frontiers FOR YOUNG MINDS

HEALTH
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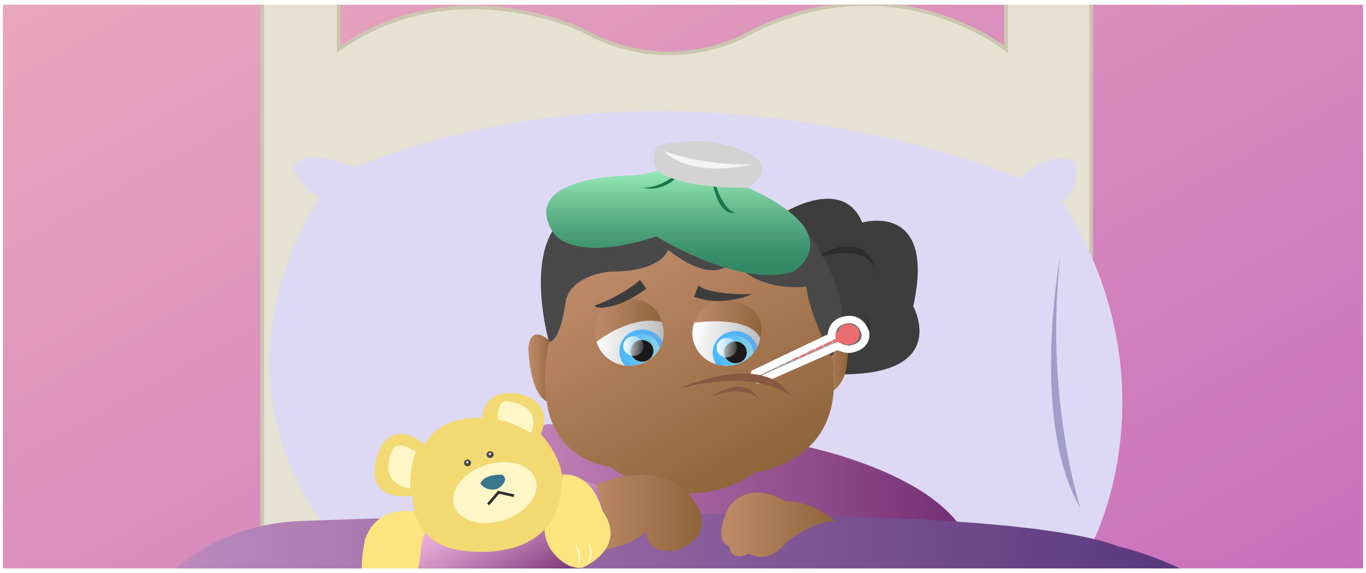

FLU, FLU VACCINES, AND WHY WE NEED TO DO BETTER

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14–15 YEARS OLD

Influenza (or flu) is a huge global problem, one billion people—1/7th of the world's population get infected with it each year. The virus does not only infect people it also infects many different animals including chickens and pigs and can have devastating effects on farms where these animals are raised. Our body has evolved ways (called the immune response) to kill the influenza virus if we are infected with it and to stop us getting reinfected with the same virus. Through the power of vaccines, we can harness the immune response to protect us against influenza. The problem with the influenza virus is that it is sneaky and can change its coat, so our body does not recognize it. Current research is looking at ways to overcome this sneaky virus and reduces the number of people who get sick from influenza.

YUCK, I HAVE GOT THE FLU

INFLUENZA

The virus that causes the flu.

VIRUS

A living thing that has to use other living things to replicate. Invading other cells to make copies of itself.

The flu, an illness caused by the **influenza virus**, ranges from mild to deadly. The illness you get after being infected with flu is particularly bad if you are very young or very old. Each year one billion people, or one in every seven people on earth, will get infected with flu and some years the numbers are higher. In the last 100 years, there have been four major outbreaks (called pandemics) of influenza in 1918, 1956, and 1976, with another more recently in 2009. To put it into context, the 1918 "Spanish flu" pandemic killed 5 to 10 times more people than the entire First World War (10 million people died in the First World War; the 1918 flu killed 50–100 million people). The likelihood that another flu pandemic will occur in your lifetime is extremely high and this is something we scientists are trying to stop.

THE FLU VIRUS

Did you know that, in addition to humans, flu can also infect chickens, pigs, dogs, ducks, cats, geese, camels, ferrets, horses, seals, and whales? Broadly speaking, viruses are made of two things, **proteins** and nucleic acids (nucleic acids are the stuff that **genes** are made of). The proteins make a coat around the genes and this coat protects them from the environment and helps the virus to infect **cells**. There are multiple types of flu virus and we categorize these types based on the two proteins that appear on the surface of the virus (Figure 1). These two proteins are called hemagglutinin and neuraminidase. These proteins are assigned a number based on their specific shape, giving us many combinations, for example H1N1 or H5N1. These different combinations of proteins on the surface of the flu virus have an important impact on which animal species the flu virus infects. For example, there is a chicken virus (H5N8) causing infections in bird populations in Europe in 2017, but this virus is unlikely to cause illness in people. This is because human lungs and chicken lungs are covered in different types of a sugar molecule, called sialic acid, and bird flu viruses like to bind one type of sialic acid while human flu viruses bind a different type.

The differences in the proteins on the surface of the flu virus also change the way the body recognizes the virus. These proteins also have an impact on how **vaccines** work, influence disease severity (how "bad" the disease is), and affect the speed with which the virus can spread from one individual to another.

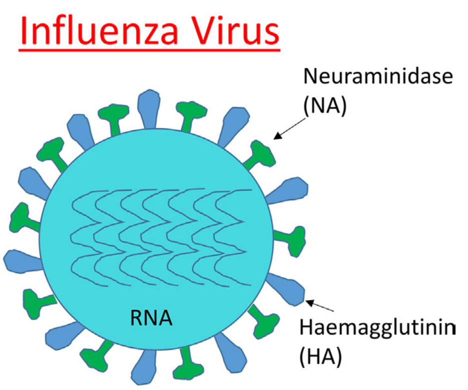

FIGURE 1

PROTEIN

The building blocks of the body. Made of individual units they can perform a range of functions from making hair molecules to recognizing viruses.

GENE

The unit of inheritance. Made of nucleic acid and carry the information that makes you–you and a duck a duck.

CELL

The basic unit of any living thing. Often combine together to make up a person or a duck.

VACCINE

A weakened form of the virus injected into the body so your immune system has time to make a protective memory, so that when it gets infected for real you do not get sick.

FIGURE 1

The influenza virus. Like all living things, influenza has genes. When it is reproducing, the virus makes copies of its genes, but not all the copies are identical to the original, this contributes to influenza's ability to change dramatically and can lead to pandemics. The virus surface has two proteins on display: hemagglutinin (HA) and neuraminidase (NA). The ways in which these proteins combine contribute to the name of the virus, for example H1N1.

But in order to understand how these proteins affect these behaviors of the flu virus, a few other things need explaining.

STEALING FROM US

A feature of all living things is their ability to replicate (make copies of themselves). The cells that make up your body are constantly making copies of themselves to replace the ones that get washed, scratched, or rubbed away. Replication is a carefully controlled process and requires an instruction book in each cell that is written in a chemical called DNA. The instructions in the DNA are called genes. Viruses, including influenza, lack the genes that allow them to make copies of themselves the way cells do, so instead they have to hijack the copying machinery of the cells they infect. Because this is the only way they can grow, viruses are described as obligate parasites—meaning they *have* to steal from other cells to survive. Influenza infects the cells lining the nose and lungs. These cells are called the respiratory epithelia. Flu sneaks into the respiratory epithelia and then from there, like a pirate sneaking onto a ship, it takes over the processes that the cells would normally use to make copies of themselves and uses these processes to make new viruses that can go on to infect other cells. Some viruses are so good at hijacking cells that they can kill you because they turn your body into an enormous virus factory so it is no longer able to function normally.

WHY DO I FEEL THIS WAY?

There are two reasons why you feel sick when you are infected with the flu virus.

1. The virus is stealing energy and resources from your body and often, in the process, the viruses kill the cells that they have infected so that they can escape from those cells to cause more infections elsewhere.
2. The infection triggers the body's defense mechanism—called the **immune response**. Many of the symptoms we associate with having flu are necessary but uncomfortable side effects of the body fighting the virus. These things include:
   a. Snot (the technical term is goblet cell hyperplasia), which sweeps any dirt and viruses out of the nose and lungs.
   b. Temperature (or fever). The viruses that infect us grow best at our normal body temperature of 37°C, so by raising the heat when we have a fever, the body is attempting to cook the viruses and kill them.
   c. Swollen glands and tonsillitis. The cells of the immune system hang out in specialized organs called lymph nodes. In the lymph nodes, the immune cells meet, talk to each other, and get activated to fight the invaders. In order to fight the invading virus, our body needs to increase the number of immune cells in the system, so these immune cells replicate in the lymph nodes and tonsils and it is this replication that we feel as swollen glands or tonsillitis.

IMMUNE RESPONSE

How the body fights off invading viruses. Can tell which cells are yours and which cells are the virus.

FIGHT THE GOOD FIGHT

The immune response serves one purpose: to spot when we are infected and to remove the infection. All living things, including bacteria, plants, fruit flies, eels, and humans, have some kind of immune system. As the organism gets bigger and more complex, so does the immune system. The major problem the immune system faces is telling what is good from what is bad. The fact that viruses kill your cells raise the alarm to the immune system, telling it that something is not right. This alarm then triggers a series of events that enable the body to fight off the infection. Our bodies have evolved a number of clever tricks (Figure 2) to outsmart viruses:

1. ***Interferons***: luckily for you, your body is able to see when there are viruses in its cells. In response to these viruses, the body makes chemicals that tell the cells to be on the lookout for more viruses and to stop making baby viruses. These chemicals are called interferons because they interfere with the viruses' ability to grow. Going back to the idea that your cells are tiny factories that the viruses have hijacked to make copies of themselves, interferons are signals from the body telling the factories to stop working, which stop the cells from making more copies of the virus. The interferons also alert the body that it is infected, triggering the body's defense mechanisms described above: snot, fever, and swollen glands.
2. *Innate immune response*: the body has some specialized immune cells that are able to kill viruses. These cells either gobble up the virus (cells called macrophages do this) or they find cells with virus in them and kill those infected cells (cells that do this are called natural killer cells), or they kill the virus floating in the blood (cells called neutrophils do this). These three cell types are the early responders—they reach infected tissues within 8–12 h after infection starts and they act to contain the infection.
3. *Adaptive immune response*: there is then a later wave of specialized immune cells that focus the response to the particular virus that is causing the infection. These cells recognize a very specific aspect of the flu virus and

INTERFERON

Part of the immune response. Chemical signals from the body that warn it to watch out for viral infection.

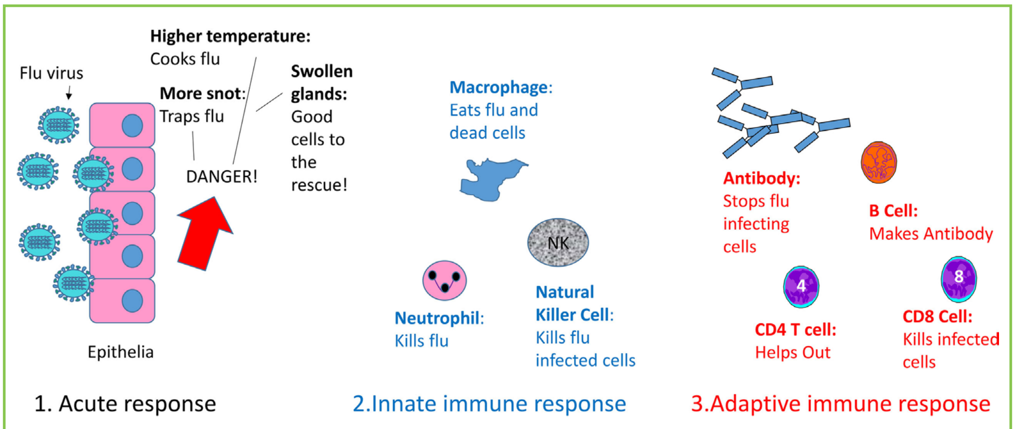

FIGURE 2

FIGURE 2

The immune response to influenza virus. There are three stages to the way the body fights of influenza infections. (1) The interferon response: the body has a rapid reaction to any kind of infection. It produces a protein called interferon that alerts the immune system that there is a virus around and gets the body ready for the fight. (2) The innate immune response: this is made up of cells that fight the viral infection, for example, macrophages that eat the virus and natural killer cells that kill the infected cells. (3) The adaptive immune response: this is the final removal of the virus from the body and leads to memory that prevents infection with the same virus in the future.

ANTIBODY

Part of the immune response. Recognize foreign chemicals and bind to them to stop infection.

T CELL

Part of the immune response. They go around the body hunting for infected cells.

IMMUNE MEMORY

How the body stops you getting infected with the same virus twice.

help to remove any remaining virus from the body. The cells involved in the adaptive immune response are called B cells, which make **antibodies** (see below), and **T cells**, which are split into CD4 cells (that help the body fight viruses) and CD8 cells (that kill cells which contain virus.) These slower-acting cells not only work to get rid of your infection but also they stop you from getting the same infection again in the future.

HAPPY MEMORIES

Having fought off the infection, the body has a neat trick to stop us from getting infected again with the same viruses. It remembers what the viruses it has seen before look like and it responds faster and stronger the next time it sees the same viruses. This process is called **immune memory** and it explains the way vaccines work. By giving someone a flu shot, we help the body to make an immune memory response, without that person going through the pain of the actual infection. There are two key parts of immune memory that protect us from future infections. These are called antibodies and T cells.

ANTIBODIES

Antibodies are amazing. They are the homing missiles of the immune system. Antibodies are so good at recognizing the shapes of proteins that they can be used to tell if you are pregnant, they can cure cancer, stop arthritis, and much more besides. Antibodies are shaped a bit like a capital Y, with two arms that recognize things and a tail that has other important functions.

T CELLS

T cells are tremendous. They are the sniffer dogs of the immune system. They go around the body hunting for infected cells. When they find cells with viruses in them, they kill those cells in a structured way—bit like when a chimney is demolished.

Speaking of vaccines, they are one of the most effective ways of reducing the number of infections. Between 1993 and 2013, 322 million illnesses and 732,000 deaths were prevented, thanks to vaccines (based on figures from the Centers for Disease Control in the USA). There are diseases that were once widespread, but because of vaccines you will never encounter them, for example polio. Even more amazing, one disease—smallpox—has been completely wiped out, meaning that no one will ever get infected with smallpox again, all thanks to vaccines. And we have vaccines against flu too.

EASY PEASY

So if vaccines are so good, why do you need to get the flu vaccine every year? Because flu is sneaky! The big problem is that flu mutates, meaning that it changes the proteins on its surface, to hide from the immune system. Here is how this happens: to replicate, a cell has to make copies of its entire instruction book (genes) so that the new cells can then go on to make more copies of themselves in the future. The process of replicating genes is a bit like using a photocopier but imagine using a photocopier to make a copy of the copy time after time; over time the quality of the copies will decline and be less readable. This happens with genes, too. The mistakes in the DNA copies are called mutations. Our bodies have ways of checking the copies to make sure they are ok (this is called proofreading). If a faulty copy is made, it is usually deleted. However, the influenza virus is not good at checking the copies it makes of itself, this means that viruses can change quickly. This leads to the emergence of new viruses with new coats each year, which is why we need a new flu vaccine every year.

1 YEAR ONLY

All of this means that the flu vaccine does work, really well, but for 1 year only. When the sneaky flu changes its coat, our immune systems fail to recognize it. It is a bit like failing to recognize someone because they had a haircut and bought a new coat. The need to replace the flu vaccine year after year is where my scientific research comes in. We are one of many groups looking to develop a universal flu vaccine—a vaccine that you have once and then never need again. We have recently shown that if a vaccine can increase the numbers one of the types of T cells (CD8 T cells) then when you are infected by the virus you are sick for a shorter amount of time [1]. We are now investigating further how to get these virus-killing T cells into your lungs so that they are ready and waiting in case flu infects you.

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We are a second class of a High School in Naples, Italy. Our school is deeply oriented towards technical and scientific subjects for which English obviously plays a key role.

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I work at Imperial College London, in the UK. I find a broad range of biological sciences fascinating—especially anything to do with infection: how bugs make us sick, how the body gets us well again, and how we can stop the bugs and help the body. I spend most of my time researching and teaching about viral infections in the lung. In addition to developing new vaccines for influenza (flu) and respiratory syncytial virus (RSV), I am investigating how the immune system protects us against these infections. *john.tregoning@imperial.ac.uk