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Reservoirs of Antimicrobial Resistance

The widespread use of antimicrobials, particularly antibiotics, has accelerated the spread of antimicrobial resistance (AMR) in microbes. A recent report by the Health and Social Care Committee called for AMR to be a 'top five policy priority'.[1] This POSTnote evaluates the main reservoirs of AMR microbes arising from the use of antimicrobials in both humans and animals.

Overview

- Antimicrobial resistance (AMR) is a natural phenomenon exacerbated by the use of antimicrobials in humans and animals.
- Microbes with AMR have been found in humans, animals and the environment, and can transfer between them, but the public health significance of this is not clear.
- The range and quality of surveillance data for antimicrobial use and AMR microbes in humans and animals has improved but there is a continuing lack of environmental data.
- Further research is needed to evaluate the potential public health impacts of AMR in microbes of animals and the environment.

Background

Microbes are microscopic life forms such as bacteria, viruses and fungi. Some microbes cause disease, others are important for our health. Antimicrobials are agents that kill or prevent the growth of microbes and include antibiotics, antivirals and antifungals. However, microbes can evolve to become resistant to antimicrobials and this process is exacerbated by human influences, such as the inappropriate use of antimicrobials in human and veterinary medicine. Antimicrobial-resistant microbes are found in humans, animals and the wider environment. Each of these reservoirs contribute to the spread of AMR.[2] In Europe, there are over 33,000 deaths every year from drug-resistant bacterial infections alone[3] and failure to tackle AMR could lead to a 10-fold rise in this death toll by 2050.[4]

The AMR (O'Neill) Review published in 2016 recommended reducing the "unnecessary use of antimicrobials in agriculture and their dissemination into the environment", noting that the "unnecessary use of antibiotics in animals and agriculture is a significant concern for human health" (see POSTnote 588).[5] The UK Government published its latest 5-Year AMR national action plan in January 2019,[6] which sets a target to further "reduce UK antibiotic use in food-producing animals by 25% between 2016 and 2020 and define new objectives by 2021 for 2025". This will be on top of the 27% reduction achieved between 2013 -2016. However, it notes that "there are gaps in our knowledge, especially on how AMR moves between and among animals, humans and the environment".[6]

This POSTnote covers:

- the spread of AMR in humans and animals;
- the main reservoirs of AMR;
- data for AMR in both humans and animals; and
- future UK priorities in this area.

The spread of AMR

Microbes can be classified depending on the extent to which they cause disease in humans (see Box 1). Of greatest concern to public health are pathogens (disease-causing microbes) that have acquired drug-resistance. Also of concern are opportunistic microbes (those that sometimes cause disease, Box 1).

Microbes can evolve quickly to adapt to their environment and have a natural ability to develop AMR. One such example is the bacterium *Staphylococcus aureus*, which can be both a pathogen and an opportunistic microbe. If a person is treated with antibiotics and they carry *S. aureus*, the antibiotic-susceptible subpopulations of *S. aureus* will be killed. Any remaining subpopulations of *S. aureus* resistant to the antibiotic, such as methicillin-resistant *S. aureus* (MRSA), can continue to grow with less competition for resources.[7,8] Even after antibiotic treatment has stopped, MRSA can persist and healthy adults can become long-term carriers.[9,10] There is a growing consensus that antibiotic resistance in human pathogens is primarily driven by antibiotic use in human medicine.[11] However, a recent systematic review looking at risk factors for antibiotic resistance in humans found that 89% of studies exclusively consider human data and only 11% consider animal and/or

Box 1: Microbial diversity

The average human body is estimated to have about 30 trillion human cells and host 39 trillion bacteria cells, although this can vary from person to person.[12] In total, it is thought that there could be up to 1 trillion different species of microbes on earth.[13] These microbes can be classified by their ability to cause disease:

- **commensal** microbes normally live in or on the body without causing disease.
- **opportunist** microbes can live in or on the body harmlessly but may cause disease following a change to the body such as a wound, or following aging, immune suppression or illness.
- **pathogens** are microbes that cause disease.

The communities of microbes inhabiting each area of the body are known as a microbiota. Microbiotas differ in composition and are defined by the location where they are found. For example, the human gut microbiota differs in composition from the human skin microbiota.[14] Microbiotas are not only present in humans, they can also be found in animals and the external environment.[15,16] There are several mechanisms by which bacteria can share their genetic information, including AMR traits, with their neighbours. One such mechanism is via 'mobile genetic elements' (MGEs),[17] which can transfer genes between different species of bacteria. This increases the potential for wide dissemination of AMR in the bacterial communities within and between different microbiota.[18,19]

environmental reservoirs.[20] Due to this bias, the quantification of risk factors for antibiotic resistance in humans should be interpreted with caution.[20]

Understanding how AMR emerges in microbes and causes them to become a significant threat to human health is a challenge. In the 1980s, the bacterium *Enterococcus faecium* (a human gut microbe) emerged as a leading cause of multidrug-resistant hospital-acquired infection.[21,22] One study analysed samples of *E. faecium* isolated from humans, animals and the wider environment, taken between 1956 -2010, with the aim of understanding this emergence (see Box 2).[23] This study illustrates the complexity of the relationship between the different reservoirs of AMR.

Reservoirs of AMR

When monitoring AMR, three main reservoirs can be considered: humans, animals and the wider environment. Antimicrobial use in human medicine is believed to be the main influence on the presence of AMR in the human reservoir. The same can be said for veterinary medicine and AMR in the animal reservoir. Exposure to waste products from humans, animals and industry influences AMR in microbes of the environment.[24,25,26,27,28] Cross-reservoir transfer of AMR can occur,[29,30,31] for example through:

- close contact between people and animals;[32,33,34]
- animal slurry spread on soil as fertiliser;[35,36]
- bathing in coastal waters;[37,38]
- wild birds acquiring resistant bacteria from the wider environment;[39,40] and
- preparation/consumption of animal products.[41,42,43,44]

These studies suggest that cross-reservoir transfer of AMR is possible, but that quantifying the public health risk of such events is difficult. This is due to the complex nature of AMR transmission.[45,46,47,48] Cross-reservoir transfer of AMR can be influenced by multiple factors, including:

Box 2: The emergence of drug-resistant *Enterococcus faecium*

In 1982, the first multi-drug resistant *E. faecium* strain was isolated from a patient with a hospital-acquired infection. A study suggests that AMR in *E. faecium* emerged following adaptations to two changes in human behaviour. The first of these occurred around 3,000 years ago when humans started to live in larger settlements and domesticate animals. Evidence suggests that this led to genetic changes in some of the bacteria that allowed them to 'jump host' and survive in animals, as well as humans.[49] The second change in human behaviour can be traced back to about 80 years ago when antibiotics were first used in human and animal medicine. This coincided with genetic changes that allowed some of the bacteria to be more capable of picking up new traits (such as AMR) on mobile genetic elements (MGEs).

- the host range of the microbe (the number of different organisms a microbe can survive in);
- the host range of the MGE (Box 1) carrying AMR; and
- the persistence of an antimicrobial agent or its residues in the environment (although this is difficult to assess).

Host range of the microbe

The host range of the 1,400 species of microbe known to cause disease in humans varies considerably.[50] For AMR to cross between reservoirs, the microbe carrying the AMR trait must be able to survive in both reservoirs. For example, *Campylobacter* species are a group of bacteria that commonly cause diarrhoea in humans and are widely found in poultry. Most human *Campylobacter* infections are acquired by consuming or handling poultry.[51] Studies in the 1990s suggested that rates of fluoroquinolone (a class of antibiotic used to treat cases of human diarrhoea) resistant infections in humans were rising.[52,53,54] Fluoroquinolones were widely used in poultry at that time and the *Campylobacter* in poultry given this antibiotic rapidly acquired resistance to it.[55,56,57] It was suggested that fluoroquinolone use in poultry was a factor driving the rising rates of fluoroquinolone resistant infections in humans and this led to fluoroquinolones being banned for use in poultry production in the USA in 2005 (Box 3).[58] Cross-reservoir transfer of resistant microbes between animals and humans is well documented. For example, samples taken from pigs and pig workers showed that they shared the same MRSA strains (see Box 3).[59] However, these cases are complex and the wider risk to public health is not well understood.[60]

Host range of mobile genetic elements (MGEs)

AMR traits are commonly found on mobile genetic elements (MGEs, see Box 1). MGEs have been shown to transfer between commensal and pathogenic bacteria,[19,61] with the potential for wide dissemination of AMR in the bacterial communities of a microbiota. MGEs carried by species of bacteria that can survive in each of the three main reservoirs have increased potential for cross-reservoir transfer of AMR. For example, extended spectrum beta-lactamase (ESBL) genes confer resistance to a group of antibiotics called beta-lactams. A group of MGEs called plasmids are primarily responsible for the spread of ESBL genes, which are frequently transferred alongside other AMR traits.[62,63] Plasmid-based AMR traits are highly mobile and transfer readily within and between different species of bacteria.[64,65,66] Infections caused by these multidrug-

Box 3: Examples of links between animal and human AMR

Fluoroquinolones in poultry and people

Between 1995 and 1996, the US Food and Drug Administration (FDA) licensed two fluoroquinolones for the treatment of respiratory diseases in poultry. By the late 1990s, the prevalence of fluoroquinolone-resistant *Campylobacter* infections in people had rapidly increased. In 2000, the Center for Veterinary Medicine proposed that the use of fluoroquinolones in US poultry be prohibited and the FDA eventually withdrew one of the fluoroquinolones (enrofloxacin) from use in US poultry in 2005.[67,68] The prevalence of fluoroquinolone-resistant human *Campylobacter* infections has continued to increase since the withdrawal of enrofloxacin.[69] The use of fluoroquinolones to treat food-borne diarrhoeal disease in humans could be maintaining the level of resistant *Campylobacter* infections. The prevalence of resistant *Campylobacter* found in samples taken from chickens and chicken meat has also remained stable since the ban on enrofloxacin, indicating that once a microbe has developed resistance this resistance can persist in the absence of the antimicrobial.[70]

MRSA in pigs and pig workers

The same strains of livestock-associated MRSA are commonly isolated from pigs and pig workers in Europe. Pig workers can be persistent carriers of livestock-associated MRSA but these strains of MRSA are rarely transmitted human-to-human.[71,72,73,74,75] A study in Australia isolated two strains of MRSA from pig workers and pigs (ST93 and ST398).[59] ST93 is the second most common strain to cause infection in people in Australia and has been associated with a range of skin and soft tissue infections. ST398 is less virulent and less transmissible in humans than ST93 but carries drug-resistance traits to many antimicrobials used in human and veterinary medicine. If a pig or human became infected with both strains simultaneously, this could lead to the drug resistance traits in the less virulent strain (ST398) transferring to the more virulent strain (ST93) and multi-drug resistant ST93 could be a serious public health concern. This appears to have occurred, resulting in the emergence of a multidrug-resistant ST93 MRSA strain, but the public health risk to those not in direct contact with pig farms is unknown.[59]

resistant bacteria are associated with high death-rates and health care costs, and limited treatment options.[76] Tracing the source of these drug-resistant infections is difficult due to the highly mobile nature of the MGEs.[45]

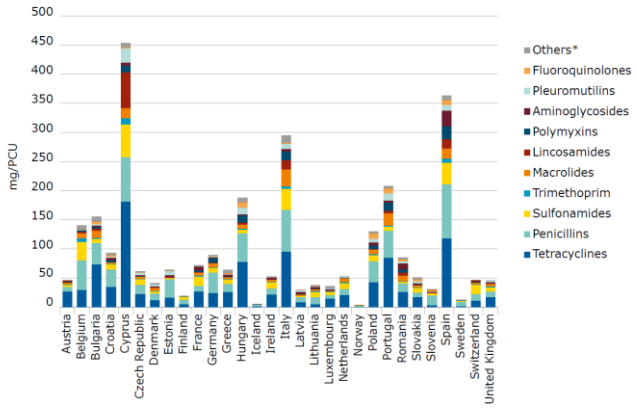
Persistence of antimicrobials in the environment

When humans and animals are treated with antimicrobials, the drugs are not always fully broken down in the body, so drug residues can be excreted into the environment. Sites where high concentrations of antibiotic residues are found include hospital and urban wastewater, and soils treated with animal manure.[77,78,79] There is evidence of the potential for emergence and spread of AMR to human commensal and pathogenic bacteria at such sites.[80,81] Antibiotics that persist in the environment, such as fluoroquinolones and tetracyclines, may be of more concern than those that are easily degraded (such as penicillins).[82]

Surveillance of AMR in animals

In the UK, the Veterinary Medicines Directorate (VMD) is responsible for producing the annual Veterinary Antibiotic Resistance and Sales Surveillance (VARSS) report. The VARSS report presents combined data on veterinary antibiotic sales, antibiotic usage, and antibiotic resistance in bacteria obtained from food-producing animals in the UK.[83]

Figure 1 Veterinary antibiotics sales in European countries[84]*



*Data are for 2016, 1 PCU = 1 kg of animal biomass.

Antibiotic sales data

Pharmaceutical companies supply annual sales data on all authorised veterinary antibiotics to the VMD, in accordance with the Veterinary Medicines Regulations 2013.[85] The Government response to the AMR Review 'committed to a reduction in antibiotic use in livestock and fish farmed for food to a multispecies average of 50mg/kg by 2018'.[86] This was achieved by 2016[87] and, in the VARSS-2017 report, the sales of veterinary antibiotics for use in food-producing animals was 37 mg/kg, a 40% reduction since 2013.[83] Prescribing of veterinary antimicrobials varies substantially across Europe (see Figure 1 and POSTnote 588).[84]

Antibiotic usage data

Many antibiotics are authorised for use in multiple animal species, so sales data cannot differentiate how much antibiotic is used per species. VMD is working with a wide range of stakeholders to improve the collection of antibiotic usage data.[88,89] The VARSS-2017 report presented antibiotic usage data from all the main food-producing animal sectors. Such data can be used to:

- provide a baseline against which to measure further interventions to reduce antibiotic use in each sector;
- investigate risk factors associated with high levels of antibiotic use and the effect of use on the development and spread of AMR; and
- allow farmers to compare themselves with their peers and encourage vets and farmers to share good practice.

Antibiotic usage data presented in the VARSS-2017 report showed that, for those food-producing animal sectors where usage data were available for more than one year (pigs, meat poultry, laying hens, gamebirds and dairy), antibiotic usage had decreased across the board.

Antibiotic resistance monitoring

Surveillance programmes evaluate antibiotic resistance in bacteria of relevance to animal health and samples are taken by private vets and submitted to the:

- Animal and Plant Health Agency (England and Wales);
- Scotland's Rural College (Scotland);
- Agri-Food and Biosciences Institute (Northern Ireland).

The main aim of such programmes is to provide a diagnostic service for vets, but they also help identify new and

emerging patterns of resistance. Any findings that are considered to pose a potential risk to human or animal health are reported to the Defra Antimicrobial Resistance Coordination group.[90] Samples monitored by the surveillance programme between 2015-2017 showed little change in the levels of antibiotic resistance in bacteria among samples submitted by private vets.[83]

The EU requires all Member States to monitor and report antibiotic resistance in bacteria sampled from healthy food-producing animals at slaughter and from food products at retail.[91,92] The Food Standards Agency collected samples from abattoirs that processed 71% of the pigs in the UK in 2017. These samples showed a reduction in the level of antibiotic resistance in bacteria from food-producing animals at slaughter, when comparing results from 2014/15 with 2016/17.[83]

Surveillance of AMR in humans

The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) was established in 2013 to support Public Health England (PHE) in the delivery of the UK 5 Year AMR Strategy 2013 to 2018.[93]

Antibiotic consumption

Information on prescribed antibiotics comes from:

- Primary care – data collected by the PHE Antibiotic Prescribing Data Warehouse cover prescribing from general practice, as well as other community prescribing such as in out-of-hours services and walk-in centres.
- Secondary care – data are obtained by the human health data science company (IQVIA) and cover 99% of NHS hospital pharmacy systems.

The latest ESPAUR report suggests that there has been an overall reduction in antibiotic prescribing, driven by reductions in primary care. Antibiotic prescribing increased in secondary care between 2013 and 2017. This was in part driven by a shortage in the supply of a key broad-spectrum antibiotic, which resulted in two or more alternative antibiotics being used as an alternative treatment.[93]

Antibiotic resistance data

AMR data from hospital laboratories is reported to a national database, the PHE's Second Generation Surveillance System, which covers 97% of hospital laboratories in England. While the levels of resistance to key antibiotics in the pathogens captured by the surveillance system remained stable from 2013 -2017, the numbers of resistant infections in people increased.

These data show that, despite a 6% reduction in antibiotic prescribing over the past 5 years, there has been a continued rise in the burden of antibiotic-resistant infections. UK AMR data are also submitted to and published by:

- The European Centre for Disease Prevention and Control's European Antimicrobial Resistance Surveillance Network programme (EARS-Net).[94]
- The World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS).[95]

Future priorities

Better surveillance data on antimicrobial usage and AMR is needed for each of the three main reservoirs, especially animals and the external environment. Progress has been made over the period of the UK 5 year AMR Strategy 2013 - 2018, for example:

- Human reservoir – the ESPAUR programme has seen an increase from 82.7% to 97% of hospital laboratories providing their AMR data. In addition, PHE has made data on AMR freely available online through the 'AMR local indicators' profile of Fingertips.[96,97]
- Animal reservoir – 40% reduction in antimicrobial use in food-producing animals, addition of new animal sectors to the VARSS reports and inclusion of data from the EU harmonised antibiotic resistance monitoring scheme.[83]

However, there is scope for further improvement. Surveillance data for the human reservoir could be more integrated with data from the animal and environmental reservoirs. [98,99,100,101,102] The UK AMR Strategy 2013–2018, contained a commitment to "better access to and use of surveillance data in human and animal sectors through new arrangements that facilitate greater consistency and standardisation of the data collected across the system and encourage improved data linkage". However, the UK One Health Report[103] highlights that this has not been fulfilled to the extent needed to draw relevant conclusions from the data currently available. In addition, there is no structural, statutory surveillance dedicated to assessing the level of AMR in the environment in the UK.[103]

In the new UK 5-Year AMR national action plan, developing an improved evidence base on AMR in the environment is a priority.[6] Furthermore, in 2018 a network comprising 23 partners (including the UK Government agencies APHA, Cefas, Environment Agency, PHE and VMD) was awarded funding with the aim to identify robust, measurable surveillance indicators and methodologies for assessing environmental AMR levels. At the European level, the EU One Health Action Plan against AMR[104] notes that because "(r)esistant microorganisms exist in humans, animals, food, and the environment" a "comprehensive, collaborative and coordinated collection and analysis of data from multiple domains, i.e. a One Health AMR surveillance system, is…essential to understand the magnitude of the problem".

In a joint response to the Health and Social Care Committee inquiry into AMR,[105,106] the Microbiology Society and Society for Applied Microbiology noted the global threat posed by AMR and called for the new AMR national action plan to:

- Make a long-term commitment to improve knowledge and understanding of AMR, conserve the effectiveness of existing treatments and develop new treatments;
- Take a joined-up approach that embraces human health, agriculture and the environment;
- Support interdisciplinary research on AMR; and
- Have a broader focus on all antimicrobials, not just antibiotics but also antifungals and antivirals.

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 Alana Dowling for researching this briefing, to BBSRC for funding her parliamentary fellowship, and to all contributors and reviewers. For further information on this subject, please contact the co-author, Pete Border.

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