General Certificate of Education
Advanced Level Examination
June 2015

Science in Society SCIS4/PM

Unit 4 Case Study of a Scientific Issue

Preliminary Material

- This Case Study Source Material should be opened and issued to candidates on or after 1 May 2015.
- A clean copy of the Case Study Source Material will be provided at the start of the Unit 4 examination.

A

Information

- The Case Study Source Material is to be seen by teachers and candidates **only**, for use during preparation for the examination on Monday 22 June 2015. It **cannot** be used by anyone else for any other purpose, other than as stated in the instructions issued, until after the examination date has passed. It must **not** be provided to third parties.
- This Case Study Source Material consists of extracts from five sources (**A**–**E**) on the subject of antibiotics.
- This material is being given to you in advance of the Unit 4 examination to enable you to study the content of each extract in preparation for questions based on the material in the examination. Consider the scientific explanations and the ideas about how science works that are involved, as well as the issues raised in the sources.
- You may write notes on this copy of the Case Study Source Material, but you will not be allowed to bring this copy, or any other notes you may have made, into the examination room. You will be provided with a clean copy of this Case Study Source Material, together with one additional source, **Source F**, at the start of the Unit 4 examination.
- You are not required to carry out any further study of the topic than is necessary for you to gain an understanding of the ideas described and to consider the issues raised. You are not required to understand any detailed **science explanations** beyond those outlined in **Sources A**–**E** and those in the *Science in Society* specification.
- It is suggested that a minimum of three hours detailed study is spent on this Case Study Source Material.

Source A: adapted from an article in Metro, 11 March 2013

Antibiotics resistance as big a risk to Britain as terrorism, claims medical chief

The danger posed by the growing resistance to antibiotics should be ranked alongside terrorism on the list of threats to Britain, the Government's Chief Medical Officer has claimed.

Professor Dame Sally Davies described the issue as a 'ticking time-bomb' and said it should be added to the National Risk Register.

The Chief Medical Officer warned that routine operations such as hip replacements could become deadly in a couple of decades if the ability to fight infection is lost.

Dame Sally said the problem is 'as important as climate change for the world' and urged the Government to raise the issue when meeting political leaders at the G8 summit in London next month.

In her latest report, Dame Sally sets out a call for action about how to tackle the 'catastrophic threat'.

She called for better protection of the current stock of antibiotics, better incentives for the pharmaceutical industry to develop new drugs and asked ministers to ensure the issue is placed on the register.

Dame Sally's report states: 'There is a need for politicians in the UK to prioritise antimicrobial resistance as a major area of concern, including on the national risk register (specifically the National Security Risk Assessment) and pushing for action internationally as well as in local healthcare services.

'Antimicrobial resistance is a ticking time-bomb not only for the UK but also for the world.

'We need to work with everyone to ensure the apocalyptic scenario of widespread antimicrobial resistance does not become a reality.

'This threat is arguably as important as climate change for the world.'

The Chief Medical Officer commented: 'Antimicrobial resistance poses a catastrophic threat. If we don't act now, any one of us could go into hospital in 20 years for minor surgery and die because of an ordinary infection that can't be treated by antibiotics.

'And routine operations like hip replacements or organ transplants could be deadly because of the risk of infection.

'That's why governments and organisations across the world, including the World Health Organisation and G8, need to take this seriously.

'This is not just about government action. We need to encourage more innovation in the development of antibiotics – over the past two decades there has been a discovery void around antibiotics, meaning diseases have evolved faster than the drugs to treat them.'

She said that there has been a 'discovery void' in the field since 1987 and pharmaceutical companies need to be incentivised to develop new antibiotics.

'We have also been waiting for the next new antibiotic to come along and treat those resistant cases

but the pipeline is drying up,' she said.

'There are no new classes of antibiotics in the pipelines across the world and there are very few in development.

'That's because we have not, as a global society, incentivised producing antibiotics. We have market failure and we really need to do something about this.'

In addition to encouraging the development of new drugs, the report highlights that looking after the current stock of antibiotics is equally important.

The Chief Medical Officer also said that more action is needed to tackle the next generation of healthcare associated infections, including new strains of pneumonia-causing *Klebsiella*, which will be harder to treat.

She said the issue should also be considered by the Department for Environment, Food and Rural Affairs because around 50 per cent of antibiotics used in the UK are given to animals.

She added that the issue is 'key for the economy' because infection – including NHS costs and people taking time off work when ill – is already estimated to cost England £30 billion a year.

The Department of Health said it will soon publish the UK Antimicrobial Resistance Strategy setting out a five-year action plan aiming to address the issue.

Source B: from www.pbs.org, 22 October 2013

Who's Trying to Fix the Pipeline Problem?

by Emma Schwartz

The problem is clear: there aren't enough new antibiotics. The question is why aren't more pharmaceutical companies filling the gap – and what's being done to try to reverse this trend?

Most experts point to three big reasons for the decline in pharmaceutical companies developing antibiotics.

The first is science. Antibiotic researchers say it's gotten harder to find new drugs. Most early antibiotics were discovered by identifying naturally occurring antibiotic properties in soil samples, but these research efforts aren't happening at the same pace anymore.

What's more, Gram-negative bacteria are inherently harder to find new drugs for because their double cell wall makes it more difficult to get enough antibiotics to penetrate and ultimately kill the bacteria.

"It is just challenging biologically to find chemicals that you and I can tolerate in large concentrations without side effect," says John Rex, clinical research director of antibiotic development at AstraZeneca, one of the few large companies in the field.

Economics have also played a major role in the shift away from antibiotic research. Antibiotics aren't easy drugs to make money off of. Unlike diabetes or blood pressure medication, where patients usually need to take the drug for life, antibiotics are short-course therapies, less likely to create a dependable market. There have been some exceptions, such as Pfizer's Zithromax, which netted over $1 billion annually. But generally, drugs for chronic disease offer a higher return on investment than antibiotics.

The relatively low market price for antibiotics is another financial roadblock for drug companies. "We're not comfortable as a society paying more than say $100, $200 for an antibiotic course, because we've been sort of spoiled by the penicillin experience," explains Brad Spellberg, an infectious disease specialist at Harbor-UCLA Medical Center. "We're willing to shell out tens of thousands of dollars for cancer chemotherapy but we're not willing to do that for antibiotics."

The third key hurdle for antibiotic development is the regulatory environment. The Food and Drug Administration requires three stages of clinical trials to test the safety and efficacy of new drugs, and the third stage requires testing a candidate drug on large numbers of people. The clinical trials can be expensive and, industry officials argue, challenging to conduct for diseases that can kill people within [days] of contracting them. They say that a new model may be necessary for testing antibiotics in clinical trials if they are to bring new antibiotics to market, perhaps clinical trials with fewer people in them.

The result is that only a handful of big pharmaceutical companies are involved in antibiotic research and development. Some smaller companies and biotechs are also doing research, but many don't have the financial ability to take a potential drug through expensive clinical trials.

Yet there are some efforts to help jumpstart further antibiotic research and development.

Among those was a law passed by Congress last year called the GAIN Act. The bill gives companies that develop new antibiotics an additional five years of patent protection. One company

already taking advantage of these incentives is Cubist, a smaller drug company that has focused on antibiotic research. It has a Phase III drug candidate targeting some Gram-negatives, which will receive this extended patent protection if it makes it through the last stage of clinical trials.

The federal government is also trying to put more attention and money toward antibiotic development research. In May, The Biomedical Advanced Research and Development Authority (BARDA), a unit of the Department of Health and Human Services involved in biodefense, awarded GlaxoSmithKline, one of the few large pharmaceutical companies still doing antibiotic research, a $200 million contract to develop new antibiotics.

An FDA committee is also reviewing potential regulatory changes to attract more companies into this research area, such as changes to clinical trials or ways to include additional kinds of data. And the National Institutes of Health continues to invest in basic research on antibiotics.

But groups like the Infectious Disease Society of America (IDSA) say more is still needed to reverse the trend before it's too late. They have proposed a plan called Limited Population Antibacterial Drug Approval Mechanism to allow potential drugs to be put in use for very sick patients with scaled-down clinical trials. They say it's similar to a program used for rare diseases and argue that the benefits for patients who might otherwise die outweigh the safety risks.

Meanwhile, there are seven potential drug candidates to address Gram-negatives in ongoing clinical trials, according to a study published this year by the IDSA. The downside is that none of them would treat all of the resistant Gram-negatives. This poses a treatment challenge for doctors because it can be several days before testing tells them exactly what kind of bacteria is causing an infection. And if doctors prescribe an ineffective antibiotic during this waiting period, they are giving the bacteria a chance to become even more resistant.

For now, the new drugs can't come fast enough. "The lack of a robust research and development pipeline is a huge problem for patients today and for the future," says Helen Boucher, an infectious disease specialist at Tufts Medical Center and co-author of the IDSA study. "That's the alarm we've been trying to sound."

Source C: from www.parliament.uk, October 2013

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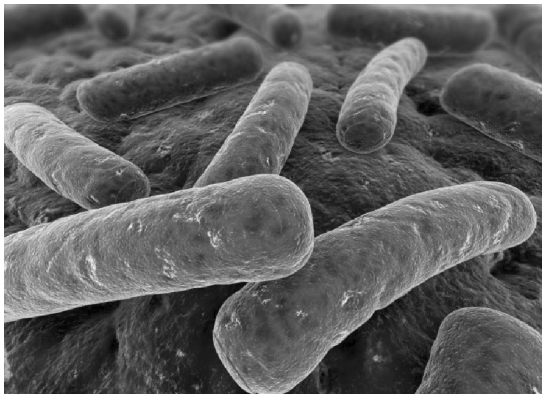
POSTNOTE

Number 446 October 2013

Antibiotic Resistance in the Environment



Disease causing bacteria are becoming increasingly resistant to antibiotic drug treatment. Diseases once controlled by antibiotics are re-emerging as serious risks to human health. This POSTnote outlines the hazards posed by resistant bacteria, the sources of resistance in the environment and measures that may reduce these risks globally.

Background

Antibiotics have revolutionised health care. For example, penicillin has saved tens of millions of lives since its discovery.[1] However, the life-saving role of antibiotics is threatened by the emergence of antibiotic-resistant 'super-bugs'.[2-4] The G8 science ministers meeting in 2013 highlighted antibiotic resistance as one of the top threats facing humanity.[5] The difficulty in tackling the global spread of resistance was also highlighted in a World Health Organisation (WHO) report which suggested that no single factor, or isolated intervention, would prove successful in reducing the threat.[6]

Antibiotic Resistant Bacteria

Antibiotic resistance is a natural phenomenon that has been present in bacteria in the environment for millennia.[7,8] However, the accumulation of manufactured antibiotics in the environment creates the conditions for proliferation of resistant bacteria,[9,10] through the processes explained in Box 1. Resistance is most likely to arise and persist in locations regularly exposed to antibiotics and with poor sanitation.[16-21] The main factors contributing towards resistance vary between countries; for example key problems include self-prescription in India,[22] unregulated pollution in developing countries, such as Cuba,[23] and antibiotic use in animal growth promotion in the USA.[88]

Overview

- The presence of resistant bacteria in the environment has been rising because of increased antibiotic use in humans and animals.[25-28]
- Resistant bacteria from human and animal origin enter aquatic and terrestrial environments. Manufactured antibiotics entering the environment create conditions for the proliferation of resistant bacteria.
- Resistant bacteria can be passed between humans, animals and the environment. It is difficult to quantify the risks associated with each of these routes because of the complexity involved.
- The current rise in antibiotic resistant bacteria is a global problem that would require international action to reverse.[25]

Once resistance is present it can be passed between distantly related species of bacteria and quickly disseminated around the globe.[25] The environmental spread of resistance is primarily governed by two factors:

- the release of substances into the environment that promote resistance
- the release of antibiotic resistant bacteria directly into the environment.[16-21]

Box 1. How Antibiotic Resistance Develops and Spreads

Antibiotic exposure promotes resistance by favouring mutations that confer antibiotic resistance in bacteria. These genetic changes can decrease cell wall permeability, preventing antibiotics from entering the bacteria; produce 'efflux-pumps' which actively remove antibiotics from the bacteria; and produce enzymes that destroy antibiotics (see below). Once resistance has arisen the use of antibiotics promotes the proliferation of resistant bacteria. The genes conferring resistance can then be transferred between bacterial species through a process called horizontal-gene transfer.

Resistant Enzymes

Of major concern is the emergence of two enzymes called NDM-1 (New Delhi metallo-beta-lactamase-1)[11] and CTX-M beta-lactamase. NDM-1 provides resistance to the antibiotics cephalosporin and carbapenem and CTX-M provides resistance to cephalosporins. The genes responsible for producing these two enzymes have successfully transferred between different bacterial species.[12-14] It has been suggested that if NDM-1 were transferred to a highly contagious bacterium there could be a pandemic against which modern antibiotics would be ineffective.[15]

In many countries antibiotic use in human medicine has been recognised as a major factor contributing towards the rise in resistance (POSTnote 416),[13,15,24] especially in developing nations where drugs regulation is poor and over-the-counter medication is readily available.[6,22] However, scientific evidence suggests that environmental factors are also contributing towards the rise in antibiotic resistance.[16-21,25-27,72] These factors include (1) antibiotics and resistant bacteria accumulating in the waste water treatment process, (2) the release of biocides, antibiotics and resistant bacteria into the environment, (3) the use of antibiotics in agriculture and (4) the direct animal to human transmission of resistant bacteria.

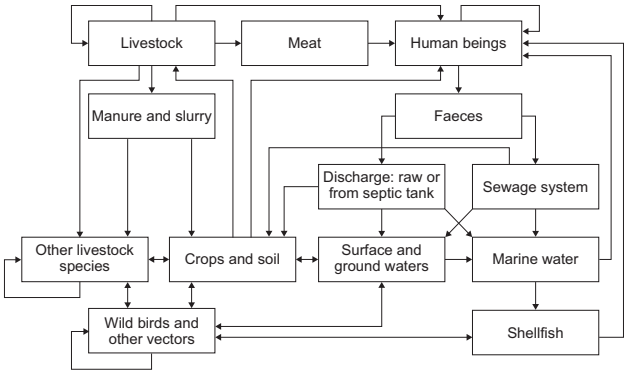
Environmental Sources of Resistance

There has been an increase in resistance to antibiotics in soil bacteria since antibiotics started to be manufactured in the 1940s.[28] There are two reasons for this:[25-27]

- Resistance is present within bacteria in the environment through exposure to naturally occurring antibiotics. However, the proportion of bacteria with resistance is increased through exposure to manufactured antibiotics.
- Antibiotics and resistant bacteria from human and animal origin directly enter terrestrial and aquatic environments, such as soil, marine areas and surface waters.

Figure 1 provides a simplified summary of the complex pathways involved in the environmental spread of resistance.

Figure 1 Links Between the Sources of Resistance[16]



Waste Water

Antibiotics and resistant bacteria from human sources have been detected in all stages of the sewage treatment process, including in treated water released to the environment[29-31] and sludge applied to farmland.[32,33] For example, the fluoroquinolone group of antibiotics, despite degrading in the environment once exposed to sunlight, have been detected on farmland.[21,34-35] Laboratory studies identified human sewage sludge applied as fertiliser as the main source.[35] The highest concentrations of antibiotics and resistant bacteria have been recorded in effluent released from hospitals and drug manufacturing sites in developing countries (Box 2).[36,37]

Box 2. Antibiotics in Waste Effluent

Hospitals and drug manufacturing sites often have the highest concentrations of antibiotics in their effluent, especially in developing countries where the majority of drugs are manufactured. One waste treatment plant in India, receiving effluent from 90 drugs manufacturing companies, was found to release 45 kilograms of the drug ciprofloxacin into the nearby river each day.[36] This equates to 45,000 daily doses. There is also evidence of untreated waste being disposed of directly into water bodies in India. Concentrations of penicillin and other antibiotics similar to those shown to promote resistance have been identified in rivers in China.[37] These sources of antibiotic pollution are of global concern.

Biocides

Whereas antibiotics are types of medication designed to kill bacteria, biocides are substances used to control a wide range of micro-organisms, including fungi, viruses and algae, in different environments. They are used as antiseptics, disinfectants and preservatives. They are present in a range of consumer, healthcare, food and industrial products. There is evidence that microbial exposure to biocides can give rise to resistance to antibiotics.[61,62] This has been demonstrated within laboratory settings for a number of biocides, notably triclosan,[61,63] but environmental studies remain scarce. Triclosan is a commonly used biocide present in deodorant, toothpaste and cleaning products.

Biocides can reach much higher concentrations than antibiotics in wastewaters and in some river water. In some waste effluent the concentration is as high as that shown to promote resistance in the laboratory.[61-64] There is also evidence that heavy metals such as calcium and zinc, which are often detected in high concentrations in waste effluent and sludge, may have the ability to promote antibiotic resistance in the environment.[65-67]

Agriculture

Globally around 70% of antibiotic use is in agriculture.[86] Antibiotics are used to treat individual animals, prevent disease (prophylaxis, regulated in the UK) and to promote rapid growth (banned in the EU since 2006). In the UK, the veterinary use of antibiotics is not monitored.[38] However, it is estimated that 30% of antibiotics are used in veterinary medicine,[39] 87% of which is in food-producing animals.[40]

A proportion of antibiotics provided to livestock enters the environment via urine and faeces.[9,10,16,41,42] The quantity of antibiotics excreted and their persistence in the environment is drug dependent. For some types of antibiotic up to 90% of a dose can be excreted in urine and 75% in faeces.[84,85] Field studies on experimental farms have confirmed that crops, such as wheat, lettuce and carrot can take up substantial amounts of antibiotics by the roots.[43,84] However, there is a lack of studies on the fate of antibiotics once in the environment and subsequent hazards posed to humans. There is greater understanding of the link between antibiotic use and resistant bacteria in the environment. Farms in the USA have been shown to have increased numbers of resistant bacteria within their lagoons when antibiotic use is increased.[41] Lagoons are then used for crop irrigation and could provide a direct route for contaminating food with resistant bacteria.[41,42]

Turn over ▸

Assessing the risk from resistant bacteria on UK farms would require relevant studies and monitoring.

Resistant Bacteria in Livestock
Resistant bacteria are being transmitted from livestock to humans both directly and via contaminated food.[43-55,84,85] Transmission from humans to animals (from owners to pets) also occurs.[87] A 2008 European Food Safety Authority (EFSA) report stated that:[44]

- the main source of resistant *Salmonella* and *Campylobacter* in humans is food, such as poultry
- animal-derived products are a potential source of MRSA in humans
- cattle is a major source of resistant *E. coli* that may colonize humans via contaminated meat. *E. coli* bacteria in the faeces of cattle in the UK and elsewhere have been shown to contain the CTX-M beta-lactamase enzyme giving rise to resistance to critically important antibiotics[73,74]
- there is potential for food handlers to contaminate food during preparation, as already detected for MRSA and resistant *Shigella*
- avoparcin (an antibiotic of last resort) used in livestock, particularly pigs, was linked to increased resistance to a chemically similar drug, vancomycin, in the life-threatening human pathogen, *Enterococcus faecalis*.[73] Avoparcin was banned for use in farming in the EU in 1997.

There is also evidence of direct animal to human transmission of resistant bacteria. For example, MRSA is usually acquired from human-to-human contact in clinical environments or from visiting countries with a high incidence of MRSA.[45] However, livestock-associated MRSA can be responsible for human cases, as has been shown in Germany.[46-48] There is also evidence of cattle-to-human transmission in Denmark and the UK,[49-52] where cattle farmers are twenty times as likely to carry MRSA as other members of the public.[53] Further evidence of resistant bacteria being passed from animals to humans comes from a study in the USA, where farm workers on intensive farms carried significantly more bacteria with resistance to multiple antibiotics than workers on antibiotic-free farms.[54] There is also evidence that resistant bacteria can be inhaled in dust particles released from intensively reared animals.[75] A recent review by the World Economic Forum suggested that resistant bacteria in livestock may potentially cause shortages of food due to untreatable infections in livestock.[55]

Aquaculture
Aquaculture in the UK has seen significant reductions in antibiotic use. Currently less than 1% of antibiotics are sold for use in aquaculture.[56] However, developing nations continue to use high levels of antibiotics. A review on global antibiotic use in aquaculture identified:[57]

- prophylactic use of medically important antibiotics, such as tetracycline
- that genes for resistance have arisen in aquaculture and been transmitted to animal and human pathogens
- that fish pathogens are one potential route for *E. coli* transmission to humans
- that a strain of resistant *Salmonella* identified in human populations around the world is believed to have originated from aquaculture systems in the Far East.[58]

In the UK, vaccines and legislation have reduced antibiotic use, but a large proportion of consumed fish are imported from non-EU countries. For example, 40% of fish produced in China is bought by EU countries.[16] Unregulated antibiotic use in aquaculture systems in China, and other developing nations, may have global implications for animal and human health.[57]

Wildlife
Recent scientific publications suggest that wild animals could be involved in the environmental spread of resistant bacteria.[9,10,16] A study conducted in a remote location in Finland found a near absence of resistant bacteria in faeces of wild animals (moose, deer and vole),[60] while a study conducted in the Wirral, UK, found high levels of resistant bacteria in the faeces of forest rodents.[59] This suggests that UK wildlife is being exposed to antibiotics and resistant bacteria of human origin,[16] indicating that wildlife could be vectors in the environmental spread of resistance.[9,10] This is likely to vary between locations.

Policy in the UK

An overview of UK and international policy is summarised in Box 3. At present, there are no discharge standards for antibiotics and resistant bacteria entering the environment. The Priority Substances listed in Annex X of the Water Framework Directive, which sets safe discharge standards for hazardous substances entering the environment, does not include antibiotics or the majority of biocide compounds (however, see Biocidal Product Regulation EU 528/2012).[78]

The Department of Health (DH) has recently published a five-year cross Government Antimicrobial Resistant Strategy and Action Plan, which covers use of antibiotics in both human and animal medicine.[72] While the report has been welcomed by groups such as the RCVS (Royal College of Veterinary Surgeons), it has been criticised for not addressing the scale of the problem by farming groups such as the Soil Association.[81] There have been a number of campaigns by groups such as the Soil Association,[68] Farmers Weekly,[69] Sustain[70] and the Sustainable Food Trust[71] calling for reductions in antibiotic use and an end to antibiotic use in healthy animals. Additionally, the poultry industry has introduced self-imposed restrictions in antibiotic use.

Box 3. Antibiotic Regulation in Agriculture and Food in the UK
In the UK, the use of medicines in agriculture and aquaculture is regulated by the Veterinary Medicines Directorate (VMD). Antibiotics should only be administered by registered veterinary surgeons. Once medication has been administered there is a period during which the animal cannot be slaughtered for food or its products enter the food chain. Best practice guidelines are available from the Responsible Use of Medicines in Agriculture Alliance (RUMA). The safety levels of antibiotics and bacteria in food for human consumption are monitored by the Food Standards Agency (FSA).

International Regulation
The World Organisation for Animal Health (OIE) is the intergovernmental body for improving animal health worldwide. Among other roles it advises on animal medication policy, antibiotic use and controlling the spread of resistance.

Alleviating the Risk of Resistance

In the past, resistance to antibiotics was less of a problem because the emergence of resistant bacteria was followed by the development of new antibiotics. However in recent decades fewer new classes of antibiotics have been developed and none are currently in production (Box 4) (POSTnote 311).[77,79]

A number of reports and scientific publications have considered the risk of antimicrobial resistance and provided recommendations on increased monitoring and other courses of action.[3-6,16,72,76,80]

Antibiotics and Biocides

Use in Humans

Campaigns have already reduced the inappropriate use of antibiotics in human medicine. However, further reductions are required and recent reviews have suggested: [3-6,16,72,76,80]

- Antibiotics of last resort should only be used when necessary. This reduces the likelihood of resistance developing and will help reserve critically important drugs. While this is often the case in the UK it is not adhered to in many developing countries.
- Access to and use of surveillance data should be improved. [72]
- There should be increased development of alternative therapies, i.e. bacteriophages (virus that kill bacteria). [72]
- Improving public education on appropriate antibiotic use.
- Use of degradable antibiotics that do not persist in the environment is increased.
- Pharmaceutical products are sourced from ethical companies which do not pollute the environment with antibiotics.
- Increased focus on the Biocidal Product Regulation (BPR, Regulation EU 528/2012 effective from Sept 2013) that requires evidence that a biocidal product will not give rise to microbial resistance. [78] The EU will also fund research on the role of biocides on the spread of resistance. [89]

Use in Agriculture

Antibiotic use on British farms is already lower than many non-EU countries, including the USA. However, countries such as Denmark and Sweden have substantially lower antibiotic use than in the UK and the French government has introduced plans to reduce antibiotic use over the next five years.[80,82] It has been argued that reductions in antibiotic use could be achieved in agriculture without affecting animal health through: [3-6,16,72,76,80]

- Improved animal husbandry and reduced crowding, which reduce disease outbreaks and thus reliance on antibiotics (see POSTnotes 391 and 404, and DH 5-year strategy).
- Improved access to and use of surveillance.[72]
- Improved treatment of animal waste before being applied to farmland to remove antibiotics and bacteria.
- Composting of manures and aeration of slurry greatly reduce bacteria numbers.
- Educating farmers to reduce antibiotic use and provide support to achieve this (available through RUMA).
- Minimising prophylactic use of antibiotics. Prophylactic use is believed to be an ongoing source of resistance by organisations such as the Soil Association.

Box 4. Antibiotic Drug Development

Development of antibiotics has been impeded by a range of factors. These include the low return on investment for development of antibiotics compared to drugs used to treat chronic illnesses and the increased difficulty in discovering new antibiotics once easier ones have been identified. Regulatory burdens have also made the development of new drugs both time consuming and expensive. This is particularly problematic for small pharmaceutical companies with limited funds.

It has been suggested that drug development could be incentivised by increased financial return through extended patents, new regulatory framework based around non-clinical (animal) trials combined with human studies rather and the use of smaller patient numbers. These changes would reduce the time and cost of developing new drugs. Collaborations between academic institutions and pharmaceutical companies could also increase the rate of drug development.

- Increased research into antibiotic alternatives in food production, such as bacteriophages.
- Reserving medically important antibiotics for human medicine (POSTnote 433). There have been campaigns to reserve fluoroquinolones, which are recognised as vital for human use by the WHO. However, the need for this has been disputed by the Veterinary Medicines Directorate (Box 3).

Improved Waste Treatment

The waste treatment process has not been designed to prevent antibiotics and resistant genes from being released into the environment. A number of improvements to the waste treatment process have been suggested.[30] These include catalytic oxidation of pharmaceutical compounds. This is a new area of research using iron and hydrogen peroxide to break down antibiotics and compounds such as triclosan[83]. Alternatively, established natural and artificial wetlands have been shown to break down high levels of antibiotics and bacteria in their root structures. Over 90% of veterinary drugs can be removed by wetlands.

It has also been suggested that establishment of hospital wastewater treatment plants and additional investment in the infrastructure of treatment plants could reduce antibiotics and resistant bacteria entering the environment. There are currently no limits for the concentration of antibiotics entering the environment; however, global safe discharge standards have been proposed.[25]

Endnotes

For references please see:
http://www.parliament.uk/documents/POST/postpn446_Antibiotic-resistance-in-the-environmentreferences.pdf

The POSTnote contained 89 references which have been removed.

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of policy issues that have a basis in science and technology. POST is grateful to Paul Coleman for researching this briefing, to BBSRC for funding his parliamentary fellowship, and to all contributors and reviewers. For further information on this subject, please contact the co-author, Jonathan Wentworth.

Turn over ▸

Source D: press release from the Soil Association, 10 September 2013

Government's antibiotic strategy will not stop excessive farm use of antibiotics

In a new report setting out the Government's five-year strategy for dealing with the rise of antibiotic resistance [1], the Chief Medical Officer, Dame Sally Davies and the Chief Veterinary Officer, Nigel Gibbens warn that 'the rapid spread of multi-drug resistant bacteria means we could be close to a point where we may not be able to prevent or treat everyday infections or diseases'. They say that 'the harsh reality is that infections are increasingly developing that cannot be treated' and blame the 'inappropriate use of these valuable medicines' and the fact that 'the development pipeline for new antibiotics is at an all-time low'.

The Soil Association, which has long campaigned for antibiotics to be used more sparingly, welcomes the report but is disappointed by the lack of specific recommendations for reducing antimicrobial use in farming. The Soil Association is concerned that the Government's strategy for controlling resistance contains only general advice that farmers and vets should use antimicrobials responsibly, but is leaving it to the industry to decide what is, and what is not, responsible.

Evidence reviewed by the Soil Association indicates the farm use of antibiotics plays a significant role in the development of resistance in certain human infections [2], especially those which cause food poisoning, such as campylobacter and salmonella, and the type of E. coli bacteria responsible for an estimated one million urinary-tract and 39,000 life-threatening blood-poisoning infections every year [3].

Soil Association policy advisor, Richard Young, said "There is a wealth of evidence showing antibiotic resistance can and does pass to humans from animals through the food chain and the environment. Some individual vets and some farmers are doing outstanding work in reducing the use of antimicrobials, but we need an effective national strategy. In relation to farm antibiotic use the Government's overall approach is weak and ineffectual.

"As it stands, the strategy will be grossly inadequate to address the huge scale of the farming problem. In our view antimicrobials should no longer be given to healthy farm animals as a cheap insurance against the possibility of disease. The strategy also contains no proposals for new legislation to ensure that farm animals are kept in healthier, less intensive conditions, even though it is clear this reduces ill health and the need for antimicrobials."

The Government report acknowledges that 'use of antibiotics in animals is an important factor in contributing to the wider pool of resistance'. The importance of education, hygiene, surveillance of resistance and of antibiotic use are all emphasised, but there are no goals set for reducing overall antibiotic use or the use of the critically important antibiotics. No commitments are made to collect antibiotic-usage data by animal species, resistance data on farm-animal E. coli, or to review the widespread practice of using antibiotics routinely in the feed and water of healthy animals – all recommendations which have previously been made by independent UK advisory committees [4].

A report published last year by Defra and Department of Health scientific advisors said that animals kept at high stocking densities were at increased risk of developing infections, while those kept extensively were least at risk [5].

Many European countries have already introduced policies which go significantly further than the UK towards reducing farm antibiotic use. The Netherlands reduced farm antibiotic use by over 50% between 2009 and 2012 and has banned routine preventative use. The Dutch have also placed new restrictions on the use of critically important antibiotics [6]. In Denmark, routine use is also prohibited, 97% of poultry no longer receive any medically important antibiotics and there is now a 'yellow-card' scheme which cautions farmers using too many antibiotics [7]. The French Government

has announced an action plan which aims to reduce farm antibiotic use by 25% in five years [8].

In the UK, in contrast, the only progress has been initiated by the industry. The poultry industry, for example, has committed to voluntarily restricting its use of some critically important antibiotics, but the Government seems reluctant to introduce legislation which would enforce this change or to extend it to other species.

The Soil Association is a member of the Save Our Antibiotics Alliance. The use of antibiotics is restricted to the treatment of ill health in organic farming, but the Soil Association also runs workshops on organic farming to help non-organic farmers develop approaches to animal husbandry which result in lower antimicrobial usage [9].

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Notes to Editors

[1] The report, entitled 'UK Five Year Antimicrobial Resistance Strategy 2013-2018' is published by Defra and the Department for Health.https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018

[2] Farm antibiotic use also plays a small role in some other infections such as MRSA and VRE. In many types of infection in humans, however, such as tuberculosis and ear infections in young children, there is no link to the farm use of antimicrobials at all.

[3] See http://www.soilassociation.org/LinkClick.aspx?fileticket=_fGgt7a0eeE%3d&tabid=1841 and http://www.soilassociation.org/LinkClick.aspx?fileticket=yCT9su5iViQ%3d&tabid=1841
For some other infections such as MRSA, there is evidence that the overuse of antibiotics is currently only a small contributor to human infections, but it appears to be a growing one and action is needed to ensure this does not increase.

[4] The Government's official position is that it does not support the routine preventative use of antibiotics in farming, but there are indications that Defra and the Department of Health do not see eye to eye on this. The Strategy report talks about 'facilitating development of sector specific prescribing guidelines, which, for example, advocate minimising the routine use of preventative antibiotics in animal health' but there are no proposals for actually stopping routine preventative use.

[5] See p. 64 of DARC and ARHAI, 2012. ESBLs – A threat to human and animal health? http://www.vmd.defra.gov.uk/pdf/ESBL_report.pdf
The report states, 'In general, for animals, the risks of acquiring bacterial infections also tend to be highest in those individuals that are ill and/or under antimicrobial treatment, followed by those kept in higher stocking density and/or mixed with other animals on a regular basis and lowest for animal kept singly or extensively.'

[6] Letter from Dutch Chief Veterinary Officer, Dr Brushcke, to Compassion in World Farming, January 2013.

[7] Danish Approach to Antibiotic Prescribing, Veterinary Record, 2013, http://veterinaryrecord.bmj.com/content/173/8/178.1.abstract

[8] Ministère de l'agriculture, de l'agroalimentaire et de la forêt, 2012. National action plan for the reduction of the risks of antibiotic resistance in veterinary medicine, http://agriculture.gouv.fr/IMG/pdf/130208PlanABR-GB-2012-BD_cle8786a1.pdf

[9] The Save Our Antibiotics Alliance was founded by the Soil Association, Compassion in World Farming and Sustain. It currently has 17 members.

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Opinion

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Treatment, promotion, commotion: antibiotic alternatives in food-producing animals

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Alternatives to antibiotics are urgently needed in animal agriculture. The form these alternatives should take presents a complex problem due to the various uses of antibiotics in animal agriculture, including disease treatment, disease prevention, and growth promotion, and to the relative contribution of these uses to the antibiotic resistance problem. Numerous antibiotic alternatives, such as pre- and probiotics, have been proposed but show variable success. This is because a fundamental understanding of how antibiotics improve feed efficiency is lacking, and because an individual alternative is unlikely to embody all of the performance-enhancing functions of antibiotics. High-throughput technologies need to be applied to better understand the problem, and informed combinations of alternatives, including vaccines, need to be considered.

Introduction: the need for antibiotic alternatives

Antibiotics have long been used for treating disease, preventing disease, and improving feed efficiency in conventional livestock and poultry production. Their use was implemented in the 1950s as a way to meet the increasing demand for food. Antibiotics given to pigs were estimated to save as much as 20% of feed per pound of weight gain [1]. Whether the same performance enhancement continues in the present remains unclear [2]. Concurrent with antibiotic use, antibiotic-resistant bacteria were isolated from animals receiving antibiotics from the earliest days. Concerns quickly arose about the development of resistant pathogens associated with animal and human diseases, as well as increases in the antibiotic resistance gene pool in commensal bacteria, but the risk was outweighed by the benefits of reduced cost to the industry [3]. In addition to improving feed efficiency, antibiotics in agricultural animals are used to improve animal welfare, and so there must be a balance between antibiotic use and preserving antibiotic efficacy for both human and animal health. Sixty years later, the debate continues in the USA and abroad. Concerns over the spread of antibiotic-resistance genes to human and animal pathogens continue to drive the debate [4].

European nations have implemented bans on the use of growth-promoting antibiotics, and the practice in the USA is under increasing regulatory and political scrutiny. The Center for Veterinary Medicine of the US Food and Drug Administration (FDA) recently issued a 'Guidance for Industry' that describes requirements for label claims and recommended restrictions on uses of antibiotics in food-producing animals [5]. This document outlines voluntary limitations on the use of antibiotics based on the risk assessment of resistance development and on the importance of a given antibiotic to human therapy. The two guiding themes for the risk assessment were that antibiotics should only be used for prevention, control, and treatment of specific animal diseases and a requirement for veterinarian involvement in the decision to use antibiotics. Although the new FDA guidance allows antibiotic use in food-producing animals to control specific diseases, the use of antibiotics for growth promotion, increased performance, and improved feed efficiency will no longer be permitted. Additionally, certain antibiotics of critical importance, such as third-generation cephalosporins, are likely to be restricted to human use in the near future even if they are important for animal disease treatment [6]. This is in part because of the demonstrated potential for veterinary antibiotics (e.g., tylosin) to coselect for resistance to antibiotics of human importance (e.g. vancomycin) [7]. It is important to recognize that the FDA guidelines may lead to more sickness and to an increased demand for therapeutic antibiotic treatment in livestock (as was seen in Denmark [8]). Alternatives to growth-promoting antibiotics are therefore only a fraction of the problem; we also need alternatives for disease prevention and control, and treatment of animals (Box 1).

Challenges of antibiotic alternatives

Alternatives to antibiotics in food-producing animals are urgently needed but present a difficult problem in part because of the complexity of the gastrointestinal (GI) eco-system. The GI tract is an intricate organization of epithelial cells (the mucosal barrier), the mucosal immune system, and microbiota. The epithelium with its mucus layer separates the microbiota, pathogens, and unfavorable environmental conditions from the host, and is also the main site of nutrient absorption. The GI microbiota competes with intestinal pathogens for nutrients and binding sites, produces chemical modulators of intestinal health such as butyrate, and influences immune maturation. A healthy microbiota filled with beneficial microbes is certainly important to animal health, but both a healthy microbiota

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Box 1. Defining commonly misunderstood concepts

Investigating alternatives to antibiotics in agriculture requires an understanding of the language of antibiotic use in agriculture. Below are the definitions of several concepts that are often used imprecisely.

Subtherapeutic vs. subinhibitory
Subtherapeutic is not synonymous with subinhibitory. A subtherapeutic dose of an antibiotic is an amount usually given for performance enhancement and is less than the amount used to treat disease (therapeutic dose). Subtherapeutic is defined by the effect of an antibiotic on the animal. By contrast, a subinhibitory dose of antibiotic is less than the minimal inhibitory concentration, which is defined as the concentration necessary for inhibition of bacterial growth under specific in vitro conditions prescribed by the Clinical Laboratory Standards Institute. Subinhibitory is defined by the effect of an antibiotic on bacteria.

Animal pathogen reduction vs. human pathogen reduction among animal commensal bacteria
Reducing the prevalence of pathogens in the animal gut microbiota can mean two things: inhibiting potential pathogens of the animal and inhibiting potential foodborne pathogens that inhabit the animal's gut. The former but not the latter is considered when discussing alternatives for antibiotics because foodborne pathogens are not targeted by antibiotics administered to animals.

Growth promotion vs. treatment, prevention, and control of specific diseases
Antimicrobial growth promoters are antibacterial compounds that are added to animal feed or water in subtherapeutic amounts for extended periods of time to enhance production performance of agricultural animals as measured by increased feed efficiency (ratio of feed input to weight gain). This use of antibiotics for growth promotion is prohibited in the European Union and the US FDA has proposed restrictions. Animals are susceptible to bacterial diseases, however, and so therapeutic doses of antibiotics over shorter timescales to treat and control specific bacterial diseases are warranted and allowed.

and its converse, dysbiosis, are poorly defined. Metagenomics, meta transcriptomics, and other 'omics' technologies provide an opportunity for defining the microbes and microbial activities that compose and maintain a healthy microbiota [9,10]. Of particular importance is the homeostasis between a healthy microbiota and the immune system because the microbiota modulates innate immune responses to prevent barrier dysfunction and regulates the function of adaptive immune mediators [11–13]. In turn, the host exerts immune tolerance, moderates inflammation, and competes with the microbiota for nutrients, all of which incur an energy cost.

Knowledge about the mechanism of how antibiotics enhance animal growth is important to the development of viable alternatives. How antibiotics increase performance is not clear, but possible mechanisms may include a reduction in total bacterial load, suppression of pathogens, thinning of the mucosal layer, and direct modulation of the immune system [14,15] (Figure **1(a)**). Some gut bacteria may decrease the energy cost to the immune system, yielding surplus calories for weight gain. Additional growth-promoting effects of antibiotics could include increased nutrient absorption by the host or bacterial community remodeling in favor of non-antagonistic or beneficial bacteria and functions [16,17]. Defining the effect of antibiotics and alternatives on the host and its microbiota will facilitate the development of efficacious solutions.

The different potential mechanisms of antibiotic growth promotion beget different alternatives (Figure **1(b)**). Using targeted approaches to reduce the carriage of specific pathogens or to alter the host immune response will be important to prevent or reduce disease burden and positively influence growth performance without the collateral effects of antibiotic treatment [18]. If the mechanism is dependent on the microbiota or its interaction with the immune system, then feed additives such as pre- or probiotics are appropriate. If the mechanism of growth promotion is via disease prevention or reduction, then the most appropriate alternatives would be vaccines or health-promoting pre- or probiotics. Below we will discuss some of the advantages and disadvantages of various alternatives to antibiotics in agricultural animals.

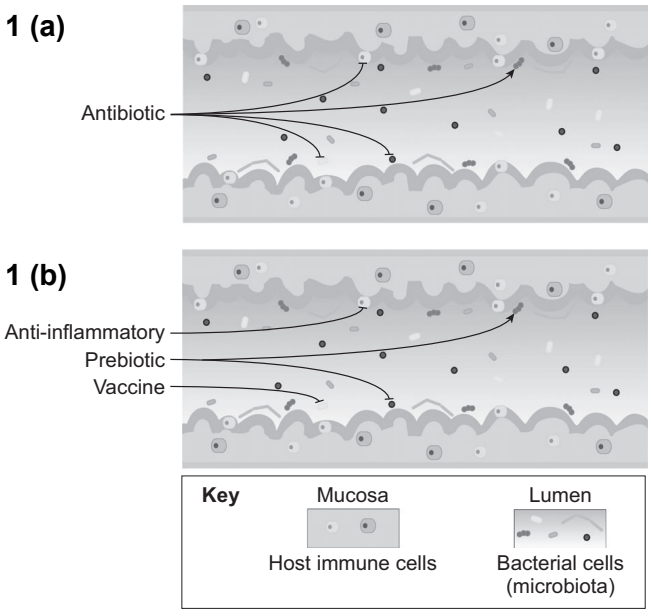

Figure 1. Antibiotics and their alternatives have many effects on the gut microbiome. Shown is a schematic representation of a longitudinal section of the gut, with the lumen in the center, surrounded by the mucosa containing immune cells. **1 (a)** Antibiotics exert positive (arrows) and negative (bars) effects on a variety of factors in the gut: they can inhibit the mucosal immune system, inhibit pathogens, or modulate the microbiota by stimulating some members while inhibiting others, or all of the above. **1 (b)** A potentiated prebiotic is presented as an example of mixed additives, an approach that might be the most comprehensive alternative to antibiotics because each separate component (i.e. anti-inflammatory, prebiotic, and vaccine) replicates a different effect conferred by the antibiotic.

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Feed additives

The nutritional components of animal feed are continually adjusted to optimize the effects on animal health and growth while being largely dependent on feed input costs. Dietary supplementation may also include prebiotics, probiotics, and organic acids. Prebiotics are selectively fermented components of feed (either inherent or added) that modulate the gut microbiota to benefit host health, such as the competitive exclusion of pathogens or the stimulation of health-promoting metabolites [19]. Primary examples of prebiotics include dietary fibers and oligosaccharides. Like prebiotics, in-feed organic acids can be inherent or added, and they function by decreasing the pH of an environment, limiting feed spoilage, and resulting in lower pathogen survival in the gut [20]. Organic acid delivery ranges from the addition of a single component such as lactic acid to complex blends created by fermentation. Probiotics confer benefits analogous to prebiotics but are living cells such as *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Bacillus*, and yeasts [21,22]. Traits important to a probiotic strain include being nonpathogenic, resistance to stomach acids and bile, having the potential to colonize the host, production of nutrients, being free of antibiotic resistance genes or having reduced gene transfer functions, and antagonism of pathogens.

The potential for the above additives to replace antibiotics is well established, and numerous pre- and probiotic products are commercially available and in active use [23–25]. However, the true efficacy of pre- and probiotics in agricultural animals remains unclear because of inconsistent experimental results [26,27]. Explanations for the disparities between studies include differences in experimental conditions, animal age, genetics, and health status. Additionally, the inconsistent results could be attributed to a lack of understanding of the mechanism of action for either pre- or probiotics, as well as unknown interactions among these products, the host, and the GI microbiota. For example, there have been studies that quantify some aspects of the GI microbiota in response to fully characterize the community, leaving the true effect on the microbiota by the probiotic (and vice versa) largely unknown. Thorough study of the changes in the microbiota and host responses to feed additives using next-generation sequencing technologies combined with systems biology approaches will greatly advance this field.

Phage therapy

An additional antibiotic alternative that has enjoyed renewed traction is bacteriophage (phage) therapy. Phage therapy involves the use of bacterial viruses (phages) to attack a specific bacterium or narrow group of bacteria with the advantage over antibiotics being that autochthonous bacteria are unharmed and no dysbiosis occurs [29]. The success of phage therapy is dependent on numerous factors. Phages have a narrow bacterial host range and do not target multiple bacterial pathogens, so the efficient use of phage therapy requires the identification of the pathogen or at least a high suspicion of their presence. It is most efficacious when the bacteria being treated are readily accessible, such as the historical treatment of dysentery [29] or the modern treatment of burn wounds [30]. In addition to being accessible, the numbers of target bacteria need to be high. Experiments using lytic phages to counter the foodborne pathogen *Salmonella enterica* serovar Typhimurium in chickens [31] and pigs [32] have reduced but not eliminated the *Salmonella* load. One confounding factor was that the inoculated phage only persisted in the gut as long as *Salmonella* remained abundant [31]. Also, therapy is most effective when phages are administered soon after bacterial infection. The seminal work of H.W. Smith and colleagues showed that K1 phages injected intramuscularly are 100% effective at curing mice of *Escherichia coli* O18ac:K1:H7 ColV+ infections when injected immediately following bacterial inoculation [33]. The efficacy of the phage treatment was lost, however, when phages were administered 16 h after infection, thus limiting phage therapy to prophylactic or immediate-treatment situations. Another reason why the efficacy of phage therapy needs constant monitoring is that the host immune response may neutralize phages (although this probably only occurs after repeated treatment) [34]. Finally, concern over the target bacteria becoming resistant to the phage often necessitates the generation and administration of phage cocktails [29]. The somewhat boutique nature of phage therapy – requiring specific, accessible, and abundant target bacteria and administration soon after infection – continues to challenge its adoption as a viable antibiotic alternative in Western countries [35].

In addition to the technical challenges, the biological and evolutionary consequences of phage therapy need to be considered. For example, it is important to avoid temperate phages for therapeutic application because of the potential for transfer of virulence or antibiotic resistance genes from the phage to the host bacterium, although even obligate lytic phages harbor genes of unknown function that could also result in undesired gene transfer [36]. One way to avoid this is the use of purified phage gene products such as lysins to selectively kill target bacteria. Phage lysins could be applied to a bacterial infection, particularly on an accessible mucosal surface, and attenuate the infection by lysing the bacteria from without [37]. The discovery and development of novel phage-derived therapeutics could benefit by the application of functional metagenomic analyses, which are a high-throughput way of bioprospecting for functions of interest such as phage lysins [38].

Vaccines

Vaccines are an underappreciated antibiotic alternative despite the availability of many effective vaccines and a general understanding of vaccine immunology. This is compared with other proposed alternatives such as prebiotics or probiotics where limited mechanistic information is wrought with highly variable efficacy. Based on the more comprehensive understanding of immune responses and protection, vaccines should be a promising antibiotic alternative for reducing the burden of animal diseases and human pathogens in food-producing animals. Additionally, it is important to note that vaccination could also reduce the use of therapeutic antibiotics because of the reduction in clinical infections. As an example, vaccination against the swine pathogen *Lawsonia intracellularis* reduced the need for therapeutic oxytetracycline administration in Danish pigs [39]. Similar decreased need for therapeutic antibiotics might also be anticipated following widespread adoption of vaccines for other pathogens.

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Broad discussion of all possible vaccines targeting animal or foodborne pathogens is beyond the scope of this manuscript due to the specificity of host–antigen interactions. We will therefore consider potential vaccines for one example – the immediate post-weaning period in swine – because it is likely to be a time during which growth-promoting antibiotics are most effective at bacterial disease reduction [40]. Oral vaccination of weaned pigs with live attenuated bacterial vaccines is thought to be the most effective approach for reducing enteric diseases in swine. Live oral vaccination is the strategy for the commercial vaccines available for the reduction of *L. intracellularis* [41] and *S. choleraesuis* [42] associated diseases, but the promise of this approach for swine pathogenic *E. coli* has not progressed to commercial products (e.g., [43]). Efficacious parenterally administered toxoid or adhesin subunit vaccines against experimental *E. coli* infections have been reported but have not been commercialized (e.g., [44]). Experimental vaccines against *B. hyodysenteriae* have been reported as subunit vaccines as well as whole cell bacterins, but evaluation and efficacy data are limited (e.g. [45]). Development of effective vaccines to prevent disease and associated production losses during the post-weaning period should be a priority in the search for replacements for growth-promoting antibiotics. Acceptance and widespread use of vaccinations as alternatives to antibiotics will depend on cost and ease of use. Cost comparisons may be difficult, but administration of live oral vaccines in feed or water could be comparable to administration of antibiotics by these routes.

Mixing additives: potentiated probiotics and synbiotics

Combinations of antibiotic alternatives hold the promise of potentiating each other's efficacy and duplicating the effect of in-feed antibiotics (Figure **1(b)**). The term potentiated probiotics refers to such combinations of probiotics with other additives (e.g. vaccines or organic acids) with the goal of synergistically increasing the effect of the probiotic [23,46]. For instance, it is possible that a prebiotic that only confers gastrointestinal health benefits could support the growth of, and be simultaneously delivered with, a probiotic that competitively excludes a potential pathogen. The most common pairing that has been tested is prebiotics with probiotics, and this combination is termed synbiotic. Like studies utilizing probiotics or prebiotics individually, synbiotic studies have found inconsistent results, with some studies reporting gains in animal performance or decreases in food borne pathogens (reviewed in [26]), but others have not (e.g. [28]). Other combinations such as probiotics and vaccines for food safety have rarely been tested, but a combination of competitive exclusion cultures and a *Salmonella* vaccine resulted in a greater protective effect than either treatment alone [47]. Another attempted approach was a probiotic *E. coli* that produced a microcin that can inhibit growth of *Salmonella*, but *in vivo* experiments were unsuccessful at reducing *Salmonella* shedding [48]. A better understanding of the effects and mechanisms of action of the various components, as enabled by high throughput sequencing, will allow for more rational potentiated probiotic designs, guiding the selection of antibiotic alternatives that best complement each other and best replicate the effect of growth-promoting antibiotics.

Concluding remarks

No 'magic bullet' alternative exists to cover the spectra of antibiotic classes and antibiotic uses in agricultural animals. Alternatives such as vaccines or bacteriophages, although limited to the control of specific bacterial species or strains, benefit from not having antibiotic side effects of perturbing entire microbial populations. Vaccine combinations or phage gene products would yield a broader bacterial target range. Interdisciplinary translational research emphasizing all three components of host health – gut microbiota, intestinal physiology, and immunology – holds promise for discovering antibiotic alternatives (Box 2). This approach is now feasible through new technologies allowing integrated research to simultaneously examine genomes, metagenomes, transcriptomes, and proteomes. As with any animal management approach, a significant challenge for antibiotic alternatives will be low cost per animal, and this challenge should diminish as demand increases. Despite the obstacles, many alternatives have been proposed and productive collaborations among biochemists, microbiologists, immunologists, nutritionists, veterinarians, and animal care managers capitalizing on the latest technologies will define mechanisms and lead to effective solutions.

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Opinion

Box 2. Considering alternatives in the context of host–microbe evolution

The effect of antibiotics and their alternatives on an animal and its gut microbiota is usually examined before, during, and after antibiotic administration. However, evolutionary factors are worthy of consideration, such as the vertical transmission of the hologenome (the combined genetic information of the host and its microbes). It is important to assess the impact of any antibiotic treatment or alternative in terms of future outcomes (e.g. subsequent generations) in addition to immediate outcomes (e.g. disease prevention, increased weight gain, etc.).

The homeostatic symbiotic relationship between hosts and their microbiota is an ancient product of a long co-evolutionary process, and it appears to be vertically transmitted [49–51]. This vertical transmission is tied to evolution because although selection acts on individual genes (both host and microbial), gene selection is influenced by ecological forces such as interactions among microbes and host factors [52]. Host genetics, by shaping the microbial community [51], and ecological forces such as antibiotics and their alternatives combine to influence host–microbial interactions. One theory of evolution, the hologenome theory, is notable in its inclusion of both the host and its microbial community. The hologenome theory considers the holobiont (the host and its microbiota), acting in concert with its total combined genetic information (the hologenome), as a unit of selection in evolution [49].

In the context of the hologenome theory of evolution, it is possible that some of the desired effects of antibiotics are perhaps being vertically transmitted in the microbiota or the host or both, and therefore maintained by the holobiont without continued antibiotic application. The influence of modern production practices, such as directed breeding, on this vertical transmission is unclear. It is additionally unknown whether or not the relatively short history of antibiotic use is sufficient time for an evolutionary change to be detected, but it is tempting to speculate that at some point the holobiont could inherit the benefits of antibiotic treatment and that these benefits would continue in the absence of antibiotics. If that is the case, then the search for alternatives in agriculture animals should focus on maintaining the evolutionary changes brought about by antibiotics in addition to replicating other effects of antibiotics.

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