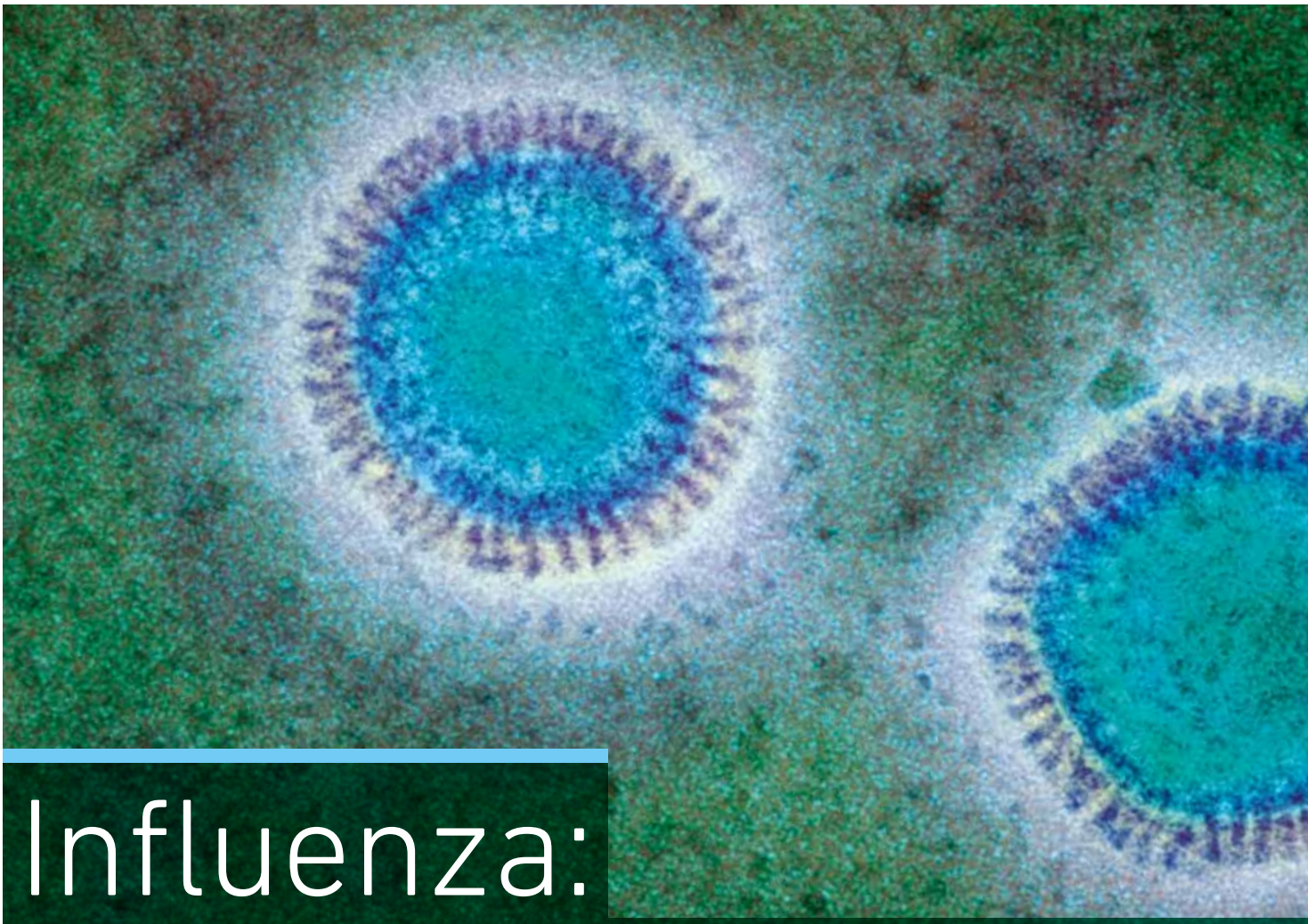
MICROBIOLOGY SOCIETY

Influenza: A seasonal disease

FACTFILE



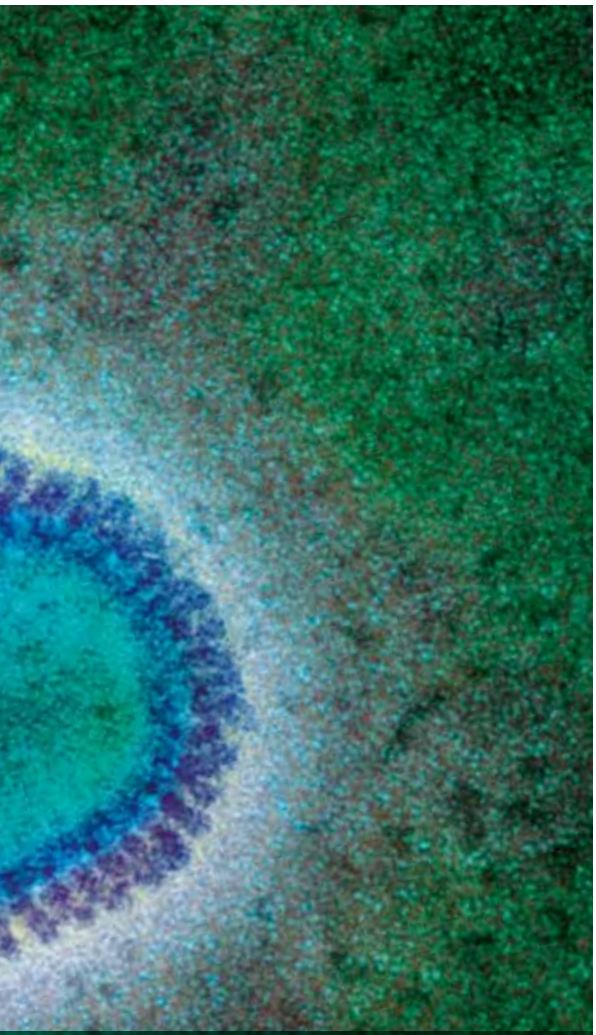
Influenza: A seasonal disease

Influenza or 'flu' is a common viral disease of the upper respiratory tract in humans (in birds it is an infection of the gut). There are three types of influenza virus: influenza A, B and C. However, a fourth type, influenza D, has recently been discovered as a veterinary infection, particularly of cows. Major outbreaks of influenza are associated with influenza virus type A or B. Influenza C is common but seldom causes disease

Influenza A is commonly associated with human disease. Each year, many countries, including the UK, experience seasonal influenza epidemics that affect hundreds of thousands of people. In addition, global influenza pandemics have been recorded throughout history and they seem to occur every 10 to 40 years. 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 first-world war). It was caused by an unusually pathogenic strain of influenza A virus.

What causes flu?

The influenza virus particle – virion – is usually spherical, but sometimes filamentous, in shape and carries its genetic material on eight pieces of single stranded RNA known as segments. Each segment carries genes that encode 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 membrane 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 as well as the release of new virions. They are also the main part of the virus recognised by our immune system as foreign, and most of the antibodies we make after infection are against these antigens.



Coloured transmission electron micrograph of a section through influenza virus particles.

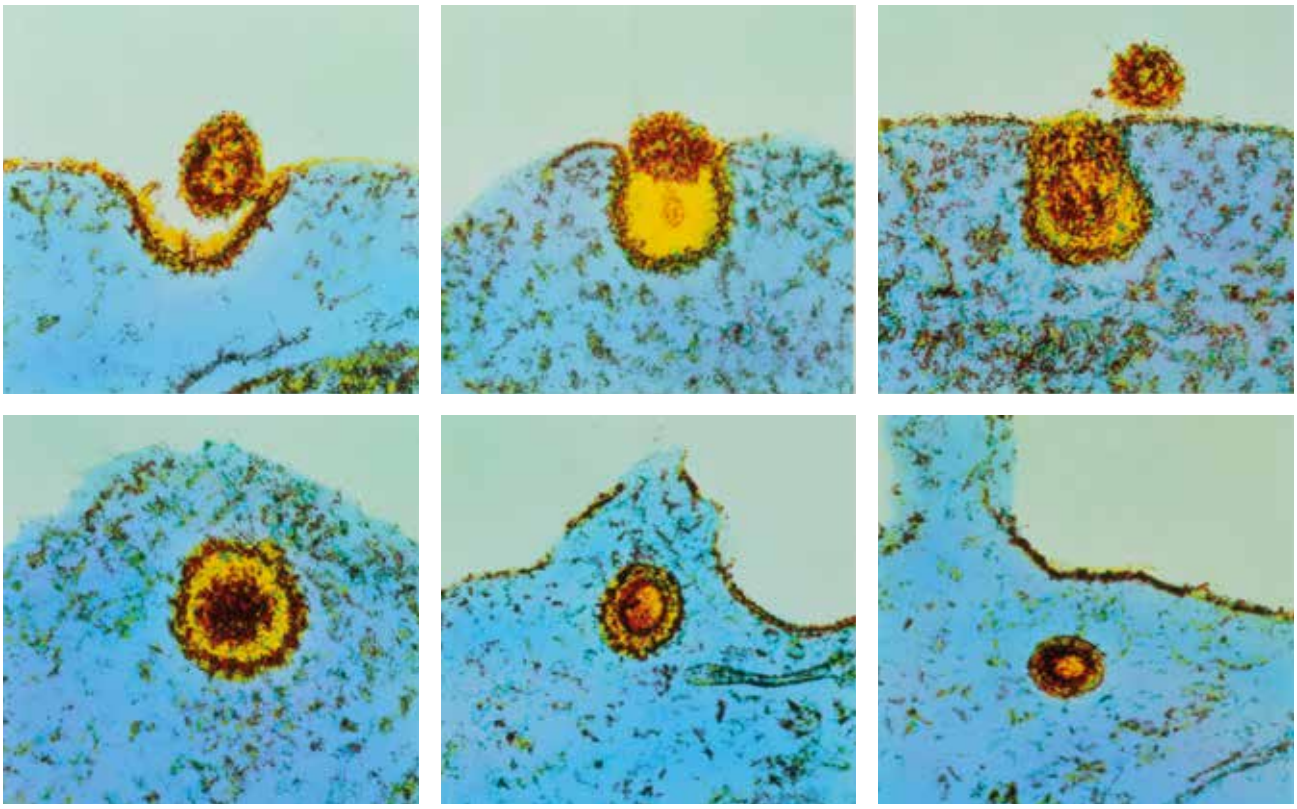
Historical caricature of the 1918 influenza pandemic. Also called the Spanish flu, this pandemic killed between 50 and 100 million people worldwide between 1918 and 1920.

Transmission

The flu virus is extremely contagious and is transmitted from person to person by droplets expelled when sneezing, coughing and even breathing. It can also be transmitted by direct contact, for example, by touching virus-contaminated surfaces such as door handles and then touching your eyes or nose. Good hygiene practices, such as correct handwashing, can help to prevent 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 viral 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



Coloured transmission electron micrograph of stages of cell infection of an influenza virus. The virus appears rounded in shape, with a core of RNA and a spiked outer coat which allows the virus to attach to host cells. Host cell cytoplasm (blue) appears granular. The top frames show the virus attaching to the cell, causing the cell membrane to fold around the virus. The lower frames show the virus penetrating the cell and infecting it.

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 flu. If the thought of free money puts a spring in your step ... it's just a cold!

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*.

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.

Tamiflu (oseltamivir) capsules in a blister pack.

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 NA enzyme and therefore preventing the virus from infecting cells.

Antibiotics are *not* used to treat influenza because they specifically work by inhibiting bacterial cell wall production or protein synthesis and 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 or binding to the host cell surface or by stopping new virions being released from the infected cell. This means that people will not be infected by the same strain of influenza after they recover from that flu. Giving a small dose of a crippled strain of influenza virus, or an injection of purified HA and NA protein as a vaccine, can stimulate the immune system to make antibodies to HA and NA to protect us from flu.

Fertilised chicken eggs can be used to produce vaccines against influenza viruses. Eggs are inoculated with a mixture of the epidemic strain and a standard strain that can replicate in chicken eggs. As the strains replicate, their genetic material becomes mixed, producing hybrid viruses known as reassortants. The reassortants are analysed, and those which have the epidemic strain surface proteins but other genes of the standard strain will be selected. These are injected into different eggs to replicate before harvesting.

Flu epidemics and pandemics

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

Antigenic drift

Influenza viruses are changing by antigenic drift all the time, constantly acquiring new mutations. Mutations in the genes coding for the proteins NA and HA result in minor changes to surface proteins at sites recognised by antibodies. If the HA antigen changes shape then the antibodies won't be able to recognise it and bind to it as efficiently. The newly mutated virus can then bind to receptors on the host's cell and infect it. This continual but gradual change of the sites recognised by antibodies is referred to as antigenic drift.

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 epidemic strains of influenza are slightly different from those that circulated the year before 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

Antigenic shift occurs in influenza A viruses only and is due to a human influenza virus acquiring new genes for the HA and NA protein from an influenza virus which infects animals. The new virus is so different from previous human and animal viruses that our existing antibodies are entirely unable to bind to it. This major change in HA and NA proteins, which allows the virus to side-step pre-existing immunity, is referred to as antigenic shift.

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. However, domesticated birds can transmit influenza to pigs. Pigs can transmit the virus to humans and vice versa. Reassortment of human and bird strains inside pigs can result in new strains of influenza A that will infect humans. That is why pigs can be referred to as a "mixing vessel".

With the increase in global transport and urbanisation, epidemics caused by these new strains are likely to spread rapidly around the world. Theoretically these pandemics could be controlled by immunisation, but a new vaccine must be produced for each new strain of flu, which takes time, 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 epidemic. This involves:

- Rapid detection of unusual influenza outbreaks and isolation of 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 services

The unpredictability of pandemics!

The WHO is on constant lookout 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 (H5 and N1 refer to the types of HA and NA proteins on the surface of this virus). 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 October 2016 the WHO had confirmed 856 cases and 452 deaths worldwide. Currently there is very limited human-to-human transmission of these viruses and neither has yet created a highly transmissible pandemic strain.

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 from 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 continues 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).

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, giving it the potential to cause a pandemic.

Taking it further

The World Health Organization is the directing and coordinating authority on international health
www.who.int/csr/disease/influenza/en

The Centers for Disease Control and Prevention in America **www.cdc.gov/flu**

The Department for Health in the UK has information about flu including guidance and preparedness
https://www.gov.uk/government/collections/seasonal-influenza-guidance-data-and-analysis

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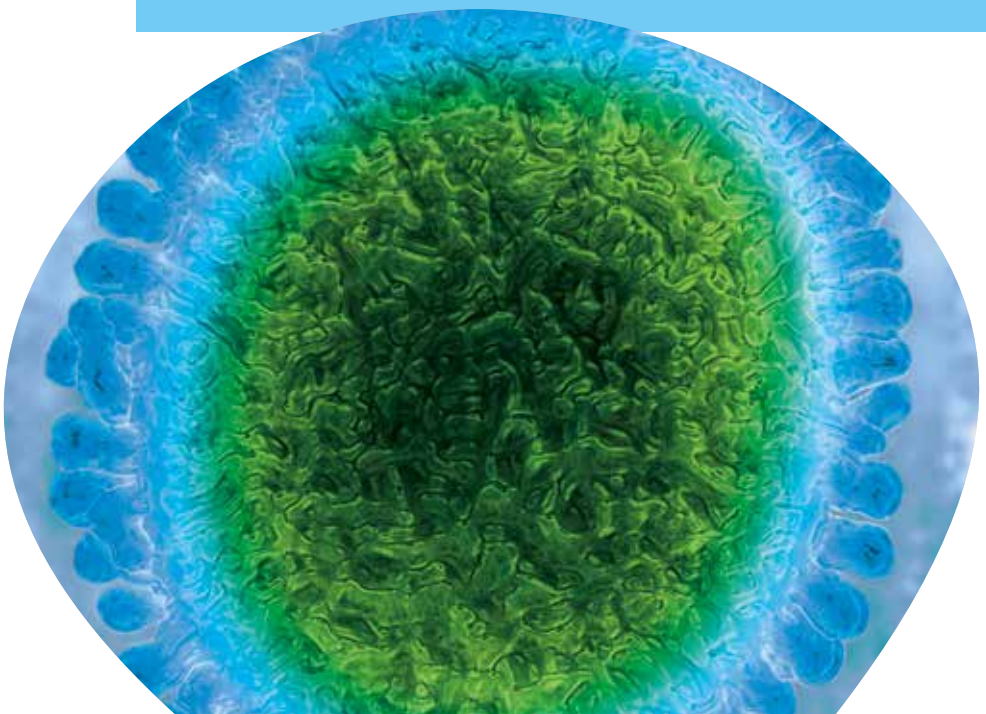
The Society produces and distributes a wide range of resources including videos to support microbiology teaching in schools and colleges.

For more information, see **www.microbiologyonline.org.uk** or contact the **Education Department, Microbiology Society, Charles Darwin House, 12 Roger Street, London WC1N 2JU, UK** (**education@microbiologysociety.org.uk**).



Front cover and right Coloured transmission electron micrograph of an influenza virus particle.