Why have a flu

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Key words
Antibody
Virus
Vaccine
Mutation

The influenza virus is small but its effects can be deadly. Fortunately, vaccines are available to prime the immune system to fight the virus. But how do they work? And if they're so good, why do we need a flu jab every year? Inflammation researcher Louise Kearney, explains

It starts off like a cold — snuffly nose, a cough, sore throat. But then the aches set in — muscle pain, headaches, shivering and fever. This isn't just a cold — it's flu. The tiny virus has made its way into your cells and is wreaking havoc while your immune system tries to fight it off, creating all those nasty symptoms.

The flu virus

The flu virus (see Figure 1) is roughly spherical and its surface is covered in proteins. The two major proteins that help the virus to infect cells are haemagglutinin and neuraminidase. Haemagglutinin binds to target cells, usually in your airway. Once bound, the host cell takes up the virus by a process called endocytosis (see Biological Sciences Review Vol. 22, No. 3, pp. 38–41), where it hijacks the cell's protein-making machinery to replicate itself — producing more copies of the virus.

When the flu virus is inside a cell, it releases its RNA and copies it (see Figure 2). One of the virus' enzymes (an RNA polymerase) runs along the RNA strand and makes a complementary strand. This is similar to the way in which mRNA is produced from our own DNA. Some of the new strands are sent to the host cell's ribosomes where they are translated into protein to coat the new viruses. Other strands of virus RNA are copied and parcelled into the new viruses, ready to be released and replicate inside new host cells. The neuraminidase protein is involved in the release of these new viruses from the infected cell.

Why do you feel ill?

Haemagglutinin and neuraminidase act as **antigens** that the host immune system may recognise and produce **antibodies** against. Infected cells trigger an immune response, and it is your body's response to the infection that makes you feel so ill. You shiver to generate heat, raising your body temperature in an attempt to kill off the virus. This shivering, along with chemicals released by immune cells, can cause the aches and exhaustion common with flu. At the same time, mucus is produced in your airways, which leads to the sore throat, cough and snuffly nose as you try to expel the virus.

The severity of the flu is influenced by many factors, including which haemagglutinin or neuraminidase is present on the virus. So far 17

jab every year?

different types of haemagglutinin and nine different types of neuraminidase have been found on flu viruses, but only a few combinations are known to infect people. These proteins are used to categorise the viruses, leading to the catchy names, such as H5N1 (bird flu) or H1N1 (swine flu), we hear on the news. These names simply mean the virus has an H5 or H1 haemagglutinin and N1 neuraminidase.

Vaccinations

Fortunately, the immune system can be primed to fight off such an infection — using a vaccine. For flu, these vaccines are given to certain groups of people (see Box 1).

Vaccinations target the **adaptive**, '**acquired**' or '**specific**' immune system (see Biological Sciences Review Vol. 22, No. 1, pp. 2–5) to train it to fight off a future infection. A small amount of inactivated flu virus is injected into the arm. This inactivated virus is unable to infect cells and cause damage — so you cannot catch flu from it — but it still has the surface proteins, which are detected by the immune

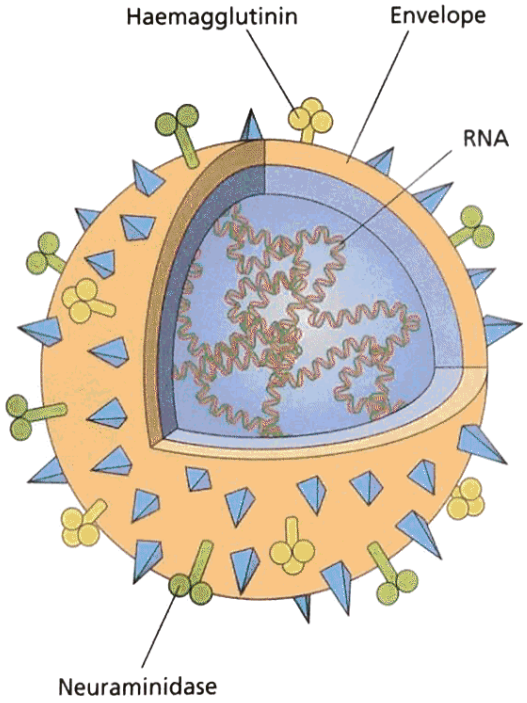

Figure 1 Flu virus. The virus contains RNA in its core, surrounded by a protective envelope. Its surface is coated in proteins

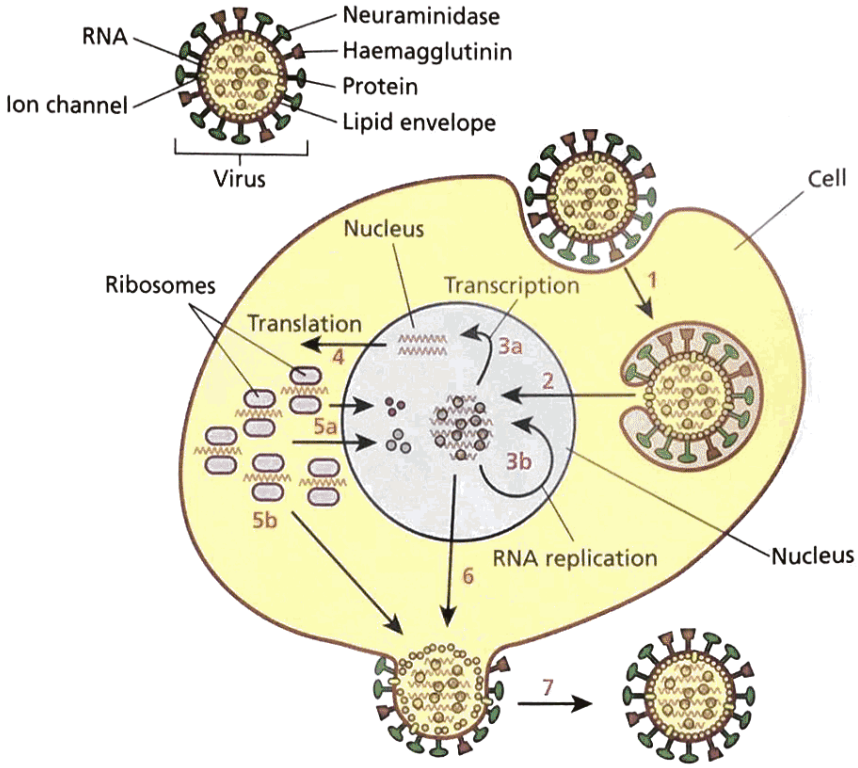

Figure 2 Replication of flu viruses. The virus enters the cell (1) and releases RNA and enzymes (2). Complementary RNA is made (3a) and translated into proteins (4). Some proteins move back to the nucleus to help make more copies (5a) whereas others are sent to the membrane to coat new viruses (5b). Virus RNA is copied (3b) and parcelled into new viruses (6). The new viruses are then released (7)

Terms explained

Acquired/adaptive/specific immunity The arm of the immune system that is specific to pathogens. It involves the production of antibodies and memory cells.

Antigen Short for **anti**body **gen**erator. These are substances (usually proteins or sugars) that are recognised by the immune system.

Antibody Y-shaped protein produced by B cells. Antibodies recognise and bind to foreign objects (antigens).

B cells Vital for the humoral immune response. B cells produce antibodies when activated.

Cell-mediated immune response This response involves killer T cells, which directly attack infected cells. The cell-mediated response does not require antibodies.

Humoral immune response This response includes the production of antibodies, which circulate in bodily fluids (which the ancient Greeks called 'humors').

Memory cells Some T helper cells, killer T cells and B cells become memory cells. Memory cells circulate around the body, ready to respond quickly the next time you are infected.

T cells Key cells in specific immunity. They can direct the adaptive immune response when presented with an antigen (T helper cells) or attack infected host cells (killer T cells).

Box 1 At risk

The NHS offers free flu jabs if you are:

- pregnant
- over 65
- living in a care home
- a carer for an elderly or disabled person
- a healthcare worker with patient contact
- have one of the following medical conditions:
  - chronic lung disease (e.g. asthma, bronchitis)
  - chronic heart disease
  - chronic kidney disease
  - chronic liver disease (e.g. hepatitis)
  - chronic neurological conditions (e.g. Parkinson's disease)
  - diabetes
  - a weakened immune system (e.g. due to HIV/AIDS or chemotherapy)

Flu is particularly harmful during pregnancy or old age because your immune system is weakened, meaning you are more likely to catch the flu and it is likely to be more severe. Flu increases the risk of miscarriage or having a premature baby, and so vaccination is recommended. Similarly, patients with the medical conditions listed are likely to have more severe complications if infected with flu, including an increased risk of developing further lung infections (**www.flu-protect.co.uk**).

Flu vaccinations are also provided for people living in care homes, not just because they tend to be over 65 but because the virus spreads easily in an environment with a lot of people in a small area. While care workers may be fit and healthy, they work closely with people who may be severely affected by flu and they can become carriers of the virus, passing it on to patients. Healthcare workers are often depended upon, so it can be disruptive for them to be ill with flu and unable to do their jobs.

system. The immune system responds as if the virus was active, and attacks it accordingly (see Figure 3).

Immune response

The antigens are presented to helper **T cells**, which then direct the **humoral** and **cell-mediated** immune responses.

The humoral response is driven by **B cells**. Once a B cell is activated by a signal from a helper T cell or by binding to an antigen, it is stimulated to differentiate into plasma B cells. Plasma B cells produce antibodies specific to the virus detected. These Y-shaped proteins are released into the blood or lymph circulation. Each B cell will make only one type of antibody and is therefore specific to the virus or bacterium to which it will respond. The circulating antibodies will bind to the antigens on the virus and make it an easier target for destruction.

The cell-mediated response requires killer T cells, which are also activated by the helper T cells. Killer

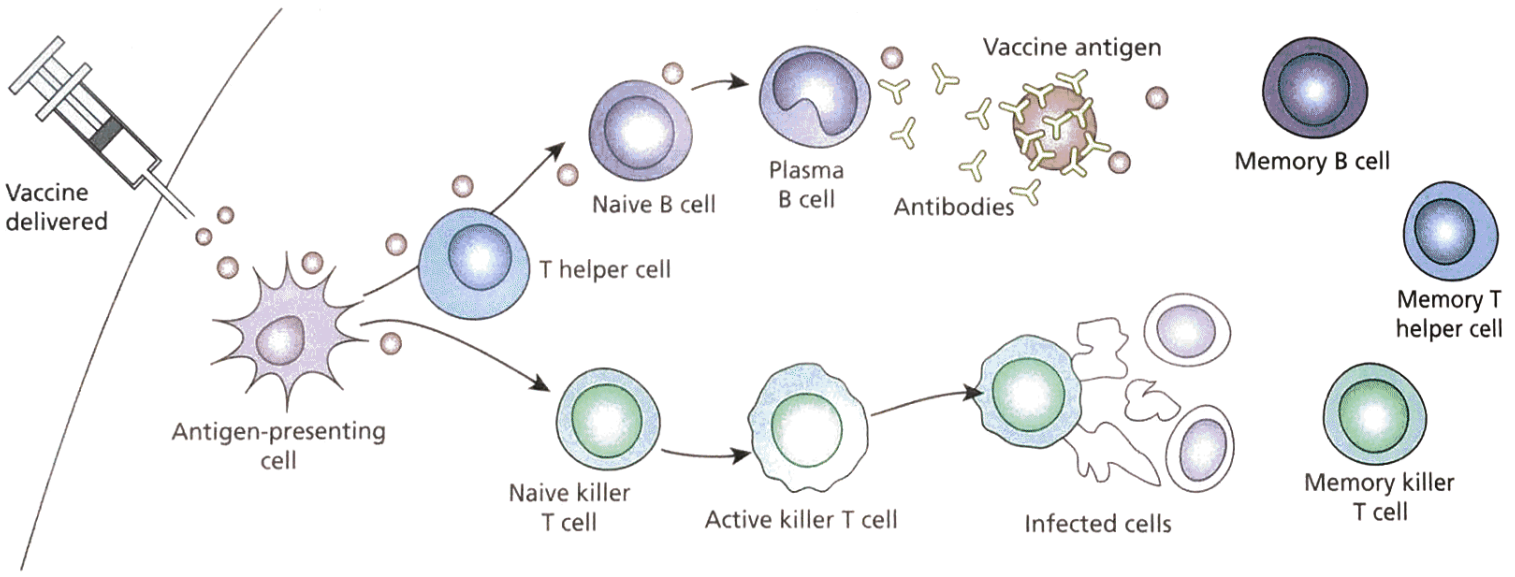

Figure 3 How vaccines work. A vaccine stimulates the immune system to respond as if the host were being infected. This leads to the production of memory cells that will reduce the severity of future attacks, because the body is already primed to respond quickly to that antigen

T cells attack infected host cells, killing them before the virus can be released and infect other cells.

Memory cells

Once the virus has been successfully destroyed, most of the helper T cells, killer T cells and plasma B cells die. Some, however, remain as **memory cells**. These memory cells enable a stronger and faster response the next time the virus is encountered, reducing the severity of future infections. The production of memory cells is the ultimate aim of vaccination, and the same principle underlies the TB jab for tuberculosis, the HPV vaccine for human papillomavirus (see Biological Sciences Review Vol. 12, No. 2, pp. 8–10) and the MMR for measles, mumps and rubella. But why then do pharmacies advertise the flu jab every year?

Mutations

The main reason is that the flu virus mutates at a very high rate. Mutations in the genes coding for the haemagglutinin and neuraminidase proteins can cause subtle differences in their amino acid sequences. The differences arise from errors when the virus replicates. Every time the RNA is transcribed, there is a chance of a mistake occurring.

RNA consists of four bases: guanine (G), adenine (A), cytosine (C) and uracil (U). For flu, there is an error in replication roughly every 10 000 bases — about the size of the flu virus RNA. This means that every time a flu virus replicates, there is likely to be a mutation. If the mutation results in a change to the code for an amino acid, then this mutation will result in a change in the coded protein's amino acid sequence.

The shape and structure of proteins depends on their amino acid sequences. If the mutations occur in an antigen, such as haemagglutinin or neuraminidase, their shape may become different enough that the host immune system no longer recognises it. As far as the host's immune system is concerned it is then effectively a new virus and new memory cells must be produced.

Predicting flu strains

As if that wasn't bad enough, if you are infected with two strains of flu at the same time, RNA from each strain can be parcelled into the same new viruses. This combination produces a strain of flu with elements of both parent strains. This can cause large changes in the antigens expressed and help the new virus evade detection.

It also makes it difficult to predict which combination to use in the vaccination, as the main strains differ from year to year. Every year the World Health Organization tries to predict the most common strains for that flu season by monitoring infections and analysing which strains are causing illness and how quickly they are spreading. Pharmaceutical companies can then mass-produce the appropriate vaccines.

The high mutation rates in the flu virus make it difficult to eradicate entirely, although scientists are currently researching ways to target other viral proteins that do not change as rapidly as the haemagglutinin and neuraminidase proteins. This will make the memory cells respond to a greater variety of flu strains and potentially reduce the frequency of vaccinations. Until then though, it looks like it's an injection every year!

Topic for discussion: ethical research?

In 2011, two groups of researchers independently created mutant strains of the H5N1 (bird flu) virus that could be transmitted between mammals — 'super-flu'. The work was partially published in the journals *Nature* and *Science*, but some elements were censored to prevent reproduction of the work. The projects were shut down while the scientific community debated not only whether research with such lethal potential was ethical, but also whether censorship of the results was the right approach.

- Debate: We should publish all data/We should censor science.
- Debate: Genetically modified virus research is unethical/ethical.

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Further reading

A step-by-step animation of how vaccines programme the immune response, with a test-yourself quiz at the end:
www.historyofvaccines.org/content/how-vaccines-work

A step-by-step animation illustrating how vaccines are made:
www.historyofvaccines.org/content/how-vaccines-are-made

An explanation of the 'at risk' groups in more detail, and why protection from flu is particularly important for them:
www.flu-protect.co.uk/patient/flu-risk-groups

More information about the H5N1 mutant flu virus research and controversy:
www.nature.com/news/specials/mutantflu/index.html

Key points

- Vaccines work by training the adaptive immune system.
- An inactive (dead) virus is injected, which is detected by the immune system.
- The antigens (proteins on the virus's surface) are presented to T helper cells.
- T helper cells instruct B cells to divide and make antibodies for that virus (humoral response).
- T helper cells also instruct killer T cells to attack infected host cells (cell-mediated response).
- Once the virus is destroyed, some cells remain as memory cells.
- These cells are ready to fight off the virus the next time you are infected, generating a larger and faster immune response.