

IMMUNE SYSTEM

BigPicture

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BRINGING CUTTING-EDGE SCIENCE INTO THE CLASSROOM

A free
resource for
teachers and
learners

ALL SYSTEMS GO!

*Inside your hard-working
immune system*

wellcome trust

BigPicture

The immune system is what keeps us healthy in spite of the many organisms and substances that can do us harm. In this issue, explore how our bodies are designed to prevent potentially harmful objects from getting inside, and what happens when bacteria, viruses, fungi or other foreign organisms or substances breach these barriers.

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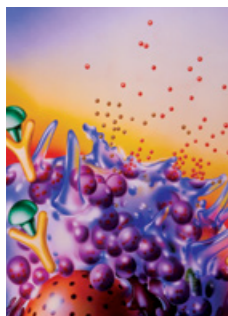
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ONLINE

All of the resources for this issue – and plenty more – can be found online at bigpictureeducation.com

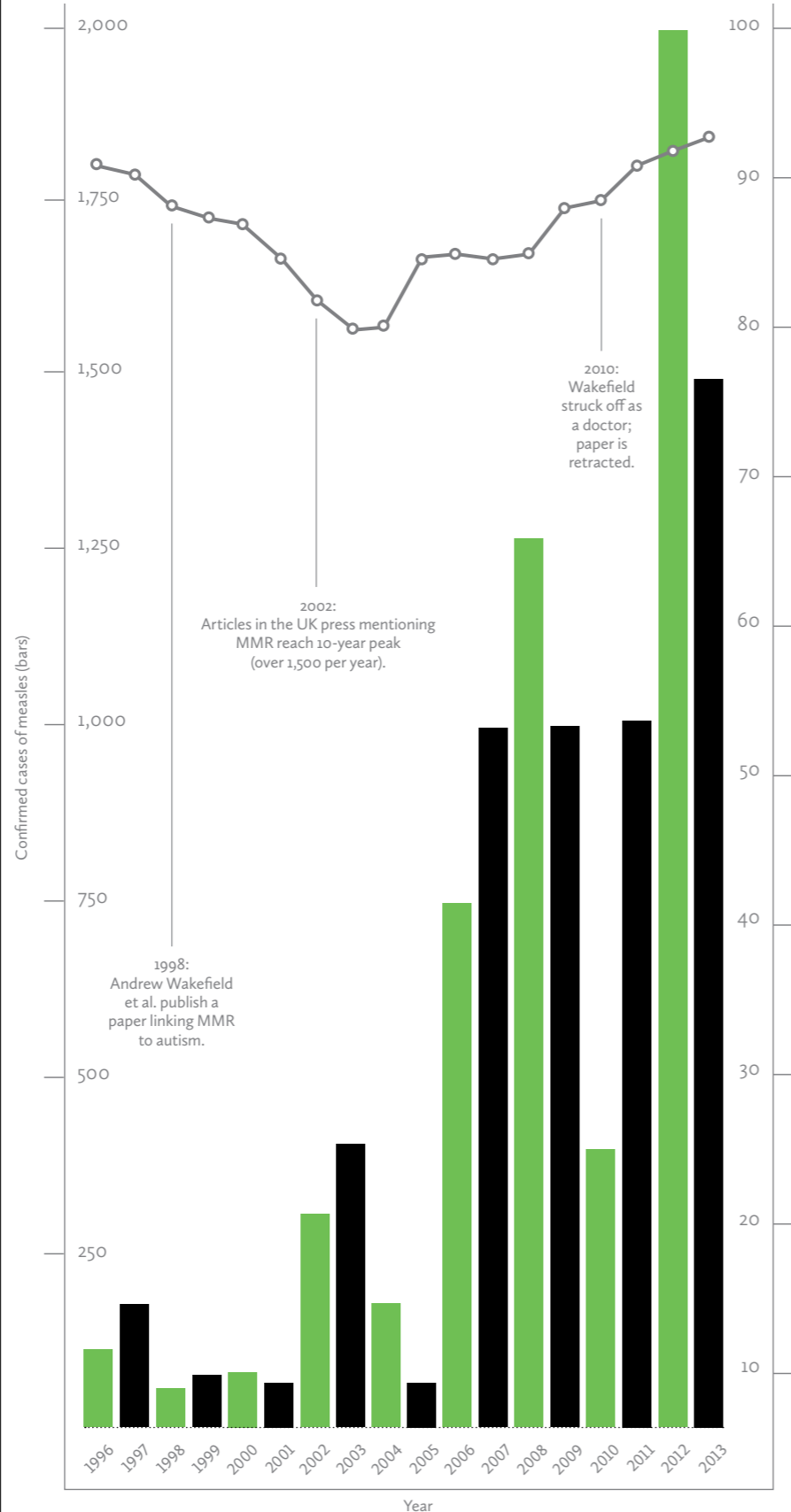


Cover: Artwork showing mast cells during an allergic response. John Barosi/Science Photo Library

IMMUNE SYSTEM BY NUMBERS

A snapshot of immunity and allergy

MEASLES CASES AND MMR VACCINE COVERAGE IN ENGLAND



MMR: the combined measles, mumps and rubella vaccine

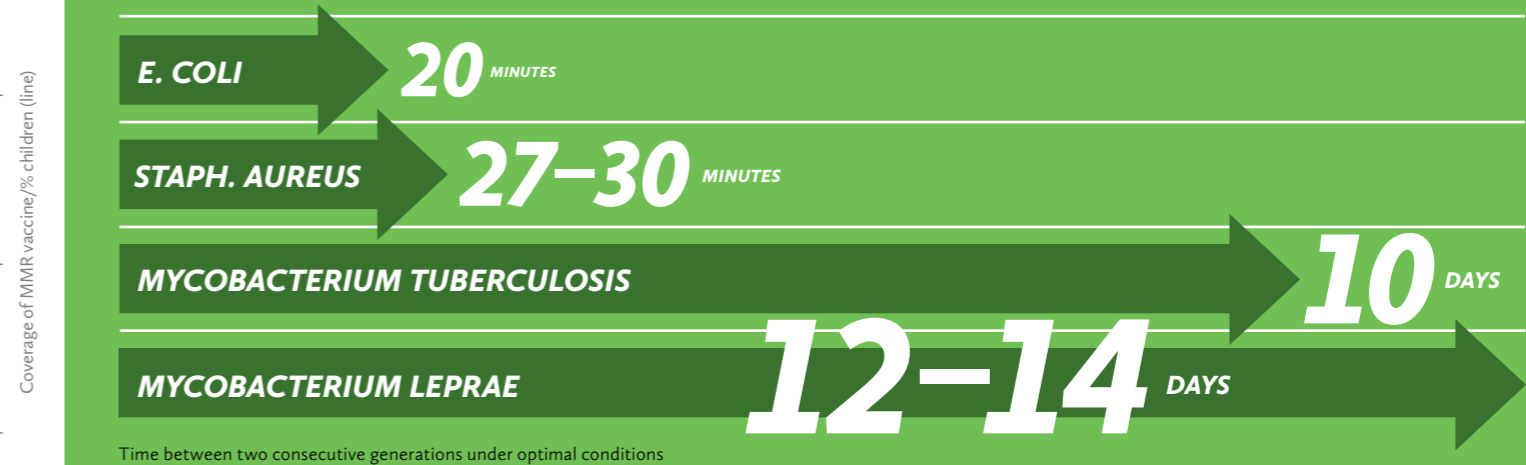
ASTHMA ACROSS THE WORLD



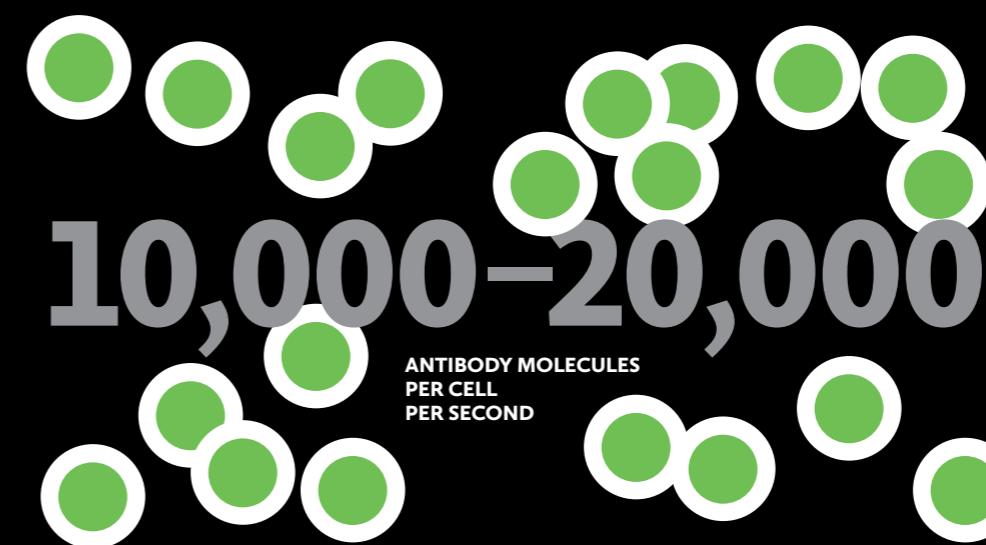
COMMON ALLERGENS



GENERATION TIMES OF DIFFERENT BACTERIA



PRODUCTION OF ANTIBODIES BY B CELLS



FINDING DATA

Putting this diagram together, we found that different sources gave different numbers for the same thing. Why don't they match? Well, data can be interpreted in different ways, and estimates can be made using different methods and/or baseline data. Which should you choose? The source itself is important – is it reliable? How valid is the original study? Are the figures recent? How might an organisation's 'agenda' affect how it calculates and presents data?

For sources and questions, see bigpictureeducation.com/immune

WHAT'S IT ALL ABOUT?

The immune system helps a living thing defend itself against infectious organisms and other foreign substances.

All **BOLDED** terms are defined in our online glossary: bigpictureeducation.com/glossary

STAYING ALIVE

What's the immune system for?

Every day, your body could succumb to hundreds of different infections or harmful substances. It is constantly under attack from microbes, parasites and other threats. The only reason you're not sick all the time – and probably the only reason you're alive today – is that your **IMMUNE SYSTEM** deals with these assaults. It does so through processes and structures that try to prevent invasion, but it can also fight off an infection or disease that tries to take hold.

Vertebrates, including humans, have very sophisticated immune systems that adapt during a lifetime to take account

of specific organisms and substances that enter the body. Most other animals and plants have immune systems too, even if they look different from ours. Both plants and animals have **RECEPTORS** on their cells that can recognise invading microbes. Plants, however, don't have patrolling immune cells like we do, so infection has to be dealt with by ordinary cells at the site of infection. And even some of the organisms that attack us have their own immune systems. For example, we're only just beginning to understand those found in **BACTERIA**.

KNOW THYSELF

How does the immune system know you're you?

Would you be able to tell one of your own cells from someone else's, or from a bacterial cell? Perhaps not. But your **IMMUNE SYSTEM** can distinguish **SELF** from **NON-SELF**. If it couldn't, its attempts to deal with foreign substances would be directed at your own cells.

Among the many different **PROTEINS** found on the cell surface are the **MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)** proteins. MHC proteins indicate that your cells are self and should be left alone. Apart from identical twins, we each have our own unique set of MHC proteins. Even a mother and her baby do not share the same ones. Scientists recently discovered that, during pregnancy, certain signals that recruit immune

cells are turned off in part of the placenta, helping to prevent the mother's body from attacking her child.

The recognition of non-self markers, known as **ANTIGENS**, on foreign materials triggers a response from the **NON-SPECIFIC (INNATE) IMMUNE SYSTEM**. Pieces of these materials are presented to cells of the **SPECIFIC (ADAPTIVE) IMMUNE SYSTEM**, and a more focused, long-lasting form of immunity is developed, in the form of **ANTIBODIES** that can recognise the antigens in the future (see page 8, 'Present and correct', for more).

For more on the immune response, see our full-colour poster.

DEFENCES DOWN

Different factors can suppress our immune systems

Not everyone has a perfectly functioning **IMMUNE SYSTEM**. Many people, at some point in life, find that their immune system is weakened by disease or ageing. Some people are born with inherited disorders that affect their ability to fight disease. Some acquire infections, like HIV (human immunodeficiency virus), that suppress their immune systems. In HIV, immune cells called **HELPER T CELLS** are destroyed, impairing the body's ability to fight ordinary infections like colds and flu. Certain cancers can suppress the immune system, and so can cancer treatments, especially chemotherapy.

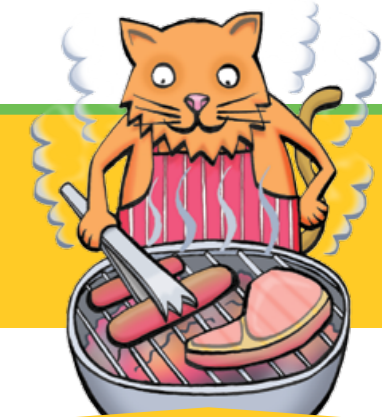
Recent reports from the USA suggest that fasting could help the immune system regenerate in people being given chemotherapy for cancer. There are also experimental drugs as well as supplements, smoothies, herbs and teas that manufacturers claim will provide an immune boost. However, scientists remain sceptical about such remedies when the evidence is weak and there is money to be made by selling them. We do know, though, that staying healthy – getting enough sleep, eating a balanced diet, exercising and avoiding stress – helps to support your immune system.



A human MHC II protein with influenza peptide. Protein Data Bank

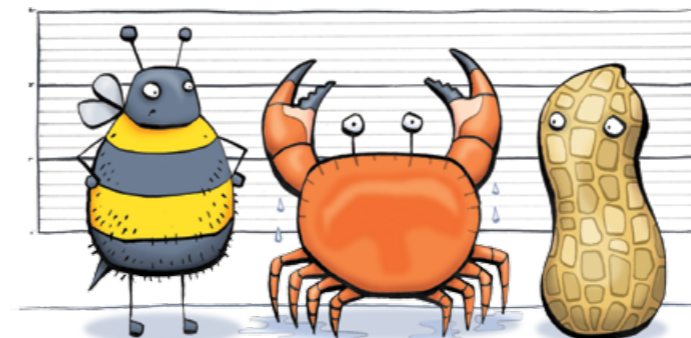
FAST FACT

An antibody can react against different antigens if part of the protein target on each antigen is similar. For example, people sensitised to cats are frequently also allergic to pork.
Source: rockymountainallergy.com/wp-content/uploads/2014/05/Food-Allergy-Update-JACI-Feb-2014.pdf



MEASURED RESPONSES

The immune system can overreact



The **IMMUNE SYSTEM** does not always behave as we would like it to. **AUTOIMMUNE** disease occurs when the immune system has trouble telling **SELF** from **NON-SELF**. In rheumatoid arthritis, for example, immune cells attack cells in the patient's own joints, causing pain and **INFLAMMATION**.

Allergies are caused by overreactions to foreign **PROTEINS** known as **ALLERGENS**. For example, in hay fever, the immune system reacts to wind-blown pollens from grasses, weeds and trees, and makes **ANTIBODIES** against them. Immune cells called **MAST CELLS** have antibodies attached to their surface, and when these bind to their specific allergens they trigger an immune response.

This response includes the release of chemicals, including **HISTAMINE**,

which are responsible for many of the symptoms of allergy. Histamine causes inflammation, drawing fluid into the affected zone and, in the case of hay fever, out of the nose. Hence the snotty mess and the antihistamine tablets. Meanwhile, in asthma, which is mainly thought of as an inflammatory disease, these chemicals may also make the muscles in the airways contract, causing breathlessness and wheezing.

Anaphylaxis is a severe and potentially fatal allergic reaction that affects the whole body, often just minutes after exposure to an allergen. It can be caused by many things, including peanuts, shellfish, eggs, bee or wasp stings, and drugs. Anaphylaxis can be fatal. People at risk often carry pen-like injectors that contain adrenaline to use in an emergency.

THAT'S DISGUSTING!

Disgust helps protect us from disease and illness

Why do we wince at the sight of wounds and recoil from rotting fruit? Is it that we're taught to avoid the sorts of things that might harbour microbes? Or is disgust more instinctive than that? The origin and purpose of disgust is still debated by psychologists. Some argue that it is a learned response while others think it is a result of millions of years of evolution. Whatever its origin, it certainly serves an important purpose: helping to protect us from disease. The fact that you are disgusted by the smell of rotten meat means that you are very unlikely to touch it or swallow it, and so your chances of getting ill are reduced. Food, however, forms an interesting part of the debate. While most people may agree that, say, vomit and faeces are disgusting, what is unappetising to eat differs across the world.

See online for our related activity – designing a poster for poo transplants.

A TALE OF TWO DISEASES

The immune system is involved in both types of diabetes

Type 1 (juvenile) diabetes: An **AUTOIMMUNE** disease in which the **IMMUNE SYSTEM** attacks the beta cells in the pancreas that produce the hormone **INSULIN**. In healthy people, naturally produced insulin controls the level of glucose in their blood, whereas people with type 1 diabetes have to inject themselves regularly with insulin to control their blood glucose levels. Extremely high or low blood glucose can be fatal.

Type 2 diabetes: Usually develops later in life, if the body becomes resistant to insulin. Eventually, tablets may be needed to control



blood glucose levels. Traditionally, type 2 diabetes has not been thought of as an immune disease. However, it is increasingly being linked to **INFLAMMATION**, a key immune response. High levels of the chemicals that cause inflammation have been measured in people with type 2 diabetes. Very recently, Danish researchers found that immune cells called **MACROPHAGES** are involved in an inflammatory response that leads to the death of pancreatic beta cells during the early stages of the disease.

INVASION AND INFECTION

There are many ways the body tries to prevent harmful substances from outside getting in. But if a pathogen does breach our defences, the non-specific immune system will respond.

KNOW YOUR ENEMY

Our bodies are homes to millions of organisms

Millions of microbes have made your body their habitat and most of them will never do you any harm. However, some can be pathogenic, which means that they cause disease. Human **PATHOGENS** include some **BACTERIA**, **VIRUSES** and **FUNGI**, as well as parasites such as tapeworms and flukes, and protozoa like *Plasmodium*, which causes malaria.

Some microbes can be good for us. It's known that the gut microbiota, the bacteria in our gastrointestinal tract, exist in a **MUTUALISTIC** relationship with us – one where both parties benefit. But it's not clear how the **IMMUNE SYSTEM** views these cells. Recent studies suggest that newly discovered populations of immune cells may help train the immune system to tolerate beneficial bacteria.

EUKARYOTES	PROKARYOTES	VIRUSES
Include: animals, plants, fungi	Include: bacteria and cyanobacteria	Do not fit many of the criteria for life
Often, but not always, multicellular	Always single-celled	No cells, just virus particles called virions (RNA or DNA inside a protein coat)
Cells use mitochondria to release energy	No mitochondria	No mitochondria
Some multicellular eukaryotes have sophisticated circulatory, nervous and immune systems	Basic immune responses	No immune system
Sexual or asexual reproduction	Usually, but not always, asexual reproduction	Viral replication by taking over a host cell

WAYS IN

Barriers help protect our insides from outside

One organ acts as your largest and perhaps most important barrier against infection. Spread out on the ground, it would cover two square metres: your skin. It's tough – skin cells are packed full of strong structural **PROTEINS** called keratins, which act as a barrier. As the cells grow outwards, they die. The stratum corneum

– the outermost layer of the epidermis, which is the outermost layer of the skin – is completely dead. **VIRUSES** can't replicate in dead cells. Microbes are often outcompeted by **BACTERIA** that live on our skin in a **MUTUALISTIC** relationship with us.

Inside our bodies, sticky mucous membranes line our airways and guts, as well as the tracts in our urinary and reproductive systems. These need to be protected because they are constantly exposed to microbes – for example, in the air we breathe and the food

we eat. Mucus traps and destroys microbes by deploying **ENZYMES** such as lysozyme, which breaks down bacterial cell walls. Cells in the stomach lining secrete hydrochloric acid, creating an acidic environment too inhospitable for many bacteria. However some bacteria, such as *Helicobacter pylori*, which cause stomach ulcers, have adapted their defences. These bacteria produce an enzyme called urease, which uses urea from human tissues to make ammonia – an alkaline chemical that neutralises the acid.

If something goes wrong with these barriers, we become more susceptible to disease. For instance, some people have genetic mutations that affect a protein in the skin called filaggrin. Filaggrin plays an important role in strengthening the skin, by helping organise the keratin filaments in skin cells and also by moisturising the skin. Filaggrin mutations weaken the skin barrier, allowing **ALLERGENS** to enter through it. This leads to some cases of eczema, asthma and hay fever.

GOING VIRAL

How diseases spread

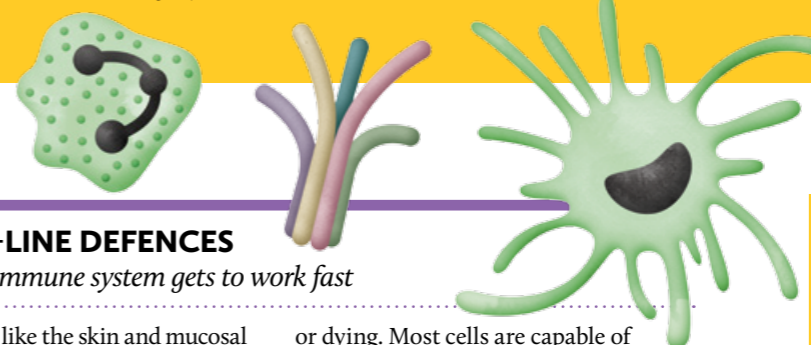
Disease spreads when the body's defensive barriers are breached. **BACTERIA** or **VIRUSES** might be transmitted directly through contact with infected bodily fluids such as blood, saliva or semen. Some viruses, like influenza, survive just long enough in saliva and nasal secretions that they can be transferred by a sneeze, whereas HIV can't, and is usually spread through sex or the sharing of needles used to inject drugs. Infectious agents can also be transmitted indirectly by other organisms – so-called vectors like the female *Anopheles* mosquito that carries the malaria

parasite. The death toll of malaria (over 620,000 people globally in 2012) has led to the mosquito being described as the world's most dangerous animal.

Not all diseases cause symptoms straight away, meaning that there may be a window for potentially spreading the infection without realising. This 'incubation period', the time between infection and symptoms starting to show, varies between infections: it is a few days for flu, but a few weeks, months or even longer for HIV.

FAST FACT

Reptiles have versatile non-specific immune systems. Compounds from alligator blood are being investigated as potential antibacterial and antifungal treatments. Source: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078517/>



SECOND-LINE DEFENCES

The innate immune system gets to work fast

Once barriers like the skin and mucosal membranes are breached, the **IMMUNE SYSTEM**'s second line of defence against invading **PATHOGENS** is its **NON-SPECIFIC (INNATE) RESPONSE**. This response is rapid, short-lived and generic, and it lacks any memory of previous infections. Through pattern recognition **RECEPTORS**, cells involved in the innate response can recognise pathogens like **BACTERIA** and **VIRUSES** but can't distinguish between, say, the viruses that cause measles and flu. Important components of innate immunity include:

NATURAL KILLER CELLS: True to their name, natural killer (NK) cells' natural inclination is to kill everything they meet. What stops them is the recognition of **SELF** markers – **MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)** proteins – on the surface of the cells they make contact with. Virus-infected cells and cancer cells have fewer of these markers and so are more likely than healthy self cells to be killed. NK cells release chemicals called **CYTOKINES**, which alert and attract other immune cells.

PHAGOCYTES: Cells that engulf – or phagocytose – microbes or other cells that are infected, damaged

or dying. Most cells are capable of phagocytosis, but the immune system employs specialist phagocytes like **MACROPHAGES** and neutrophils to deal with foreign matter. They begin by wrapping themselves around the offender, enclosing it in a vesicle called a phagosome before breaking down the contents with hydrolytic **ENZYMES**. The remains are presented (so-called **ANTIGEN PRESENTATION**) to other specialised immune cells that initiate a more targeted immune response.

INFLAMMATION: When the receptors of cells involved in the non-specific immune system are engaged by pathogens, the cells release molecules that trigger inflammation. Increased blood flow brings in more cells to deal with the problem, and also leads to swelling and pain, which alert you to the fact that something is wrong. Greater blood flow also causes an increase in temperature, which can inhibit the replication of some bacteria and viruses.

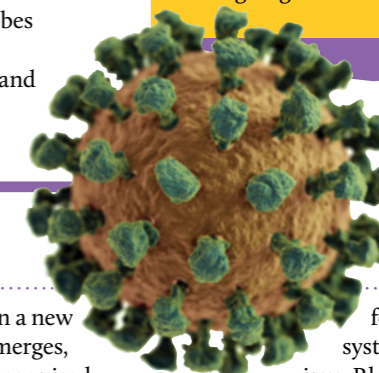
COMPLEMENT: A set of around 30 **PROTEINS** in the blood plasma that can be activated by the presence of microbes or antibody-antigen complexes. Complement can destroy pathogens and activate phagocytic cells.

OUT OF SIGHT

Some infections are with us for life

Some microorganisms can lie latent in our cells for months or years. Although they may not multiply and don't cause disease during this time, they remain undefeated by the **IMMUNE SYSTEM**. A common example is herpes simplex virus 1 (HSV-1), which causes cold sores. It persists in nerve cells in the peripheral nervous system (outside of the brain and spinal cord) and can be reactivated by factors like stress, illness or sunlight to cause new cold sores.

Another herpes-type **VIRUS** is cytomegalovirus, which causes severe developmental abnormalities if contracted by an unborn baby. In children and adults, cytomegalovirus might cause only one bout of flu-like disease, but it takes up lifelong residence in the body just like HSV-1. Cytomegalovirus can recur and cause more-serious problems in people with weakened immune systems, like those undergoing chemotherapy.



COLD OR FLU?

People sometimes confuse these very different viruses

At the root of most runny noses are one of two different kinds of **VIRUS**: orthomyxoviruses (influenza) or rhinoviruses (the common cold). There are many different strains of each, but influenza viruses generally cause much more severe symptoms.

Viruses evolve very quickly, meaning that under the selective

pressure of our **IMMUNE SYSTEMS**, new cold and flu strains can emerge within a single season. Viruses have only a few **GENES**, which means that one mutation can make a big difference. It's this ability to adapt, known as antigenic variation, that produces viruses that can dodge our defences.

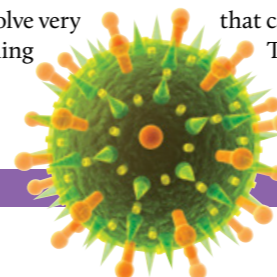
The immune system might produce **ANTIBODIES** to deal with one strain,

but when a new strain emerges, it isn't recognised.

Flu can be fatal – the 1918–19 **PANDEMIC** killed more people than World War I – so it is the subject of intense research. Much of this research focuses on variation in H (haemagglutinin) and N (neuraminidase)

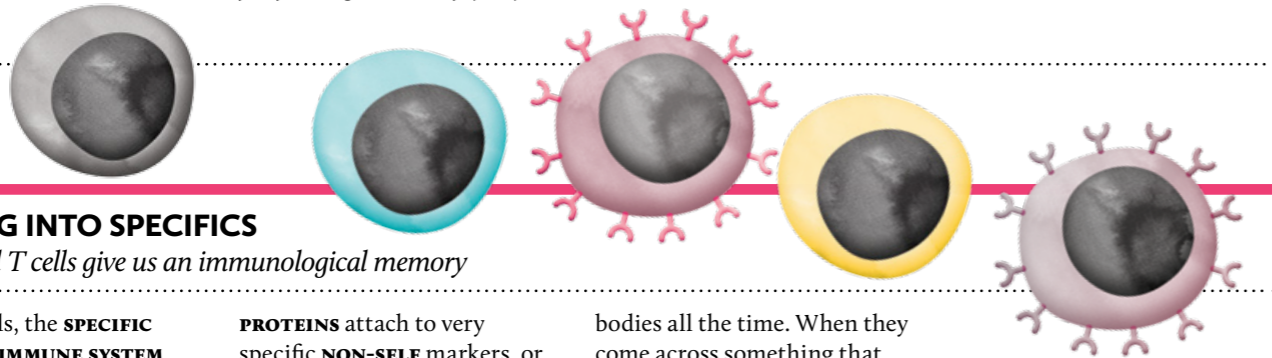
PROTEINS embedded in the virus's outer coat. Changes to these proteins make it harder

for the host immune system to recognise the virus. Rhinoviruses, though less deadly, are also remarkably adept at avoiding the human immune system. Some dampen immune responses by interfering with the signals that attract immune cells, while those that receive a strong immune response seem to evolve even more rapidly to escape it.



THE SPECIFIC IMMUNE RESPONSE

The specific immune system helps us fight off pathogens and other foreign substances, as well as preparing the body for future attacks.



GETTING INTO SPECIFICS

B cells and T cells give us an immunological memory

In mammals, the **SPECIFIC (ADAPTIVE) IMMUNE SYSTEM** provides long-lasting protection against specific microbes or substances. It maintains a 'memory' of all the previous infections it has fought. **B CELLS**, which are made in the bone marrow, produce **ANTIBODIES**. These

PROTEINS attach to very specific **NON-SELF** markers, or **ANTIGENS**, of **PATHOGENS**. **T CELLS**, which are made in the bone marrow but then mature in the **THYMUS** gland, express cell-surface **RECEPTORS** that fit the antigens on pathogens.

Cells specific to lots of different diseases patrol our

bodies all the time. When they come across something that they recognise as a potential threat, they work to eliminate it. The B-cell response involving antibodies is often referred to as the **HUMORAL IMMUNE RESPONSE**, whereas T cells are associated with the **CELL-MEDIATED IMMUNE**

RESPONSE. However, immune responses generally require a coordinated attack involving components of both the humoral and cell-mediated responses, and the specific and non-specific branches.

PRESENT AND CORRECT

Antigen recognition is a key part of the immune response

ANTIGENS are **NON-SELF** markers that alert cells of the **SPECIFIC (ADAPTIVE) IMMUNE SYSTEM** to the presence of potential danger. You can remember what antigens do by

considering them as **antibody generators**. Antigens may pose no threat on their own – they are just components, such as **PROTEINS**, of **BACTERIA** or **VIRUSES** that are recognised by our immune cells. In the case of the influenza virus, however, the H (haemagglutinin) and N (neuraminidase) protein antigens are actually key to the replication cycle of the virus. Viruses use H to bind to host cells and N to detach

themselves as they leave. One important way in which the specific and non-specific branches of the **IMMUNE SYSTEM** cooperate is in the processing and recognition of antigens. Some **PHAGOCYTES** like **MACROPHAGES** can act as **ANTIGEN-PRESENTING CELLS**, although there are numerous other cells that do this job, including some **B CELLS**. The presenting cells break up foreign substances and then

display antigens from them for other immune cells to recognise. The antigens are presented bound to **MHC** proteins, the same molecules that are used to discriminate between **SELF** and non-self. When they encounter **MHC-antigen** complexes, immune cells issue a string of immunological orders. Some **T CELLS** will send out chemical signals called **CYTOKINES**, which activate both B cells and other types of T cells.

APPLIANCE OF ANTIBODIES

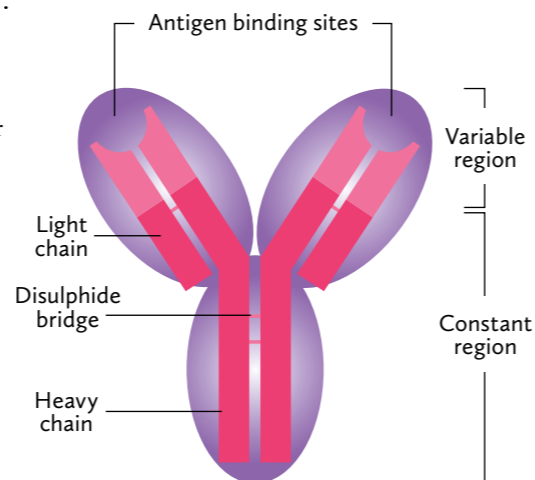
We can exploit the ability of antibodies to bind to a specific antigen

MONOCLONAL ANTIBODIES (mAbs) are sets of identical antibodies that come from genetically identical immune cells and all bind to the same substance. Drug developers use them to create drugs capable of targeting specific types of cells. The breast cancer drug Herceptin (trastuzumab) is a monoclonal antibody that specifically targets breast cancer cells by binding to a **PROTEIN** called HER2 on the surface of the cells. The HER2 protein drives the growth of cancer cells and Herceptin blocks that growth.

Antibodies (see diagram, right) can also be used in test kits. The pregnancy test, for example, uses an antibody to bind and

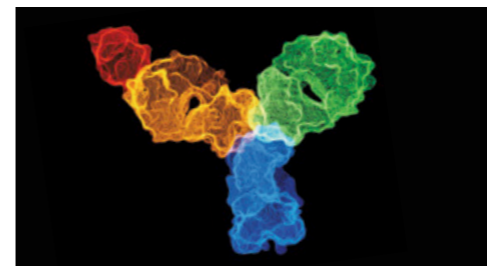
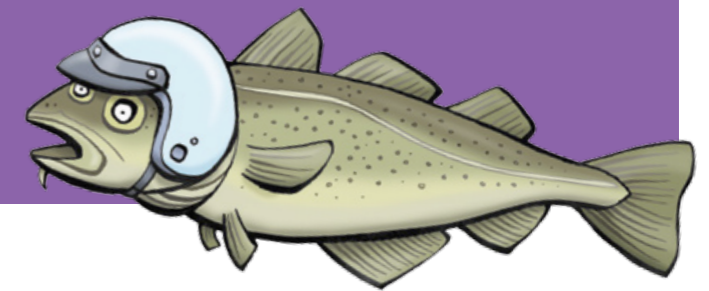
detect in blood or urine a hormone called human chorionic gonadotropin, which is produced in early pregnancy.

If you have been infected by a particular **VIRUS**, say, you will have antibodies against it in your body, so monoclonal antibodies are also useful in diagnostic tests. One of the most common methods of detecting HIV uses an antibody-based test called an **ELISA** – an **ENZYME**-linked immunosorbent assay. It is more accurate a few weeks after initial infection, because it takes a while for the body to build up antibodies against the virus. So early tests are often repeated or alternative methods are used to confirm the diagnosis.



FAST FACT

Atlantic cod lack the genes for several key immune system proteins, including MHC II and CD4. They compensate by having ten times more genes for MHC I than related fish and humans. Source: nature.com/news/2011/110810/full/news.2011.470.html



ANTIBODIES ATTACK

Antibodies are specialised proteins that bind to antigens

PROTEINS are considered the workhorses of cells, and **ANTIBODY** proteins play no less of a central role in the body's defence against disease. Antibodies, made by **PLASMA B CELLS**, are Y-shaped globular proteins called **IMMUNOGLOBULINS** (Ig).

Each type of antibody binds to a specific **ANTIGEN**. The ability to recognise a specific antigen comes from the diversity within the antibody structure. As for all proteins, antibody structure is determined by the sequence of different amino acids in the protein chain (the primary structure) and how it folds to form a 3D molecule (the tertiary structure).

There are different broad classes of immunoglobulin: **IGA**, **IGD**, **IGE**, **IGG** and **IGM**. The classes are defined by the amino acid sequence in the 'stalk', or constant region, of the Y structure. IgA, for instance, is important at the sticky mucosal surfaces where many **PATHOGENS** try to enter, like in the intestines. IgE in the blood binds to **ALLERGENS** and parasitic worms. And as well as differences in the stalk, there are differences in the amino acid sequences making up the 'arms', or variable regions, of the Y, which bind to antigens. These differences determine which pathogen an antibody is for.

Being able to recognise danger is one thing, but what does the antibody do about it? Lots, actually. Some, like IgA, can neutralise pathogens just by binding to them. Others act as labels for **PHAGOCYTES**, which recognise the stalks of antibodies stuck to the outer surfaces of invading pathogens and proceed to destroy them. Antibodies also trigger components of the **NON-SPECIFIC (INNATE) IMMUNE SYSTEM**, including the **COMPLEMENT** system (see page 7, 'Second-line defences').

An IgG molecule bound to an egg white protein (red). J. C. Revy, ISM/Science Photo Library

REJECTION

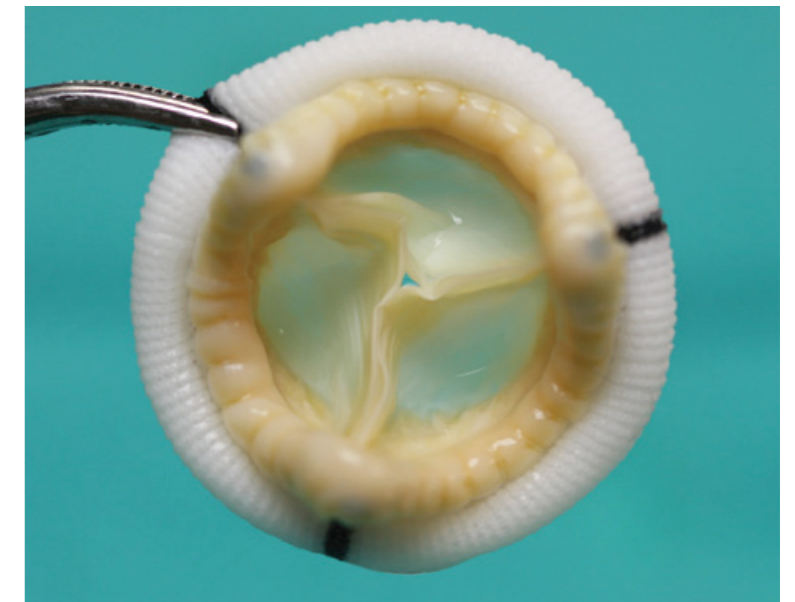
Organ donation requires a good match between donor and recipient

If a person needs an organ transplant, close relatives are potential donors. But the donor's blood group and tissue type must be compatible with the recipient's. Tissue type is determined by a set of **GENES** that code for **MHC (SELF) PROTEINS**. Children inherit these genes from their parents, half from their mother and half from their father. Sometimes, the parents share some of the same genes, so the child may end up having a tissue type very like one or other parent, who may be a 'perfect match' for donation. Or the child may end up with a tissue type that is not really close to either parent. In this case, an unrelated donor may be a better match. Better matches reduce the chance of the recipient's **IMMUNE SYSTEM** rejecting the donated organ as **NON-SELF**.

Family members are not always good matches, and for some organs, like hearts, the donation can come only from someone who has died. Organ shortages mean that animals have also been considered as donors. In 1983, the surgeon Leonard Bailey transplanted a baboon heart into a newborn baby. 'Baby Fae' lived for only 20 days, as her immune system rejected the organ. However, since then, many children born with heart defects have received replacement heart valves from pigs or cows. Transplanting tissue from one species to another is called xenotransplantation. The tissues are chemically treated to mask the **ANTIGENS** that the immune system reacts to.

People who receive transplants may have to take immunosuppressive drugs for the rest of their lives, with the unfortunate side-effect that they become more susceptible to infections. Different drugs address different aspects of the immune system, and many transplant recipients take drugs that reduce the activity or growth of **T CELLS**.

For more on the cells and processes behind the immune system, see our full-colour poster.



A heart valve taken from a pig. Naren Vyavhare lab

BUILDING IMMUNITY

Immunity is lasting protection against a particular disease or infection. Researchers are working to find new ways to build immunity, as well as exploring how to exploit the immune system to make new medicines.

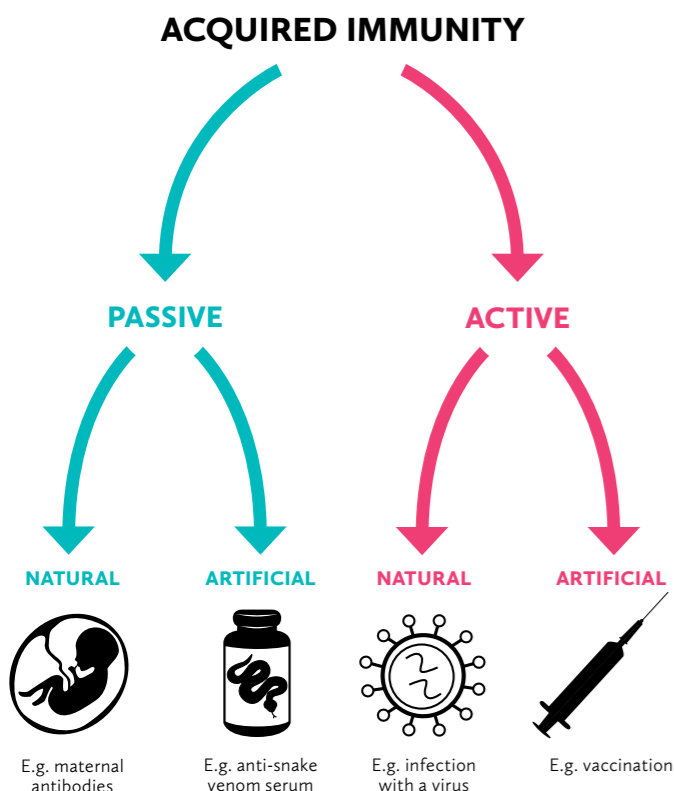
LONG-TERM PROTECTION

There are several different types of immunity

During the first few months of our lives, we were all protected from infections by **ANTIBODIES** passed on to us by our mothers – in the uterus (via the placenta), and in breast milk. This type of immunity is known as **PASSIVE IMMUNITY**. The antibodies last only a few months, though, so infants must quickly start developing their own long-lasting **ACTIVE IMMUNITY** to protect them against different diseases. The **THYMUS** gland, where **T CELLS** mature, is most active just after birth and before puberty.

Before they are six months old, babies in the UK are immunised against diphtheria,

tetanus, whooping cough, polio, rotavirus, meningitis C and other infections. The components of each **VACCINE** encourage the **IMMUNE SYSTEM** to develop its own defences against the disease. This is known as 'artificial' active immunity, whereas the kind of immunity that develops when the immune system comes into contact with the infectious agents of disease – often making you ill – is known as 'natural' active immunity. Being immune to a disease means that you shouldn't get ill with the same infection again. If a **VIRUS** evolves, though, you can still catch the new strain.



A SHOT IN THE ARM

Vaccines come in different forms

VACCINATIONS work by giving the **IMMUNE SYSTEM** a controlled first exposure to a disease. Exposed to the **ANTIGENS** in the **VACCINE**, your immune cells start making **ANTIBODIES** and also produce long-lived **MEMORY T** and **B CELLS**. If your immune system encounters the same antigen again, the memory cells ensure that many specific antibodies are made quickly and in greater quantity, so you are much less likely to get ill from that disease.

What is in a vaccine? Some use only pieces of the **PATHOGEN** – certain antigens or **DNA** encoding antigenic **PROTEINS** – that trigger an immune response but don't cause disease on their own. Other vaccines contain dead (inactivated) pathogens. Some vaccines, such as the measles, mumps and rubella (MMR) vaccine, are made with live attenuated (weakened) versions of the pathogen. Live vaccines are usually the best at provoking an immune response but they have to be kept refrigerated. They also pose the very small risk that the live pathogen will mutate to an infectious form. For example, it's estimated that the live **VIRUS** in the oral polio vaccine can cause paralysis in about 1 in 2.5 million doses of the vaccine. Ideally, vaccines against a particular pathogen will be delivered into the body the same way as the pathogen itself, such as a vaccine against influenza that is inhaled.

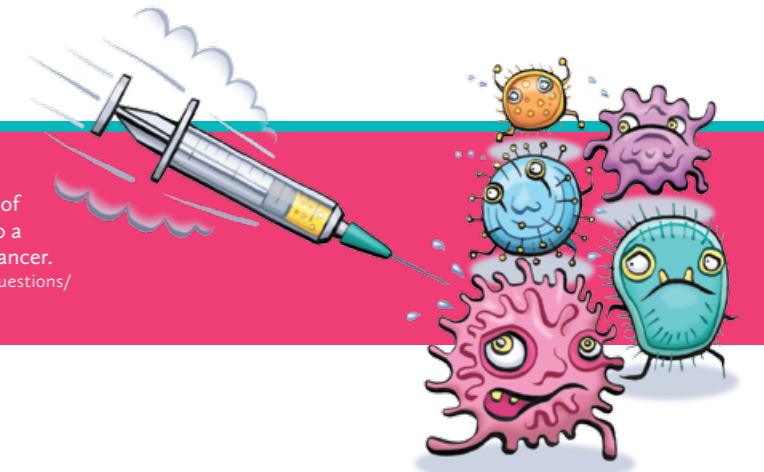
So why don't we have vaccines for all diseases? For some, scientists haven't been able to provoke a strong enough immune response using the usual vaccine designs. For others, there may be several promising vaccines, but rigorous safety and efficacy testing means that it may take years before a vaccine becomes available. Or it may be that more funding is needed.

Vaccination can completely wipe out some diseases, as in the case of smallpox, which was declared eradicated in 1980. In other cases, to keep a disease from spreading, a high proportion of the population must be vaccinated. This is called 'herd immunity'. The measles outbreak in Wales in 2013 was due to falling vaccination levels, which meant that infected people were more likely to come into contact with others who were unprotected.

See more on MMR and vaccination on pages 2 and 12.

FAST FACT

Some cancers are caused by viruses: for example, most cases of cervical cancer are caused by human papillomavirus (HPV). So a vaccine against HPV is effectively a vaccine against cervical cancer. Source: cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/what-is-the-hpv-virus



OUTBREAK

How can science keep up with Ebola?

The Ebola **VIRUS**, which uses fruit bats as a host, causes an acute illness that is often fatal in humans. It first emerged in 1976 in Africa, and outbreaks have occurred many times since. In March 2014, the worst outbreak of Ebola to date began. At the time of writing, several countries in West Africa were involved, including Guinea, Sierra Leone, Liberia and Mali, and a small number of cases outside of Africa had been reported. By the end of October, nearly 5,000 people had died from this outbreak.

There is no **VACCINE** or cure, but in the summer of 2014 some doctors began to give untested treatments to patients, prompting debate around whether the risks associated with a vaccine or treatment that hasn't been tested in humans are more acceptable than the risk of death from a disease.

In August, the World Health Organization stated that it was ethical to use untested drugs in this case, as long as the patients gave informed consent and the researchers collected and shared the results.

In August 2014, the Wellcome Trust (the charity that publishes *Big Picture*) and other research funders, including the UK government, made £6.5 million available for research into Ebola, including its prevention, diagnosis and treatment. The first vaccine trial using the funding began in Oxford in September 2014. Alongside this work, safety trials of a different vaccine were launched in the autumn of 2014, using healthy volunteers in Germany, Gabon, Kenya and Switzerland.

For more on Ebola, see our online resources at bigpictureeducation.com/immune

UNDEREXPOSURE

Is being exposed to dirt good for you?

Could being too clean actually make you ill in the long run? Some people think that it is healthy for our **IMMUNE SYSTEM** to encounter lots of foreign substances early on in life, so that it doesn't become oversensitive. This is the thinking behind the so-called hygiene hypothesis, proposed in 1989, which suggests that rising levels of allergies are linked to being too clean. There is evidence both for and against this hypothesis, and the picture is very complex and multifactorial. High standards of hygiene are important for protecting children from infection, and while it may be useful to expose them to certain **PATHOGENS**, at certain doses, at certain times, we don't know exactly what those are.

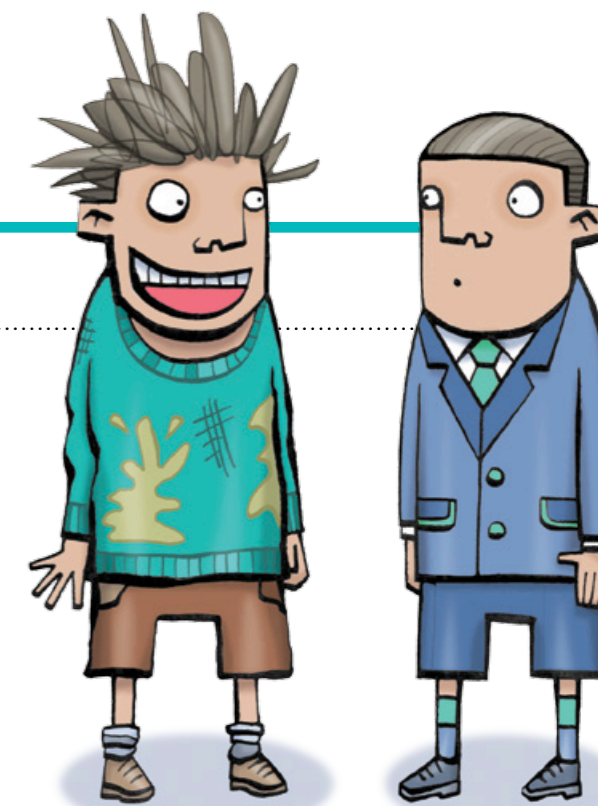
In recent years, the hygiene hypothesis has also come to encompass a whole range of diseases besides allergies, from **DIABETES** to depression. But it is difficult to untangle the many factors that may contribute to a person's risk of getting a disease. **GENETICS**, diet, pollution and exercise may all play a role.

INVESTIGATING IMMUNOTHERAPY

New therapies are looking to use the immune system directly

Immunotherapy is a treatment approach intended to ramp up the body's natural immune response in order to fight off disease. For example, a drug called ipilimumab effectively puts **T CELLS** into permanent destruction mode and is used to treat advanced skin cancer. The downside of this approach is that the **IMMUNE SYSTEM** is very powerful, so although the T cells may kill the cancer cells, they can also attack healthy cells. These side-effects can themselves be fatal.

Immunotherapy is also used in allergic diseases to try to reduce allergy symptoms by gradually increasing the immune system's tolerance of an **ALLERGEN**. Patients receive tiny amounts of the offending **ANTIGENS** under the tongue or by injection, and the amount given is gradually increased. Benefits of immunotherapy have been shown for hay fever, rhinitis (**INFLAMMATION** of the inside of the nose), and allergies to insect bites or peanuts.



THE BIG QUESTIONS

Explore some tricky issues around the ethical, legal and social aspects of the immune system and health.

VACCINATION: WHO DECIDES?

Personal choice and public safety may clash

For certain diseases, there are established thresholds or targets for **VACCINE** coverage, above which herd immunity protects the whole population from **EPIDEMICS**. With measles, for example, 95 per cent of a population must be immune to maintain herd immunity.

Some parents decide not to get their children vaccinated. This could be because they are worried about potential side-effects or because vaccinating conflicts with their religious beliefs. These children remain protected as long as coverage doesn't fall below the critical threshold for herd immunity. However, if there is an outbreak, unvaccinated children will be susceptible and will help the disease to spread. And some children cannot be vaccinated, either because they are too young or because they have an illness that makes **VACCINATION** unsafe. These children are also put at risk if herd immunity is compromised.

In the UK, parents decide whether their child is vaccinated or not. In New York

State, children must have the required vaccinations before starting school. There are limited exemptions for parents with religious objections. A recent legal case focused on a school that would not allow unvaccinated children to attend during a measles outbreak, in order to prevent the disease from spreading.



PROS OF MAKING CHILDHOOD VACCINATION COMPULSORY

- Greater coverage makes outbreaks less likely.
- Children are protected from outcomes of decisions that they were not able to make themselves.

CONS OF MAKING VACCINATION COMPULSORY

- Very rare allergic reactions and other side-effects due to immunisations.
- Conflicts with religious beliefs and parents' rights to make health decisions about their own children.

DISCUSS!

- 1) Is there a moral and social obligation to vaccinate in order to protect the wider community?
- 2) Should parents be legally obliged to have their children vaccinated against MMR (measles, mumps and rubella)?
- 3) What should be done if parents disagree over the vaccination of their child(ren)?

For real-life data on UK adults' and young people's views on vaccination, see bit.ly/1CG5zWE



Images: Stockphoto/Sezayadigan, Stockphoto/pioneer111, Stockphoto/photographerridde, Stockphoto/RidwanAida, Stockphoto/PemMalyshnev

FAST FACT

Tuberculosis (TB) has been linked to a decreased risk of allergic asthma. Researchers are exploring using mycolic acids from the bacterium that causes TB to treat asthma.

Source: asthma.org.uk/research-harnessing-natural-compounds-to-treat-asthma



ORGAN DONATION: WHOSE CONSENT?

A potential donor's wishes may not be known

In the UK, around 1,000 people die each year while waiting for an organ transplant. Those who eventually receive an organ donation wait an average of over three years. Some 11 per cent of people on the waiting list for organ donations are from black, Asian and minority ethnic groups and ideally need transplants from people of the same ethnic backgrounds, as they are more likely to be a good match. However, under 4 per cent of those on the organ donation register are from these groups.

Kidneys can be given by living donors, as can parts of the pancreas, lung and liver, but other organs must come from deceased donors – usually people who have suffered brain death or for whom a decision has been taken to remove life support.

In England and Scotland, if a person consents to organ donation, then their wishes should be respected. If someone's wishes are not known or cannot be determined, then the decision passes to a

relative. The law has recently been changed in Wales and 'presumed consent' will be adopted from December 2015. This means that people must opt out if they do not want to donate their organs – anyone who does not opt out will be considered a potential organ donor.

PROS OF PRESUMED CONSENT

- Waiting times for transplants and the number of deaths on the waiting list may decrease.
- Law is clarified in the event of the death of a relative.

CONS OF PRESUMED CONSENT

- People who have not opted out may become donors even if they were against donation.
- Forces people to make decisions about death, potentially confronting cultural taboos or conflicting with religious beliefs.

DISCUSS!

- 1) Why do you think many people do not add their name to the organ donation register?
- 2) Should family members be able to override donation decisions on behalf of deceased relatives?
- 3) How might a change in UK law affect the waiting list for different groups of people?



INFECTIOUS DISEASE RESEARCH: WHAT'S ALLOWED?

Keeping deadly viruses secure in the lab

In 1918, 'Spanish flu' emerged, killing millions of people. In 2014, scientists aiming to understand the public health risk of modern bird flu **VIRUSES** introduced mutations into one to make it more similar to the 1918 strain. They published the results of their research in the journal *Cell Host & Microbe*, showing that the modified strain was more deadly to mice and ferrets than currently circulating wild strains. According to their study, however, the new strain was not that dissimilar to the circulating strains. Some scientists criticised the work as being irresponsible.

Smallpox was declared eradicated in 1980, but there are still stocks held at two sites across the world. In 2014, the World Health Organization was debating whether to destroy these last remaining stocks of the virus. Some scientists believe further samples of the virus remain undeclared and that the potential for misuse by rogue organisations exists. There are, however, unapproved anti-smallpox drugs, which could be used in the case of a bioterrorist attack.

PROS OF DESTROYING SMALLPOX STOCKS

- No chance of an accidental release of the smallpox virus.
- No chance of the live virus falling into the hands of terrorists or criminals.

CONS OF DESTROYING SMALLPOX STOCKS

- Excludes the possibility of learning from historical **PATHOGENS** in the future, using techniques that haven't been developed yet.
- Some scientists argue that we would be less prepared for bioterrorist attacks.

DISCUSS!

- 1) Should scientists be allowed to manipulate dangerous pathogens in the lab?
- 2) If research is allowed to continue, should the results be made public?
- 3) Should the known smallpox stocks be destroyed?



REAL VOICES

Three people talk about the role of the immune system in their lives. Meet Ann Lee Hussey, a volunteer working on polio immunisation; Brittany Elce, a student who has Crohn's disease; and Professor Bobby Gaspar, who researches immune diseases.

ANN LEE HUSSEY

Volunteer with Rotary International



What do you do?

I work with Rotary International to lead teams of volunteers working on the polio immunisation campaigns in countries across Africa and Asia. I've been doing this since 2001, and have participated in 25 trips.

What is polio?

It's a **VIRUS** that is spread through oral-faecal contact and so occurs in areas where there is poor sanitation. The poliovirus enters through the mouth, replicates in the digestive tract and is egested in the faeces, which means the virus spreads easily among unprotected children. The poliovirus enters the nervous system and attacks the nerves along the spine. The most common effect is crippling of the legs, although the virus may affect the spine or upper limbs. Over 50 per cent of patients will have issues later on in life, called post-polio syndrome.

Have you yourself had polio?

I contracted polio in 1955, in one of the last large **EPIDEMICS** on the east coast of the USA. I was 17 months old so I don't remember the actual experience. But I do remember that I had multiple surgeries, starting when I was three years old. Both of my legs have been affected. I still can't wear high heels or normal ladies' shoes as a rule.

What kind of vaccine do you use?

We've been using an oral **VACCINE** for many years – for several reasons. First, because

it's less expensive. Second, because it can be easily administered by someone other than a registered nurse or healthcare worker. Most importantly, after the vaccine has been ingested, some of it is passed through the faeces and spreads to unvaccinated children, offering **ACTIVE IMMUNITY** to those we have missed. We vaccinate children up to five years old. But if there's an outbreak in a country that was previously polio-free, we sometimes extend into young adults.

Do people know what polio is?

There are polio survivors around, so people do see those that have been disabled. But they're not seeing polio as something as rampant as they used to, which means it can be hard to make people understand the importance of immunisation.

What other challenges are there?

Conflict is our biggest problem. Whenever there's a breakout of conflict or war, like in Syria, then it is harder to reach those children. We have all the tools in place, we know how to do it, but if we don't have access, then it's really hard.

Where is polio a major problem?

The three countries that are now endemic [have polio widespread in the population] are Nigeria, Pakistan and Afghanistan.

endpolionow.org

BRITTANY ELCE

Sixth-form student who has Crohn's disease



What do you do?

I'm doing A levels in English Literature, Health and Social Care, and Travel and Tourism. I also work part-time at McDonald's.

How were you diagnosed?

When I was 16 I had diarrhoea for a whole year. I kept being told by doctors that it was IBS [irritable bowel syndrome], but one night I had really, really bad pains and my parents took me to A&E. They did a colonoscopy [where a thin camera is used to examine the colon] and diagnosed me with Crohn's disease, an inflammatory disease affecting the digestive system.

How does it affect your life?

The symptoms that I have include diarrhoea and extreme stomach pains. I struggle to digest certain foods, so I avoid acidic fruit like apples and oranges, as well as onions and spicy food like chillies and curries. I avoid fizzy drinks. I take tablets every morning and every night. I'm on steroids, which are keeping my **INFLAMMATION** down. I'm also on calcium tablets and folic acid to ensure that I get all the nutrients I need and to make sure that the steroids don't weaken my bones. Crohn's doesn't massively affect my life now as it's under control, but it did when I first got it. I will have flare-ups in the future though.

crohnsandcolitis.org.uk

What's the hardest thing about Crohn's?

At first, I found it quite hard to tell people about it, but then I figured out that people are really understanding, and it's nothing to be embarrassed about. I've had a lot of trouble recently with all the public toilets being closed. If you have Crohn's it's so worrying because you need to know where the nearest toilet is when you go out.

What does the future hold?

I'm supposed to be starting my long-term tablets soon, which I'll be on for the rest of my life. The doctors spoke about surgery but it's not an option they're looking at right now – if the inflammation stays down then it should be OK.

Why is it important to talk about Crohn's?

I found out about Crohn's and Colitis UK on Facebook, and have joined a lot of Crohn's support groups there. It's good to talk to other people with Crohn's, and it's helpful to hear about different diets and the side-effects of different tablets.

I think that everybody should be aware of Crohn's. I had diarrhoea for a whole year and because I waited so long to go to the doctor it got a lot worse. If somebody knows about Crohn's, then they can go to the doctor's and check out any symptoms they're worried about.

BOBBY GASPAR

Paediatrician, Great Ormond Street Hospital



What do you do?

I came to Great Ormond Street about 20 years ago as a children's doctor, intending to stay for about six months. I'm still here.

What do you work on?

I work on primary immunodeficiencies. These conditions result from a single genetic defect, which means that children are born without an **IMMUNE SYSTEM**, so they can't fight infection effectively. Over 200 genetic defects have been identified. They range from people who get relatively minor but recurrent infections on a regular basis to those who have no immunity at all and are susceptible to all kinds of infection from a very early age.

Severe combined immune deficiencies – SCID – is a blanket term for very severe immune deficiencies. Probably 15 to 20 children are born with SCID per year in the UK.

What causes SCID?

The immune system is pretty complex. It's got lots of different white cells that have different functions. A major group of immune cells are the lymphocytes. Children with SCID have very low numbers of lymphocytes because a genetic defect stops these white blood cells being made.

The term 'bubble babies' is often used, because in the past children had to be kept in plastic bubbles as they were vulnerable to everything. Nowadays, they are kept isolated in very clean cubicles and there are strict restrictions on who they can see and where they can go.

Is there a cure?

Up until 20 years ago, the only way we could rebuild the immune system was to give children a bone marrow transplant, from a healthy individual. But that only works if there is a good matched donor available.

We wanted to try and find a better way of correcting these conditions. So we take the child's own cells, usually from the bone marrow, and in the laboratory put a working copy of the **GENE** into them. We've got a delivery vehicle, or vector, which is based on HIV. We disable the **VIRUS** – taking out the bad bits – but keep the properties that HIV has to get into cells.

What's next?

Immune deficiencies are the first conditions in which gene therapy has been shown to correct a genetic disease. We're still working on gene therapy for SCID, but we're also working on it for other immune deficiencies that are less severe but which still cause significant problems.

Gene therapy is currently only available at a few specialised centres worldwide, including Great Ormond Street Hospital. However, in the future, we want to make gene therapy into an approved genetic medicine so that it is available for babies with SCID wherever they might be.

iris.ucl.ac.uk/iris/browse/profile?upi=HBGAS19

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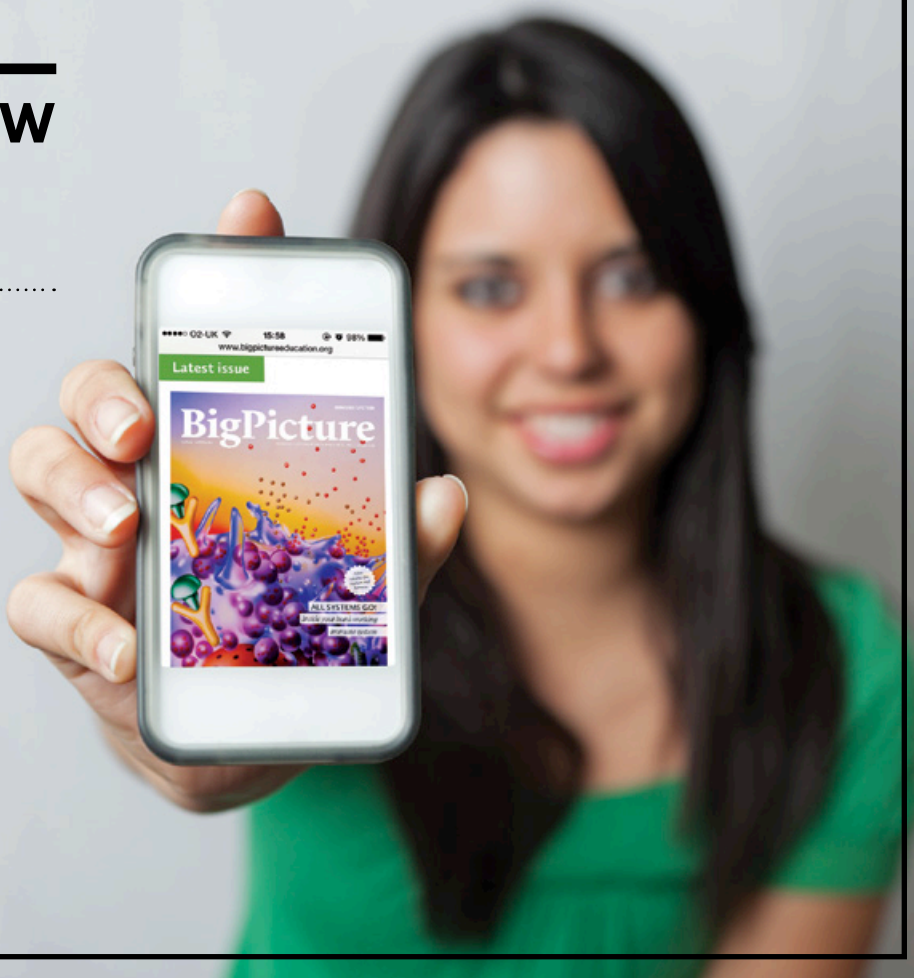
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