ANTIBIOTIC RESISTANCE

Problems, challenges and solutions

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THE PROBLEM

Antibiotics are one of medicine's real success stories. Since their appearance nearly 100 years ago their ability to quickly kill or stop the growth of harmful bacteria has undoubtedly saved many people from chronic disease and even death.

In recent decades, however, antibiotic use has become a problem.

It's estimated that up to half of all the antibiotics prescribed are unnecessary or are not prescribed appropriately.[1] Too often, without a serologically-confirmed diagnosis, busy doctors may prescribe a broad-spectrum antibiotic that kills a wide range of bacteria "just in case". Studies continue to show that patients expect and/or doctors unnecessarily prescribe, antibiotics for viral infections, for which they are ineffective.[2]

This overuse is a problem because bacteria have a near limitless ability to adapt. Pressure on bacterial communities from antibiotic overuse causes them to evolve resistance. Resistant bacteria no longer respond to antibiotic treatment.

Rates of resistance have also gained pace because bacteria are not restricted by geographical or ecological borders – and sometimes not by species. Thus the movement of people and animals around the world helps them to spread.[3] In addition, resistance in one organism can easily be passed on to other unrelated organisms.[4]

Pressure on bacterial communities from antibiotic overuse causes them to evolve resistance. Resistant bacteria no longer respond to antibiotic treatment.

In 2018 a World Health Organization global survey of patients with bacterial infections revealed high levels of resistance to a number of serious bacterial infections in both high- and low-income countries. The most commonly reported resistant bacteria were *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Salmonella spp*.[5]

As resistance grows, a growing list of human infections – such as pneumonia, tuberculosis, blood poisoning, urinary tract infections, sexually transmitted and food-borne diseases – are becoming harder, and sometimes impossible, to treat.

The loss of effective antibiotic treatments affects both primary and secondary diseases. For instance, many common medical treatments and procedures – joint replacements, organ transplants, cancer therapy and rheumatoid arthritis therapy – are dependent on the ability to fight secondary infections with antibiotics.

If the ability to effectively treat those infections is lost, the ability to safely offer people medical treatment will be lost with it.

Beyond drug use

Exact figures on illness and especially death are hard to find and most are gross underestimates. Globally it is estimated at least 700,000 people die each year due to drug-resistant diseases[6] a figure that is projected to soar to 10 million by 2050. In the UK at least 12,000 deaths each year can be attributed to bacterial resistance.[7] In Europe official figures suggest that antimicrobial-resistant bacteria causes an estimated 33,000 deaths each year.[8] In the US it's 35,000.[9]

Paying attention to all the ways in which antibiotics are used is crucial in helping to reverse this trend. For instance, it's estimated that more than 70% of the antibiotics prescribed in the world are veterinary medicines used to treat the livestock in our food system.[10]

The animals that produce our meat, fish, milk and eggs are given the same types of antibiotics that humans use. As in humans, much of this use is medically unnecessary. For instance, antibiotics are added to feed as a "just in case" treatment, and in some parts of the world they are routinely used as growth promoters.

Animal waste applied to fields or leaching into waterways helps spread resistant bacteria beyond the farm. Some studies have shown that antibiotic

ANTIBIOTIC vs ANTIMICROBIAL

The microbial world is vast. This report focuses on antibiotic resistance (ABR) – that is the ability of bacteria to develop resistance to antibiotic treatment. However antibiotic resistance is part of a much larger problem of antimicrobial resistance (AMR), the ability of any type of microorganism – bacteria but also viruses, fungi and some parasites) to develop resistance to treatments such as antibiotics, antivirals, antifungals and antimalarials. As a result of the increasing failure of the whole range of antimicrobial treatments, infections of all types are getting harder to treat.

residues remain in the animal products we eat.[11]

Less well known is the fact that that honey bees are also reared largely in intensive systems. That means, like other types of industrial 'livestock' they are routinely treated with antibiotics.

Research from the US[12] has found that honeybees treated with a common antibiotic, tetracycline, tended to have lower levels of beneficial bacteria in their guts and elevated levels of *Serratia*, a bacterium that is lethal to bees. Treated bees were also half as likely to survive the week after treatment compared to untreated bees.

This impact on our bees has a direct effect on both the environment and humans since bees are a keystone species necessary for the pollination of many plants and food crops.

The rise in multidrug-resistant bacteria is rightly attributed to the overuse of antibiotics but it's also important to consider other factors – such as climate change and pollution

Certain chemicals used in home health products are also problematic. Triclosan – a synthetic antibacterial widely used in products like toothpaste, hand cleaners and even sunscreens – is driving the development of resistant bacteria.[13]

Triclosan enters streams and rivers through domestic wastewater and leaky or overflowing sewers and, via a process called horizontal gene transfer,[14] it can pass resistance on to bacteria there.

In the same way, washing fabrics treated with triclosan or other antibacterial chemicals, such as silver and trichlocarban, can contribute to the development of resistant bacteria.[15]

Environmental amplifiers

Although the rise in multidrug-resistant bacteria is rightly attributed to the overuse of antibiotics in human and animal medicine, it's also important to consider other factors – such as climate change and pollution.

For instance, scientists have found that climate variability has made *Vibrio cholerae*, the bacterium that causes cholera, more robust. While it normally prefers a warm tropical atmosphere, under pressure from a changing climate, it has rapidly evolved to be less sensitive to temperature changes.[16]

There is evidence that *Yersinia pestis*, the bacterium that causes bubonic plague (known commonly as the Black Death), favours a warmer climate.

Just a 1°C increase in spring temperatures could lead to a more than 50% increase in incidence of the disease that wiped out nearly half the European population in the mid-1300s.

Even air pollution can drive bacterial resistance. A major component of polluted air is black carbon, which is produced through the burning of fossil fuels such as diesel, biofuels and biomass.

New research has shown the bacteria that can cause respiratory infections, such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, become more resistant to common antibiotics when exposed to airborne pollutants like black carbon.[17]

Harmful to human health

Overuse of antibiotics is also linked to a range of chronic human health problems.

The human gut contains more than 100 trillion individual bacteria, from more than 500 different species – all in a delicate balance. This is our 'gut microbiome'. A healthy microbiome is critical for an optimally functioning immune system.[18]

THE INFLUENCE OF NON-ANTIBIOTIC DRUGS

Several non-antibiotic medications can have a devastating effect on the microbiome – making it harder to fight off bacterial infections.[24]

German researchers recently found that a quarter of the 923 non-antibiotic drugs they tested – including acid-reducing medications, antivirals, blood-pressure medications, anti-psychotics and chemotherapy drugs – had this effect.

They also found that that consumption of non-antibiotic drugs may promote antibiotic resistance in part because the general resistance mechanisms of microbes to human-targeted drugs and to antibiotics seem to overlap.

These are serious and worrying findings given that as a population we take many non-antibiotic drugs – especially acid-reducing medications and blood-pressure drugs – often for long periods of time.

From immune-related disorders like allergies and asthma to the ability to fight off pathogens, our microbiome is now understood to be deeply involved in controlling our health.[19]

Scientists now suspect that antibiotic use, and especially overuse, can have effects on everything from the immune system to glucose metabolism, food absorption, obesity, stress and behaviour.

For instance, antibiotic use in babies under 6 months of age is linked to being overweight at the age of 3.[20] This effect has also been seen in farm animals as well as experimental animals. [21]

In children there is also a significant association between early antibiotic use and the development of food allergies, according to data from the US.[22]

The scientists found that the risk of developing a food allergy increased with the number of antibiotic prescriptions a child had and was much greater in those children who received broad-spectrum antibiotics as opposed to more targeted ones.

Yet another study has shown that antibiotic overload can lead to a greater risk of inflammatory bowel disorders such as Crohn's disease.[23]

A threat to the natural world

The highest concentrations of antibiotics in soil or water are usually found in areas adjacent to hospitals, wastewater treatment plants and farms with large numbers of livestock or where soils are treated with manures.

One eye-opening study[25] discovered there is often significant pollution near pharmaceutical factories in countries like India and China (where some of the highest rates of bacterial resistance are seen).

Outside of one plant in India, for example, 95% of water samples taken contained multidrug-resistant bacterial strains.

Wastewater treatment plants aren't designed to fully remove antibiotic or other pharmaceutical compounds. This means resistant bacteria can quickly and easily spread through human populations as well as into the natural environment where they have a damaging effect on aquatic and soil organisms essential to a healthy environment.

Many microbial species found in the environment, for example, play important roles in natural cycles of nutrients, food production and climate regulation. Some help to degrade harmful contaminants such as pesticides.

How to cope

We use too many antibiotics. We use them for the wrong things, at the wrong times and in amounts that are risky for us individually and as a society.

There is an urgent need to find a way out of a vicious cycle which is making essential medicines less and less effective. There is also a need to take prevention more seriously.

The stronger your immune system is, the less likely it is that you will succumb to any kind of 'bug'. Many foods and herbs help treat uncomplicated infections without the need to resort to antibiotics.

A GLOBAL STRATEGY FOR USE

Many health agencies around the world now promote the notion of 'antibiotic prudence' or 'antibiotic stewardship'. What does this mean? It involves first and foremost recognising that resistance is a widespread problem, that it is largely man-made and that doctors have a role to play in addressing it.

Part of good antimicrobial stewardship is selecting the right drug at the right dose and for the right length of treatment in order to cure an infection, while minimizing the risk of adverse effects on the patient and promoting resistant bacterial strains.

It's worth remembering that most illnesses are self-limiting and, provided you are otherwise healthy, antibiotics may not need to be your first line of treatment if you succumb to an infection.

The benefits of this approach can be seen in modern approaches to, for example, urinary tract infections where a combination of functional foods such as cranberry or probiotics, good hygiene and extra hydration can deliver good results.

A similar approach can be found in wound healing where advances in dressings such as hydrocolloids, as well as research showing that antibacterial Manuka honey and, again, good hygiene can help prevent infection and speed healing.

In this way healthcare practitioners can ensure that today's patients – and tomorrow's – can continue to benefit from antibiotic treatment when it is needed.

Disease does not simply arise in a vacuum. Thus, diet, lifestyle, stress levels, physical fitness, hygiene, environmental pressures, are all integral to a multifaceted approach to prevention – and also to any ongoing treatment regimen.

PREVENTION

The immune system is the body's first line of defence in the prevention of disease. The healthier your immune system, the greater your ability to fight off any harmful invaders like pathogenic bacteria – and the less likely you are to succumb to sickness.

A healthy immune system has the ability to produce a million specific antibodies within a minute and to recognise and disarm a billion different invaders. To do this effectively the immune system is dependent on a myriad of nutrients.

Many foods and herbs help treat uncomplicated infections without the need to resort to antibiotics

It is thought that most known vitamins, minerals, amino acids and fats are synergistically involved in this response. Specifically lack of vitamin A, B-complex, C and E suppress immunity, as do deficiencies of iron, zinc magnesium and selenium.

Bone marrow, the lymphatic system, the thymus, liver and spleen are important immune system organs, but the foundation of the immunity is cradled in the health of the gut microbiota.[26]

A healthy gut wall is packed full of lymphocytes (white blood cells) poised to safeguard the body. Lymphocytes produce immunoglobulins, commonly known as antibodies, which identify and help the body fight off infective agents.

The most important one in the gut is Secretory Immunoglobulin A (IgA), which protects the body from bacteria, viruses and parasites. A healthy microbiota also produces many other important cells that are used in the immune response.

Disruption of the innate bacterial community, that forms a layer on the gut wall, compromises the immune system.

Fewer immune cells are produced, fewer nutrients necessary to support the body's entire immune system are absorbed and partially digested food and toxins move through the damaged gut wall, adding to the strain on an already compromised immune system.

Including antibacterial foods that support gut health and strengthen the immune system is key to prevention. Those listed below are known to be particularly beneficial.

Onion (*Allium cepa*)
Onion has a long been used as food and medicine. Louis Pasteur was the first to describe the antibacterial effect of onion. Research has shown it is the sulphur-containing compounds and the flavonoid quercetin in onion that confer these antibacterial benefits. Onion extract has been found to inhibit the growth of methicillin-resistant *Staphylococcus aureus* (MRSA)[27] and *Mycobacterium tuberculosis*.

Mushrooms (*Agaricus*)
Mushrooms are the fruiting body of certain fungi. Among the most widely studied varieties is Shiitake (*Lentinus edodes*), which has significant food and medicinal benefits.

Both the fruiting body and the fungal mycelium (the root-like network connecting groups of growing fungi) naturally produce antimicrobial compounds and many of these target specific bacteria.[28]

Several pharmaceutical antibiotics have been developed from fungi and it is thought that fungi may still be an untapped source of antibacterial drugs in the future.

Edible mushrooms are also rich in prebiotic carbohydrates that provide food for beneficial bacteria in the gut, which supports a healthy microbiome and immune system.

Garlic (*Allium sativum L.*)
Garlic has been used as food and medicine since ancient times. It has a number of different medicinal actions including being antibacterial and providing beneficial effects on the immune system.

Recent research has found that garlic can be effective against many types of bacteria including *Salmonella* and *Escherichia coli*.[29] Many strains of tuberculosis are now resistant to antibiotics but garlic can be, and is, both a prophylactic and a treatment for this disease.[30]

Ginger (*Zingiber officinale*)
Ginger root has been a culinary ingredient and medicine since ancient times. Studies show that ginger has the ability to fight many strains of bacteria.[31] Ethanol extracts of ginger used on *Staphylococcus aureus* and *Streptococcus pyogenes* have a similar effect to pharmaceutical antibiotics such as chloramphenicol and ampicillin.[32]

Ginger also aids digestion, which helps to support gut integrity. The ideal diet to support immunity is no different from the ideal diet we should be eating every day. It is estimated that there are 820 million people in the world who do not have enough food to eat. In addition there is an epidemic of obesity and overweight. All of these forms of malnutrition compromise the immune system which is fundamental to preventing disease.[33]

Herbal Help

The immune system is your body's ultimate defence system against infectious agents such as bacteria. Most of the time, supported by a healthy diet and lifestyle, it deals efficiently with health challenges. But at times when extra support is needed, natural remedies such as herbs can be helpful.

Herbal medicine is one of the most widely used forms of medicine on the planet. The World Health Organization acknowledges its importance to people all over the world and supports its appropriate use to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses.

"Appropriate use" means the use of herbs that not only have a long tradition of safe and effective use but which have also stood up to scrutiny by modern science.

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Research into many traditional herbs and other natural remedies shows they have immune boosting and antibacterial properties that can help treat uncomplicated infections.

These are attributed to the wide range of chemicals that plants produce to protect their own health and to help them grow and cope with challenges in their environments, such as insect and animal predators, bacterial, fungal and other disease-causing organisms and even climate challenges.

Many of the herbal remedies included below are commonly available in health stores, online and, depending on your level of knowledge, confidence and skill, some can even be foraged and prepared at home.

Herbs can be taken as teas, tinctures or capsules or, for skin infections, applied externally as balms, creams and oils and even poultices.

Always follow the instructions on the label and if in doubt seek the advice of a qualified herbalist.

Goldenseal (*Hydrastis canadensis*)
Goldenseal is a natural antibiotic that can be used to treat mucous membrane ailments like chronic sinusitis and chronic urinary tract infections and in inflammatory conditions caused by allergy or infection. It is often found combined with echinacea in immune stimulating herbal formulas.

Its active component, berberine (also found in barberry, Oregon grape and tree turmeric) has been shown to have a broad antibiotic effect and can be useful in the treatment of acute diarrhoea caused by a range of nasty bugs including *Staphylococcus aureus*,[34] *Escherichia coli*, *Giardia lamblia*, *Salmonella* and *Vibrio cholerae*.[35]

Japanese knotweed (*Polygonum cuspidatum*)
Gardeners may know it as an invasive species, but as a herbal remedy, Japanese knotweed is particularly useful for hard-to-treat infections, especially those involving bacterial biofilms.[36]

Biofilms are colonies of bacteria that clump together under a protective 'film' that hides bacteria from the immune system and keeps antibiotics from reaching them.

The presence of biofilms is now recognized as a key factor in many chronic infections that don't respond to treatment.

The key to Japanese knotweed's effectiveness is a high level of resveratrol, a compound often associated with grapes and red wine, but also abundant in other plants like peanuts, cocoa, blueberries, bilberries and cranberries.

Extracts have been shown to be effective against *Borrelia burdorferi*,[37] which causes chronic Lyme disease and *Propionibacterium acnes* (a cause of acne) where the long-term use of antibiotics has encouraged biofilm formation.[38]

Echinacea (*Echinacea purpurea, Echinacea angustifolia*)

Among the most widely used of natural remedies, numerous studies have shown echinacea to be antioxidant, antiviral and antibacterial.[39] This combination makes it extremely valuable in treating respiratory infections such as colds, flu, catarrh and bronchial infections.

It has been shown to limit the growth of *Escherichia coli*, *Propionibacterium acnes*, *Clostridium difficile*, *Haemophilus influenzae* and *Staphylococcus aureus* and as such can be useful for intestinal and skin infections, including herpes.[40]

In respiratory infections there can sometimes be co-infection with bacteria and viruses and, so, because of its dual action on bacteria and viruses echinacea may be a good choice.

Uva ursi (*Arctostaphylos uva-ursi*)

The leaves of uva ursi are traditionally brewed into a tea to improve urinary health. In particular it has a long history of treating urinary tract infections (UTIs).[41]

Up until the development of sulfa antibiotics, the principal active component of uva ursi, arbutin, was frequently prescribed as a urinary antiseptic. This is because arbutin breaks down into a substance called hydroquinone glucuronide.[42] When this is eliminated through urine, it prevents bacteria from adhering to tissue in the area, thus reducing the risk of infection.

Tea tree (*Melaleuca alternifolia*)

The Aborigines traditionally crushed fresh tea tree leaves and inhaled the volatile oils to relieve colds and headaches. Modern research has shown that *Escherichia coli* and *Staphylococcus aureus* infections can all be inhibited by tea tree.[43]

It has also been shown to have antimicrobial, antiseptic, antiviral, anti-fungal and expectorant properties making it effective against a wide range of organisms including those that cause candidiasis, herpes, athlete's foot, impetigo and ringworm.

Oregano (*Origanum vulgare*)

Prized for centuries for its healing qualities, oregano is traditionally used to treat complaints as diverse as indigestion and diarrhoea, rheumatism and stubborn coughs.

The food industry often relies on rosemary extract to kill bacteria that can contaminate leafy vegetables

It has a broad spectrum antibiotic action that may help treat respiratory and other infections. The essential oil is particularly useful in helping to clear sinuses and thin phlegm.

Oregano essential oil contains a high level of a substance called carvacrol which has been shown to be effective against many types of bacteria[44] including *Bacillus cereus*, *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas fluorescens*, *Salmonella typhimurium*, *Vibrio cholerae*, and *Vibrio vulnificus*. Carvacrol has also been shown to boost the effectiveness of several conventional antibiotics.[45]

Liquorice (*Glycyrrhiza glabra*)

A traditional folk remedy popular in Chinese and European medicine, liquorice is commonly thought of as an anti-inflammatory and expectorant herb.

But modern studies have also shown that it has a significant antibacterial activities against *Staphylococcus aureus* – a main source of infection in both hospitals and the community – as well as *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*[46] and the fungus, *Candida albicans*.

A range of substances found in liquorice including 18 beta-glycyrrhetinic acid, licochalcone E, Licochalcone A, glabridin (GLD) and Liquiritigenin (LTG) are thought to be responsible for its antimicrobial effects.

Rosemary (*Rosmarinus officinalis*)

A kitchen cupboard staple, rosemary is known to contain a number of different volatile oils that have been shown to be active against a range of bacteria.

The food industry often relies on rosemary extract to kill bacteria such as *Listeria monocytogenes*, *Escherichia coli* and *Salmonella enterica* that can contaminate leafy vegetables.[47]

Apple cider vinegar

Traditionally fermented vinegars, brewed from fruits or grains, have been used for centuries to kill bacteria and fight infection.

The organic acids in vinegar (mainly acetic acid) pass easily into the cell membranes of microorganisms[48] leading to bacterial cell death. This antibacterial activity is one reason why vinegar remains a popular natural household cleaner.

Acetic acid can also break up the biofilms[49] responsible for many stubborn bacterial infections.

Apple cider vinegar, in particular, has been shown to be effective against *Escherichia coli* and *Staphylococcus aureus*. Research suggests it could also be a useful, inexpensive and non-toxic disinfectant against drug-resistant tuberculosis bacteria[50] as well as other hard-to-kill mycobacteria.

Cannabidiol (CBD)

A recent discovery is that cannabidiol (CBD), an active component of cannabis, can kill 'gram positive' bacteria such as *Staphylococcus aureus*, which can cause skin infections, and *Streptococcus pneumoniae*, which can cause strep throat).[51] Its effectiveness has been compared to that of conventional antibiotics like vancomycin or daptomycin.

CBD also appears to be able to penetrate the biofilms that can make bacterial infections so hard to treat. It has not, however, been shown to be effective against gram-negative bacteria such as *Salmonella* (found in undercooked foods) and *Escherichia coli* (the cause of urinary tract infections, diarrhoea and other ailments).

Phages are viruses that attack and kill bacteria; 'bacteriophage' literally means 'bacteria eater'

Raw Honey

Honey has been used to support immunity and heal infections for millennia. Manuka honey is by far the most well-known healing honey. A powerful immune stimulant and antibacterial, it has made its way into hospitals as an effective alternative for wound healing. But manuka is not the only healing honey.

Raw honey is also considered an important antibacterial treatment, especially for skin infections. Its effectiveness is due to the presence of a range of lactic acid bacteria[52] which produce a variety of active antimicrobial compounds.

These lactic acid bacteria have been shown to kill pathogens such as including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* (VREF), among others.

Phage therapy

In the late 1920s when antibiotics were being developed, another treatment – bacteriophages – was also being studied. Antibiotics reached the marketplace first and were so successful that research into bacteriophages, or 'phages', stalled. But as resistant bacteria have become more of a problem, attention is turning once again to phages.

Phages are viruses that attack and kill bacteria (bacteriophage literally means 'bacteria eater').

Just as there are many kinds of bacteria, there are several types of phages found in nature, each linked to a specific type of bacteria.

Although phage therapy isn't routinely used in Western medicine, it is used in Eastern European hospitals[53] particularly in paediatric, surgical and burns units.

The evidence for phage therapy is encouraging but not yet robust. So far it consists mostly of laboratory testing and case studies. These show effectiveness against *Clostridium difficile*, and a range of bacteria[54] that can cause food poisoning including *Salmonella*, *Listeria*, *Escherichia coli*, *Mycobacterium tuberculosis*, *Campylobacter* and *Pseudomonas*.

In fact, the processed food industry has been quicker than the medical community to pick up on the potential of phages. For instance, the US Food and Drug Administration (FDA) has approved of some phage mixtures to help stop bacterial growth in pre-prepared foods.

Phages have many advantages: they are naturally occurring, can be used on their own or in combination with antibiotics and, crucially, their use hasn't yet been linked to any adverse effects in patients.

But they have some disadvantages too. The fact that the action of specific phages is limited to specific bacteria is seen as a barrier to commercialising them. Doctors would, for instance, need to know exactly what bacteria is at the root of an infection before prescribing a particular phage.

This has led some scientists to try and genetically engineer[55] broad spectrum phages for medical use. But this brings up a complex question of environmental control. What happens if, for instance, these engineered organisms enter the natural environment, either from the lab or when excreted form the body?

Additionally, it's not known if phage therapy may, with wider use, trigger bacterial resistance.

Nevertheless, phages are worthy of more study as a more natural approach to infection control, especially in vulnerable patients whose health might be compromised by long-term antibiotic use.

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