ALL SYSTEMS GO!
Inside your hard-working immune system
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.

INSIDE

IMMUNE SYSTEM BY NUMBERS
A snapshot of immunity and allergy

WHAT’S IT ALL ABOUT?
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THE SPECIFIC IMMUNE RESPONSE
Investigating the role of T cells and B cells

BUILDING IMMUNITY
Looking at how we build long-term defences

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Discussing difficult questions around the immune system

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Talking to people with a personal perspective on the topic

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

PRODUCTION OF ANTIBODIES BY B CELLS

MEASLES CASES AND MMR VACCINE COVERAGE IN ENGLAND

GENERATION TIMES OF DIFFERENT BACTERIA

E. COLI
20 MINUTES

STAPH. AUREUS
27–30 MINUTES

MYCOBACTERIUM TUBERCULOSIS

MYCOBACTERIUM LEPRAE
12–14 DAYS

Time between two consecutive generations under optimal conditions

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.

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 future’). 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, impeding 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.

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 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 pollen 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.

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.

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 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.

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.


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’ve 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: 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 or faeces are disgusting, what is disgusting to eat differs across the world. See online for our related activity – designing a poster for poo transplants.

MORE ONLINE: bigpictureeducation.com/immune

BIG PICTURE 21: IMMUNE SYSTEM

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

Support your immune system. 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 future’). For more on the immune response, see our full-colour poster.

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But it’s not clear how the pathogens be pathogenic, which means that they cause disease. Human most of them will never do you any harm. However, some can Millions of microbes have made your body their habitat and nasal secretions that they can be transferred by a sneeze, and\n
spreading of diseases: How GOING VIRAL Sometimes, but not always, pathogens cause disease. For example, Rhinoviruses, though small and not as dangerous as orthomyxoviruses, can cause colds. Rhinoviruses can infect the respiratory tract and cause symptoms such as runny nose, sneezing, and cough. They can also cause fever, sore throat, and body aches. If something goes wrong with these barriers, we become more susceptible to disease. For instance, some people have genetic mutations that affect the brain's ability to produce serotonin (a chemical that helps regulate mood and behavior.) These bacteria produce enzymes called such as lysozyme, \n
One organ acts as your largest and most important barrier against infection. Spread out on the skin, it is the outermost layer of the epidermis, which is the outermost layer of the skin – is completely dead. Viruses can replicate in this dead cells. Viruses are often outcompeted by bacteria that live on our skin in a microbical 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 we 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 the brain's ability to produce serotonin (a chemical that helps regulate mood and behavior.)

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 are more likely than healthy self cells to be killed. NK cells release chemicals called cytokines, which alert and attract other immune cells. PHAGOCYTIC CELLS: 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 20 proteins in the blood plasma that can be activated by the presence of microbes or antibody and trigger a cascade of events that include the release of inflammatory mediators and the recruitment of immune cells to the site of infection. Inflammation also helps to create a hostile environment for microbes by weakening the skin barrier, allowing allergens to enter through it. This leads to some cases of eczema, asthma and hay fever. \n
Reptiles have versatile non-specific immune systems. Compounds from alligator blood are being investigated as potential antibacterial and antifungal treatments. 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 (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. \n
In the body’s defensive barriers are breached. Bacteria of 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 transmitted by a sneeze, whereas HIV can’t, and is usually spread through sex or the injection of drugs. Some infections 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 600,000 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.

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 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. Many vaccines are used to induce the immune system to make antibodies that can protect us from infection. 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. \n
Some infections are with us for life for the rest of our lives. One example 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.
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, 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.

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.

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 (Major Histocompatibility Complex) 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 1985, the surgeon Leonard Bailey transplanted a baboon heart into a newborn baby. ‘Baby Fae’ lived for only 10 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.

Antibodies attack

Antibodies are specialised proteins that bind to antigens

Proteins are considered the workhorses of cells, and antibodies 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 example, is important at the sticky mucosal surfaces where many pathogens try to enter, like in the intestines. IgG 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 ‘stains’ on the immune system. The non-specific (innate) immune system, including the complement system (see page 7, ‘Second-line defences’).
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 active immunity is most active just after birth, is in the neck, before it moves to the breastbone.

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.

Bringing immune to a disease is, in general, making you ill - is known as 'natural' active immunity. However, the immune system 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.

**What is 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 (inactive) pathogens. Some vaccines, such as the measles, mumps, and rubella vaccines, are made with live attenuated (weakened) versions of the pathogen. Live vaccines are usually the best at provoking an immune response but they have the risk of the live pathogen mutating to a new, more dangerous 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 aren’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 none that are safe and effective, or that testing means that it may take years before a vaccine becomes available. Or it may be that more funding is needed.

### 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 system starts making **antibodies** and also produce **T** cells 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.

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### 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 human. 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 10,000 people had died from this outbreak.

There is no **vaccine** or cure, but in the summer of 2014, some doctors began to give experimental 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 £65 million available for research into Ebola, including its prevention, diagnosis and treatment. The first vaccine trial using the **vaccine** the **vaccine** in Sierra Leone, Liberia and Mali, and a small number of cases outside of Africa had been reported. By the end of October, nearly 10,000 people had died from this outbreak.

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

### Investing in 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.

### 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 over-sensitive. 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’s 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.
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 vaccinations.
• 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 children?

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

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 background, as they are more likely to be a good match. However, under 1 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.

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

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?

INFECTIONIOUS 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.

DISCUSS!
1) Should scientists be allowed to manipulate dangerous pathogens in the lab?²
2) Should research aimed at providing_dates_for_vaccines_be_worked_on?
3) Should the known smallpox stocks be destroyed?

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

Source: asthma.org.uk/research-harnessing-natural-compounds-to-treat-asthma
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 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 sometimes occurs in areas where there is poor sanitation. The poliovirus enters through the mouth, replicates in the digestive tract and is excreted 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 who have lived after an infectious polio will suffer some long-term disability. I was one of the last of the large epidemics on the east coast of the USA. I was 17 months old when I got polio – 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 who 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 it used to be, which means it can be hard to make people understand the importance of immunisation.

What other challenges are there?
There are so many. Our biggest problem? Whenever there’s a break-out of conflict or war, like in Syria, that’s 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 for polio have widespread populations in Nigeria, Pakistan and Afghanistan.

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 diarhoea for a whole year. I kept being told by doctors that it was IRS (irritable bowel syndrome), but one night I had really nasty 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 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.

What’s the hardest thing about Crohn’s?
At first, I found it quite hard to talk to 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 treatment soon, so I’ll be on for the rest of my life. The doctors spoke about surgery but it’s not on 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.

crohnsandcolitis.org.uk

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 immune deficiencies. 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 a lot of different specialised cells that have different functions. A large 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’re kept isolated in very clean cubicles, and there are strict restrictions on who can see them 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 it is available for babies with SCID wherever they might be.

irisc.ulc.ac.uk/iris/browse/profile?upi=HBGAS0

More information and facts about gene therapy can be found at: pe-56091/30K/11–2014/LR

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