

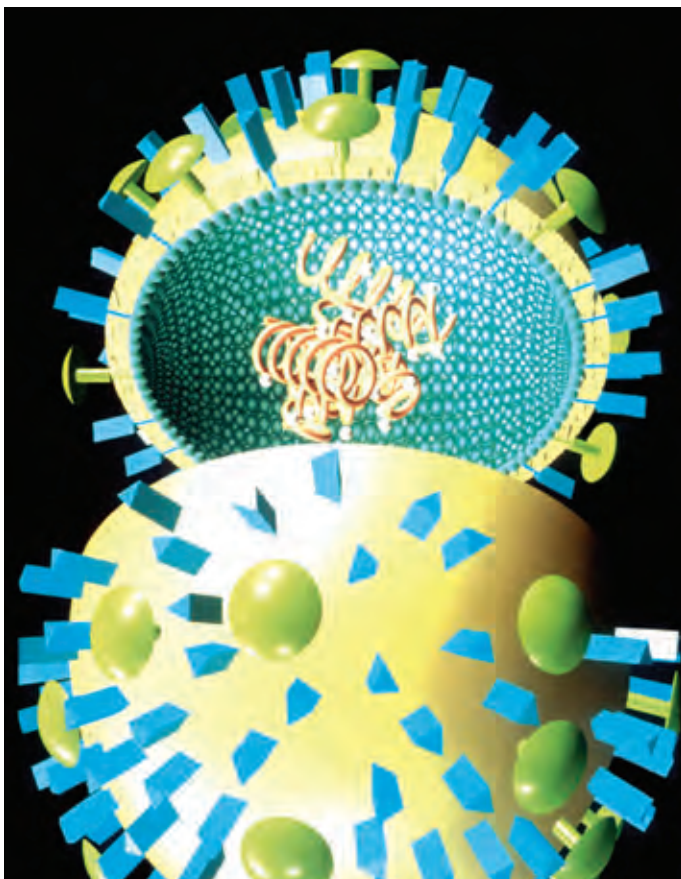
# INFLUENZA

A seasonal disease

## 📄 Influenza

Influenza or flu is a common viral disease of the upper respiratory tract. There are three types of influenza virus: A, B and C. Major outbreaks of influenza are associated with influenza virus types A or B. Infection with type B influenza is usually milder than with type A. Influenza C is common but rarely causes disease.

Influenza A is the most virulent type and is commonly associated with human disease. Between 1918 and 1919 flu is thought to have killed over 50 million people (6 times as many as died as a consequence of the World War I). This global pandemic possibly infected 50% of the world's population and up to 20% died. It was caused by an unusually pathogenic strain of influenza A virus. Other global influenza pandemics have been recorded through history and they seem to occur every 10 to 40 years. Each year, many countries, including the UK, experience seasonal influenza epidemics that affect hundreds of thousands of people.



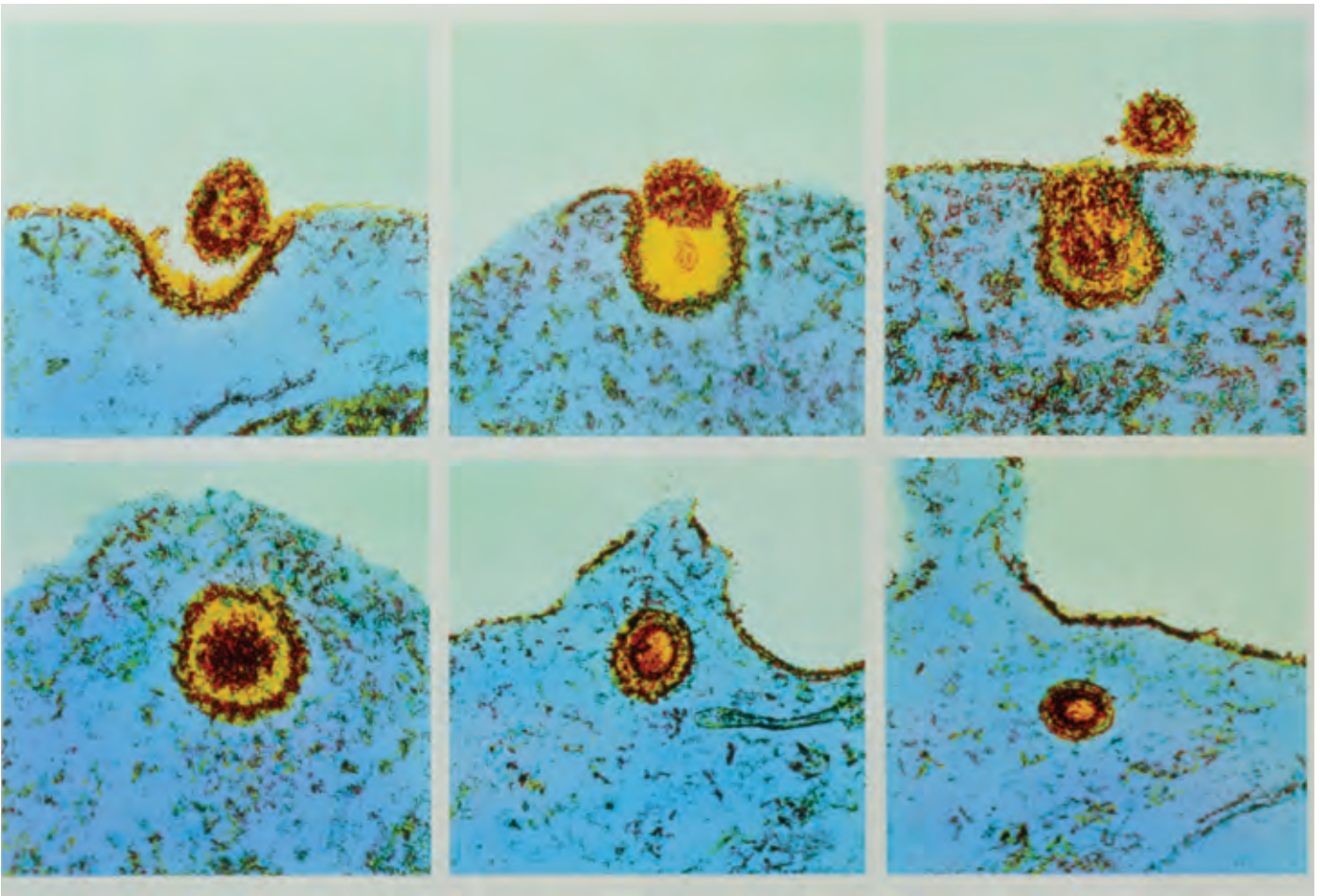
Caricature of the H1N1 1918 flu pandemic

## 📄 What causes flu?

The influenza virus particle - virion - is usually spherical in shape and carries its genetic material on eight pieces of single stranded RNA known as segments. Each segment carries genes that encode for proteins that the virus needs in order to replicate inside the infected host cell. The genome is protected by a membrane envelope. Protruding from the virus envelope are hundreds of copies of two different varieties of viral glycoprotein spikes. Approximately 80% of the spikes are haemagglutinin (HA) and the remaining 20% are neuraminidase (NA). The HA and NA surface proteins are involved in viral attachment and entry to host cells. They are also the main part of the virus recognized by our immune system as foreign, and most of the antibodies we make after infection are against these antigens.

Computer artwork of an influenza virus particle split open to reveal the core of RNA genetic material. This is surrounded by a membrane envelope (yellow). In the envelope are two types of protein spike, haemagglutinin (H, blue) and neuraminidase (N, green), which determine the strain of virus.





The stages of cell infection of an influenza virus. The virus appears rounded in shape, with a core of ribonucleic acid (RNA). It has a spiked outer coat which allows the virus to attach to host cells. Host cell cytoplasm appears granular. At top frames (3 images) the virus attaches to the cell, causing the cell membrane to fold around the virus. At lower frames (3 images) the virus penetrates the cell, infecting it, and causing more influenza viruses to be produced. This virus is contagious and invades mucus cells in the respiratory tract.

## ☐ Transmission

The flu virus is extremely contagious and is transmitted from person to person by droplets expelled when sneezing and coughing. It can also be transmitted by direct contact, for example by touching virus-contaminated surfaces such as door handles and then touching the eyes or nose. Good hygiene practices, such as correct hand washing, are very important in preventing infection.

## ☐ Infection and replication

Influenza viruses infect epithelial cells in the upper respiratory tract (nose and throat). If the infection is severe the virus can eventually reach the lungs and cause pneumonia. The respiratory tract's first line of defence is a protective layer of mucus. The virus NA protein can cut through this enabling the virus particle to reach the epithelial cell surface. The virus then uses its HA protein to attach to a receptor on

the host cell's plasma membrane and is taken into the host cell by endocytosis. The ribonucleoprotein core, that contains the viral RNA and the viral polymerase used for replication, is released into the cytoplasm and moves into the nucleus. Viral RNA is replicated. The host cells' own ribosomes are hijacked to make proteins from the viral mRNAs. New copies of the RNA genome are shuttled out of the nucleus and up to the plasma membrane where they combine with the newly made viral proteins and bud out of the cell's plasma membrane, acquiring their envelope in the process. Finally, using the NA protein to cut themselves away from the infected cells, the new virions move away to infect other cells.

The host cells are damaged when they become infected by the virus. The patient's immune system responds by releasing chemicals called cytokines

which stimulate leukocytes (white blood cells) to travel to the site of infection and fight the virus. Most of the symptoms are in fact caused by the body's immune response. These include:

- ▶ high fever
- ▶ chills
- ▶ severe fatigue
- ▶ headaches
- ▶ muscular aches and pains
- ▶ non-productive cough
- ▶ sore throat

When the NA protein of influenza breaks down the mucus lining the epithelial cells, this also leaves the cells more susceptible to infection by other pathogens, such as bacteria like *Staphylococcus aureus* and *Haemophilus influenzae*.

Woman suffering from flu



The antiviral drug Tamiflu®

## ☐ Treatment

Most people recover from flu within 1-2 weeks but more serious illness, and even death, can result from secondary infections e.g. bacterial pneumonia. This is more likely in infants, the elderly, people who are immunocompromised and those with chronic lung disease such as emphysema.

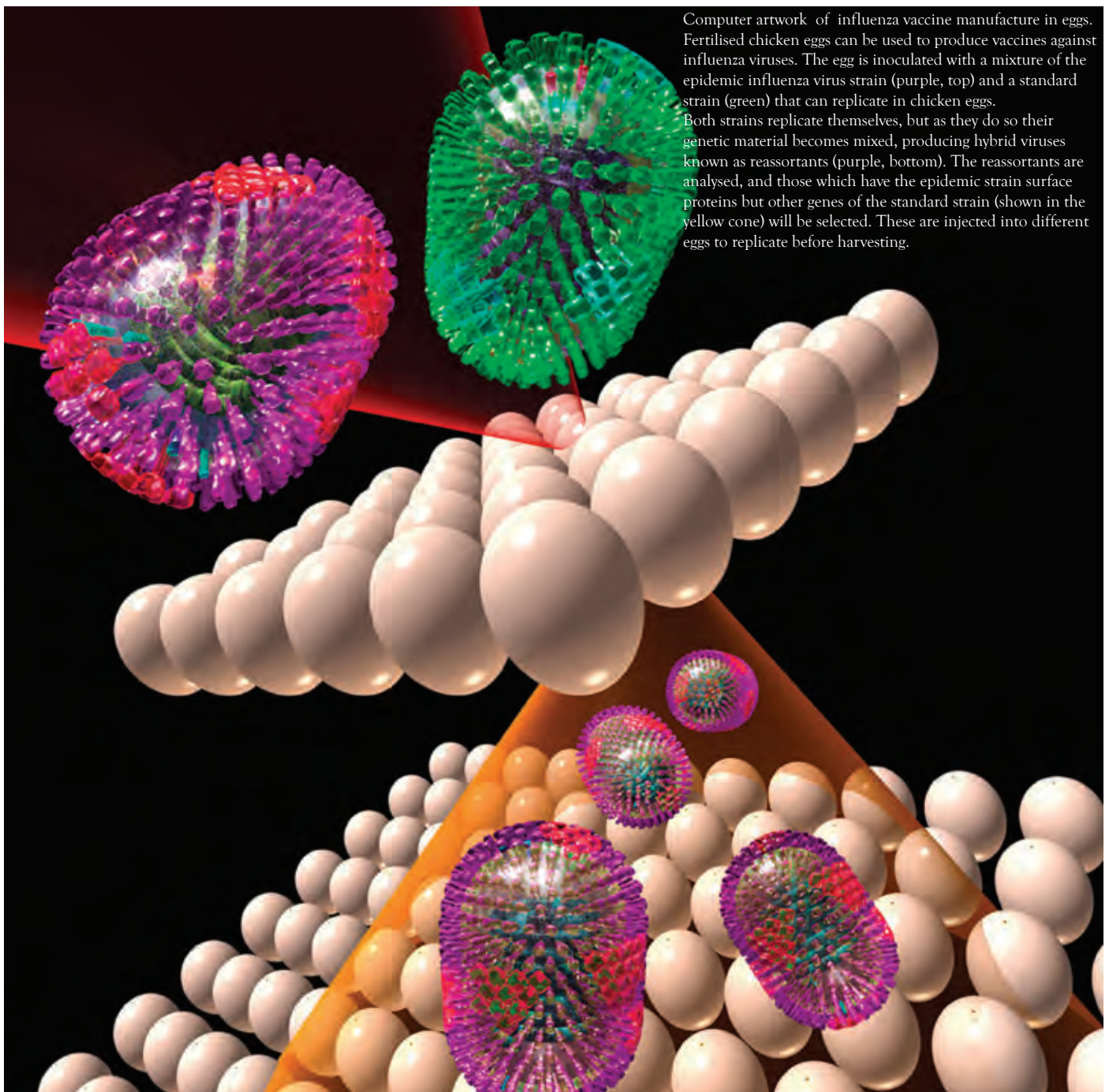
There are two ways of tackling the disease: treating the symptoms and attacking the virus. The symptoms can be alleviated with drugs to reduce fever and pain such as paracetamol. Antiviral drugs can be effective against influenza but must be administered within the first 2 days of symptoms appearing. Drugs such as oseltamivir (Tamiflu®) attack the virus by inhibiting the enzyme neuraminidase and therefore prevent the virus from infecting cells.

Antibiotics are not used to treat influenza because they work by inhibiting bacterial cell wall production and protein synthesis and block cell metabolism and have no effect on viruses. They can be used to treat secondary bacterial infections.



## ☐ Vaccines

Antibodies that recognize the HA and NA surface proteins of the influenza virus can protect us from infection by stopping the virus reaching the host cell surface. This means that people will not be infected by the same strain of influenza after they recover from flu. Giving a small dose of a crippled strain of influenza virus or an injection of purified HA protein as a vaccine, can stimulate the immune system to make antibodies to HA to protect us from flu.



Computer artwork of influenza vaccine manufacture in eggs. Fertilised chicken eggs can be used to produce vaccines against influenza viruses. The egg is inoculated with a mixture of the epidemic influenza virus strain (purple, top) and a standard strain (green) that can replicate in chicken eggs.

Both strains replicate themselves, but as they do so their genetic material becomes mixed, producing hybrid viruses known as reassortants (purple, bottom). The reassortants are analysed, and those which have the epidemic strain surface proteins but other genes of the standard strain (shown in the yellow cone) will be selected. These are injected into different eggs to replicate before harvesting.

### Cold or flu?

The terms *cold* and *flu* are often used interchangeably but they are in fact distinct diseases caused by very different viruses. A cold is caused by several groups of viruses; the most common is rhinovirus and usually lasts between 2 and 4 days. Symptoms include runny nose, sneezing and mild fatigue. Flu is much more serious than a cold. Symptoms may last for a few weeks and the illness can be much more debilitating. If in doubt, remember the £50 test: if a £50 note is pinned to your front door and you are incapable of dragging yourself out of your sick bed to collect it...you have the flu. If the thought of free money puts a spring in your step...it's just a cold!

### Flu epidemics and pandemics

The influenza virus genes are made of RNA and are more prone to mutations than genes made of DNA. Influenza viruses undergo constant genetic variation.

#### Antigenic drift

Influenza viruses are changing by antigenic drift all the time. Mutations in the genes coding for the proteins NA and HA result in minor changes to surface proteins. If the HA antigen changes shape then the antibodies won't be able to recognise it and bind to it. The newly mutated virus can then bind to receptors on the host cell and infect it.

This is why it is possible for an individual to be infected more than once with influenza and why there is a global surveillance team that monitors the evolution of human influenza strains. Every year a new strain of virus emerges and the vaccine must be updated so that the antibodies it induces are a good match to the antigens of the strains that are circulating in the community.

#### Antigenic shift

This occurs in influenza A viruses only and is due to the reassortment of RNA segments from two different viral strains infecting the same cell producing viruses that have entirely new antigens. Wild birds get influenza infections all the time. Sometimes these avian viruses spread to chickens and cause outbreaks of 'bird flu' that can devastate poultry farms.

Most bird flu viruses cannot infect humans. It is thought that most new strains of flu originate in

China where many people live in crowded conditions, often in close contact with domesticated pigs and birds. Birds can transmit influenza to pigs. Pigs can transmit the virus to humans and vice versa. Recombination of human and bird strains inside pigs can result in novel strains of influenza A that will infect humans.

With the increase in global transport and urbanization, epidemics caused by these new strains are likely to spread rapidly around the world. Theoretically these epidemics could be controlled by immunisation, but a new vaccine must be produced for each new strain of flu, so vaccines may not be immediately available in the threat of an epidemic. The World Health Organization (WHO) has developed a 'global influenza preparedness plan' which advises countries on how to prepare for the possibility of an pandemic. This involves:

- ▶ Rapid detection of unusual influenza outbreaks and isolation of possible pandemic viruses
- ▶ Measures to prevent spread of the disease, including: public health education, travel and trade restrictions and quarantine procedures
- ▶ Contingency plans for storage, distribution and safe administration of pandemic and routine influenza vaccine
- ▶ Provision to maintain adequate health care resources, including antiviral drugs, personnel and hospital resources



Computer artwork showing two influenza viruses (pink and green) infecting a pig cell (pink sphere). The viruses use the host cell's machinery to reproduce copies of themselves. During this process the two genomes may be mixed and repackaged to form a new strain (purple). If the new strain is able to infect humans this introduces a new strain to which the population has no immunity to, giving it the potential to cause a pandemic.

## 📌 The unpredictability of pandemics!

The WHO is on constant look out for the first signs of a pandemic. For some years there has been public concern that a strain of avian flu called influenza A H5N1 will mutate into a form that is easily transmitted between humans and cause a pandemic. The virus occurs in both wild and domesticated birds where it is transmitted in saliva, faeces and nasal secretions and has a high mortality rate. A small number of humans have contracted this strain of bird flu, mainly by close contact with poultry, and by July 2009 the WHO had confirmed 436 cases and 263 deaths worldwide. Currently there is very limited human to human transmission of the virus.

In April 2009 scientists were surprised by the emergence of a novel influenza A H1N1 (2009) virus from Mexico. Popularly called 'swine flu', the strain contains a combination of genetic material that is typical to avian, swine and human flu viruses. It spread very rapidly around the world, causing 11,000 cases in 42 countries in the first 4 weeks. On 11 June 2009 the WHO declared the first global flu pandemic for 40 years. The pandemic was officially declared over in August 2010 although the strain continued to circulate.

The H1N1 (2009) strain was included in the 2010/2011 seasonal flu vaccine along with two other influenza strains. The H1N1 (2009) virus is expected to continue to circulate as a seasonal influenza strain for the foreseeable future and because of this, more people will develop immunity to this current version of the virus. However, the virus is also expected to change over time, meaning that immunity to this current strain may not protect against future strains of the virus. Global influenza surveillance will continue to track the evolution of H1N1 (2009).

### Taking it further

[www.who.int/csr/disease/influenza/en/](http://www.who.int/csr/disease/influenza/en/)  
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## Picture credits

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