate the immune response of the human body to the viral infection and to avoid the damaging inflammatory process in the lung.

In the face of an influenza epidemic outbreak, research groups are investigating the possibility of producing infection-fighting human monoclonal antibodies. B-lymphocytes are isolated from volunteers who have been inoculated with seasonal influenza vaccine and then the cells are made immortal to produce such antibodies. The rapid generation of such antibodies could potentially be used for diagnosis and treatment of newly emerging strains of influenza.

The public would no doubt welcome new treatments for flu. Whether these will ever be able to stop the infection in its tracks once it has started is unclear, but certainly a treatment that could prevent a fatal outcome of influenza in elderly and at-risk patients would be of genuine clinical value if, as some experts believe, another pandemic is always just around the corner.

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