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Antimicrobial Resistance: A Food Safety Concern

Summary

Antimicrobial agents transform and extend lives. They prevent death and disability from infection. They play a vital role in the welfare of animals, including food producing animals and companion animals. Antimicrobial resistance (AMR) has impacted on every day clinical practice for many years. AMR makes it more difficult and more costly to prevent and treat infection. These difficulties are increasing rapidly. AMR is recognized as a major global challenge for public health and for sustainability. We understand why AMR is happening. We understand what is required to respond. It is clear that a "One Health" approach is needed to deliver the sustained and coherent global action required. Reducing antimicrobial use and slowing the spread of AMR organisms in all sectors will mitigate AMR. New antimicrobial agents and new approaches to prevention and treatment of infection are required to adapt to AMR. The response to the challenge, to date, has been more effective in some countries than in others. Building the global consensus to act remains challenging, leading to the description of AMR as a "super-wicked problem".

Antimicrobial Resistance Matters

Antimicrobial agents play a vital role in the treatment of many infections. Infection is invasion of the tissues by microorganisms. The impact of infection for the person varies from discomfort and inconvenience to catastrophic life threatening illness. For example, septic shock and meningitis can progress rapidly to death. Death is much more likely in the absence of early effective treatment. In life-threatening infection the doctor cannot take the time to establish which organism is causing the infection and which antimicrobial drug they can rely on to work before they choose a treatment. In

septic shock the likelihood of death as a result of sepsis increases with delay in effective antimicrobial treatment (Paul, Shani, Muchtar et al., 2010). Other consequences of delayed effective treatment include longer illness, longer hospital stay and a recovery that is less complete. Even for more common and typically milder infections such as cystitis (bladder infection) a delay in effective antimicrobial drug treatment may mean more days of discomfort and disruption to social and economic activity.

With the best available laboratory diagnostic systems it usually takes hours or days before the laboratory can name the infecting organism and test to determine which antimicrobial drug can be relied upon to work. Many of the antimicrobial drugs that the doctor could count on to work reliably 20 years ago are no longer reliable. Increasingly, the doctor is forced to use newer drugs or drugs that may be more toxic, more costly, and less effective in order to be reasonably confident that they are using a drug that effectively targets the infecting organism. Even with that extra precaution, it is now common to find 1 to 2 days after treatment started that different or additional antimicrobial drugs are needed for optimal treatment.

Antimicrobial agents are also essential in some circumstances to prevent infection. When major surgery requires opening the abdomen or when chemotherapy temporarily destroys the bone marrow, antimicrobial agents often provide the vital bridge that prevents infection until the wound is closed or the bone marrow is recovered. As antimicrobial drugs become less reliable and less effective the risk of infection for people who need these complex treatments increases. Therefore, at a personal level, AMR is a problem that already has or soon will impact on our own health and wellbeing or the health and wellbeing of people we know. At the wider level AMR is a threat to the overall sustainability of healthcare services because it is associated with poorer outcomes and it increases costs (Lomazzi, Moore, Johnson et al., 2019).

The importance of AMR is well established at a global policy level. In 2021 the Food and Agriculture Organization, World Organization for Animal Health, World Health Organization and UN Environment Programme published guidance on "Antimicrobial Resistance and the United Nations Sustainable Development Cooperation Framework". This document referred to AMR as "*currently one of the greatest global threats*" resulting in "*millions of deaths, long lasting disabilities and increased healthcare costs*" (https://www.who.int/publications/i/item/9789240036024). In September 2021 the G20 health ministers referred to the need to protect antimicrobials as "*one of the pillars of medicine*" and committed to building capacity for surveillance of antimicrobial use and resistance (https://www.gov.uk/government/news/g20-ministerial-health-declaration-published). The 2016

report, tackling drug-resistant infections globally: final report and recommendations, (O'Neil, J. 2016) has been very influential in contributing to this global consensus https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

AMR has very significant implications for food production. This is both in terms of the direct impact of difficult to treat infections on animal welfare and the demands placed on food production systems to demonstrate that they are acting to contain this major threat to public health (Food Safety Authority of Ireland 2015).

One Health

The World Health Organization defines 'One Health' as an "*integrated, unifying approach to balance and optimize the health of people, animals and the environment*" (https://www.who.int/news-room/questions-and-answers/item/one-health). One Health is also accepted as central to the response to antimicrobial resistance. The one health approach is important in managing infection, including infection with AMR bacteria because many of the microorganisms that cause infection can cause infection in both animals and humans. The capacity of microorganisms to survive in the environment often plays an important part in their spread from one host organism to another including spread from animal to human hosts and vice versa. One Health brings together actors in many diverse sectors including but not limited to medical, veterinary, sanitation, environmental and food production and processing. This cross sectoral working identifies and implements solutions to major challenges such as AMR that cannot be adequately addressed by any one sector in isolation (https://www.who.int/teams/one-health-initiative)

The background to AMR

Microorganisms

There are four large groups of microorganisms as follows: bacteria, fungi, parasites and viruses. The phenomenon of AMR is a significant problem amongst all four groups. This bulletin will focus primarily on AMR in bacteria. The principles are similar in relation to all microorganisms.

In the clinical context microorganisms are often divided into two key groups. Organisms that commonly cause infection and disease in otherwise healthy people are referred to as pathogens. Organisms that live in or on humans and animals but rarely cause disease in otherwise healthy people are often called commensals. The boundary between the categories of pathogens and commensals cannot be defined sharply. Many pathogens only cause disease in a minority of people exposed to the organism. Many commensals can cause life threatening disease in people with conditions that make them more vulnerable to infection. The global population is aging. A growing number of people of all ages with complex conditions now survive for long periods with the support of certain medical treatments that impair immune function. This means that, in many countries, there is a much higher proportion of people vulnerable to infection than was the case 20 years ago. The issue of AMR encompasses pathogens and commensals. It relates to organisms associated with humans and animals and the environment. Thus AMR exemplifies a challenge that requires a One Health response (McEwen and Collignon, 2018).

Antimicrobial agents and antibiotics

Antimicrobial agents are a very large and diverse group of substances that inhibit the growth of microorganisms. The inhibitory effect of an antimicrobial agent on an organism is not an "all or nothing" effect. The degree of inhibition of a microorganism varies with the organism and depends on the concentration and duration of exposure to the antimicrobial. The degree of inhibition also depends on the matrix in which exposure occurs and the physiological status of the organism at the time of exposure. Antimicrobial agents, in the broadest sense, include disinfectants and certain metals but the main focus of concern is antimicrobial agents that are administered to humans and animals to prevent and treat infection. Antibiotics can be narrowly defined as antimicrobial agents, such as penicillin, that are produced by one organism (in this case fungi of the genus penicillium) and that inhibit growth of certain other organisms (in this case many bacteria). In practice the term antibiotic is widely used to refer to any therapeutic antimicrobial agents used to treat bacterial infection including both naturally occurring and synthetic compounds. It is in that sense that it is used subsequently in this bulletin.

Antibiotics and the Class Concept

The vast number of different antibiotics available for therapeutic use in humans and animals can give a false sense of assurance. Most of the antibiotics fall into a relatively small number of classes of antibiotic. Members of a class are very similar to other members of that class. Antibiotics target and

block a specific critical function in the microorganism. Antibiotics in the same class target the same function. For example, there are hundreds of penicillins that all belong to the same class of antibiotics. They all target a small group of related enzymes that synthesize the bacterial cell wall. An organism that has developed a mechanism to protect the target or a substitute way to perform the target function is generally resistant to some degree to all or most of the antibiotics in the penicillin class. In the past it was often the case that certain members of a class of antibiotics would be promoted for use in animals and other members of the same class promoted for use in humans. (Hornish RC, Kotarski 2002). This practice is of little or no value as a response to the challenge of antimicrobial resistance.

The World Health Organization places antimicrobial classes into three categories. Critically important, Highly important and Important in relation to their importance for human healthcare (https://apps.who.int/iris/bitstream/handle/10665/325036/WHO-NMH-FOS-FZD-19.1-eng.pdf). Among the Critically Important Antimicrobial (CIA) classes are third generation cephalosporins (for example cefotaxime, ceftriaxone and ceftiofur) and carbapenems (for example meropenem). The third generation cephalosporins and the carbapenems are referred to as examples in this bulletin.

The Antimicrobial Advice Ad Hoc Expert Group of the European Medicines agency has developed a categorization to guide use of antibiotics in animals using the CIA classification. Furthermore, the WHO promotes the AWaRe (Access, Watch and Reserve) classification in human prescribing to emphasise the need to protect those agents that are most critical (https://www.who.int/publications/i/item/2021-aware-classification). In the AWaRe classification antibiotics are categorized as Avoid, Restrict, Caution and Prudence in order of importance of limiting use (https://www.ema.europa.eu/en/news/categorisation-antibiotics-used-animals-promotes-responsible-use-protect-public-animal-health).

Defining Antibiotic Susceptibility and Resistance

Assessment of susceptibility of an organism to an antibiotic is based primarily on laboratory tests. The tests measure the lowest concentration of the antibiotic that prevents the test organism from growing. This is called the minimum inhibitory concentration or MIC. The test must be standardized to give results that are reproducible and meaningful. The method of measurement of the MIC is defined in an ISO standard (ISO 20776-1:2019). Categorizing the organism as susceptible or resistant is based on applying a complex set of rules to interpret the MIC. The European Committee for Antimicrobial Susceptibility Testing/EUCAST is on source of rules for interpretation of MIC results

(https://www.eucast.org/eucast_news/news_singleview/?tx_ttnews%5Btt_news%5D=464&cHash=ea8540c0fbdaa71b3bbcb3bf765239de). These rules take account of available evidence about the organism, the antibiotic, and the effectiveness of that antibiotic for treatment of infection with that species of organism.

Intrinsic and Acquired AMR

The bacteria *Pseudomonas aeruginosa*, commonly detected in many environments, was never inhibited by the antibiotic ampicillin. This is intrinsic AMR. By contrast, the gut commensal and food indicator organism *Escherichia coli* was rapidly and completely inhibited at very low ampicillin concentrations when ampicillin was first discovered in 1958. In most parts of the world today most *E. coli* cultured from humans, animals, or the environment are not readily inhibited by ampicillin. This represents a change from the natural condition of *E. coli* and is considered acquired AMR. The focus of global public health concern in relation to AMR is acquired AMR and particularly acquired resistance to therapeutic antibiotics. This cannot be divorced entirely from resistance to disinfectants and metal ions. As discussed later there is an interdependence between resistance to the different therapeutic antibiotics and these groups of non-therapeutic agents.

Of note, in the food production context, microbial biofilm represents a particular AMR phenomenon. Organisms that are readily inhibited by an antibiotic in the ISO standard test method may be resistant to high concentrations of the same antibiotic when the organism is growing as biofilm (Stewart and Costerton 2001). Although biofilm resistance is an important phenomenon it is distinct from the issue of acquired AMR in that it is not related to a durable change in the organism's genome. Biofilm resistance is not considered further in this bulletin.

The biology of change in microorganisms

Many microorganisms have a very short life cycle. The replication time for some common bacteria, such as *E. coli* may be as short as 20 minutes in ideal growth conditions. The replication process requires the organism to copy the nucleotide sequence of its genome. The genome copying process is imperfect. The new sequence may vary from that of the parent genome at a number of points. These "copying errors" contribute to point differences between individual cells in a microbial population. Much more extensive changes in the genome also occur commonly in bacteria due to gain or loss of mobile genetic elements (MGEs) that may carry multiple new genes to a host organism (Taggar G, Rheman MA, Boerlin P & Diarra MS 2020)

Genome change may be silent, so that it produces no change in how the organism functions. If the genome change causes a change in function results that change may be neutral, advantageous or disadvantageous compared to the function of the parent "wild type" organism. The impact of any change in function is dependent on the matrix and conditions in which the organism is growing. As per Darwinian selection if the variation is advantageous the variant will displace the original form (that is replace the wild type) in that matrix. The speed and extent of displacement of wild type organisms depends on the degree of advantage conferred on the variant. Because bacteria reproduce so quickly in ideal circumstances, an organism with a substantial advantage can entirely replace the wild type in hours or days. If the new variant is disseminated it will tend to displace the wild type in every other similar matrix or habitat where it is introduced if the same selective pressure applies.

The processes of genome variation, selection and dissemination, as described above, are not at all specific to AMR. They are the natural processes of change and adaptation in microbial populations.

Selection and AMR

AMR is a special case of selection because human activity is driving a rapid global change in microorganisms that is harmful to health and threatens sustainability. A potent antibiotic in a matrix has an exceptionally powerful selective effect. If the wild type organism is inhibited from growth, a resistant variant that develops or spreads from elsewhere can largely replace the wild type within hours or days. If the resistance is coded on a MGE the property of resistance can also transfer to other species of bacteria in the matrix so that they also become resistant. The presence of antibiotic is the engine that drives displacement of the wild type.

Most MGEs that code for resistance to antibiotics and other agents represent sequences that are naturally present in certain species of environmental organisms. The antibiotics and other antimicrobials we manufacture and use are often based on compounds that exist naturally in particular contexts in the environment (cephalosporins, penicillins, tetracyclines and others) or are similar to compounds that occur naturally (for example fluoroquinolones). Over millennia, genes that confer resistance to these naturally occurring substances have emerged in certain environmental species. However, prior to the antibiotic era these genetic elements were rare or absent from most human and animal pathogens and commensals.

As mentioned, third generation cephalosporins are considered a critically important class of antimicrobials. A key bacterial mechanism of acquired resistance to the third generation cephalosporins

is a group of enzymes, called extended-spectrum Beta-lactamases (ESBL). The CTX-M family of ESBLs have become very widely disseminated in humans and animals as use of third generation cephalosporins increased in the later decades of the 20th century. The genes encoding CTX-M enzymes occur naturally in certain species of bacteria (*Kluyvera ascorbata*) but were not detected in zoonotic pathogens such as salmonella or common commensals such as *E. coli* prior to the widespread use of third generation cephalosporins (Rodriguez MM, Power P, Radice M et al., 2004). The mobilization of the gene from its natural host into *E. coli* and other species is a natural phenomenon, as outlined above. It is likely that this mobilization has occurred many times in history but it was a change that conferred no benefit in the human or animal matrix until this matrix was flooded with third generation cephalosporins in the latter part of the twentieth century. Initially ESBL mediated resistance was rare outside of hospitals and other intensive healthcare settings. Subsequently ESBL's disseminated widely into animals and the environment (Galvin S, Boyle F, Hickey et al 2010, Hooban, Fitzhenry, Cahill *et al*. 2021, Hooban, Fitzhenry, O'Connor et al. 2002)). Extensive use of third generation cephalosporins in humans preceded extensive use in food animals by many years. Ceftiofur, for example, was not authorized the European Medicines Agency until 2005 https://www2.zoetis.ie/content/_assets/Image/PDF/Beef-Cattle-PDF/naxcel-epar-summary-public_en.pdf. (Committee for Medicinal Products for Veterinary Use. 2009). Therefore ESBL's were long established as a human health problem before extensive use of these agents in food animals. However. ESBLs subsequently became common in food producing animals. It is likely that use of third generation cephalosporins contributed substantially to ESBL's becoming established in animals and that this served to further amplify and disseminate ESBLs

Carbapenems are another class of critically important antimicrobials. They are reliably effective against ESBL *E. coli* and other Enterobacterales and have become vital for effective early treatment of some people with life threatening infection. However, carbapenems are now also compromised by another group of bacterial enzymes (carbapenemases). Bacteria of the family Enterobacterales that produce these enzymes are known as Carbapenemase Producing Enterobacterales (CPE). CPE are a particular concern because we do not have many good choice of antibiotic for treatment of life threatening infection with CPE. Carbapenemase enzymes can also inactivate penicillins and cephalosporins. The phenomenon of CPE is in many ways very similar to what was observed with ESBL about two decades earlier. The genes that code for the most common CPE enzymes (OXA) appear to have been mobilized from a genus of environmental bacteria (*Shewanella spp.*) in which it is intrinsic (Poirel, Heritier & Nordman 2004The rapid global dissemination of CPE has been described (Munoz-Price LS, Poirel L, Bonomo RA et al.2013). Notwithstanding global dissemination, at present CPE remains strongly

associated with exposure in hospitals and healthcare settings. Although CPE has been reported from community settings, companion animals, food animals and the environment it is not yet common in these settings (Anderson & Boerlin 2020, Kuang X, Zhang Y, Liu J, 2022, Mahon BM, Brehony C, McGrath E, 2017, Prendergast, O'Doherty, Burgess et al 2021, Mahon, Brehony, Cahill et al 2019) . It is reasonable to hope that if carbapenems and other broad spectrum agents such as third generation cephalosporins are not used or are use very sparingly in animals for food production that CPE will remain rare in food animals.

Is AMR Reversible?

If selective pressure is reduced sufficiently or removed by reducing antibiotic use reversion of bacterial populations to dominance of wild type pathogens and commensals in human and animals is predicted but it is likely to occur very slowly. The selective effect of antibiotic in a matrix is very powerful and drives rapid dominance of resistant variants. Absence of antibiotic has, at best, a weak selective effect in favor of wild type. Months of gradual reversion towards wild type in the gut of a human or animal is likely to be reversed very quickly by transient reintroduction of a relevant antibiotic. Reversion to wild type is complicated also because MGEs frequently carry genes that code for resistance to multiple different classes of antibiotics. An MGE may also code for resistance to disinfectants such as quaternary ammonium compounds and to metal ions (Jiang X, Xu Y, Li Y, 2017, Bearson BL, Trachsel JM, Shippy DC, 2020). Intermittent reintroduction or persistent residues of any agent that the MGE codes against, be that antibiotic, disinfectant or metal ion, will support persistence of organisms carrying the entire MGE.

Does Food Play a Role in AMR?

There is unequivocal evidence that food is a vehicle for transmission of AMR. The evidence is most clear in relation to foodborne zoonotic infection with AMR resistant organisms. Obvious examples include the incident in 2021-2022 of documented salmonella infection of 150 people in 10 countries for which a range of chocolate products was the vehicle of infection (Larkin, Pardos de la Gandara, Hoban, 2022). That organism was resistant to six classes of antibiotic. In 2011 there was an outbreak of Shiga-toxin producing *E. coli* in Northern Germany. The vehicle of infection was identified as sprouts and the organism was resistant to penicillins and cephalosporins (mediated by an ESBL enzyme) as well as to fluoroquinolones (Frank C, Werber D, Cramer JP et al. 2011). These are striking examples of a more widespread phenomenon. There were 52 702 cases of salmonellosis reported in the EU/EEA in 2020 (EU One Health Report 2020) many of which are AMR. This is the tip of an iceberg. It is estimated that,

globally, there are 2.1 to 6.5 million cases of zoonotic salmonellosis annually (Ao, Feasey, Gordon et al 2015). A high proportion of certain common serotypes of salmonella are now resistant to multiple antibiotics. *Campylobacter spp*, also primarily a food borne zoonosis, is estimated to cause 96 million cases of infection per year (Kirk, Pires, and Black et al 2015). Acquired AMR is also common in *Campylobacter spp*.

The evidence for the role of food in dissemination of AMR in commensals, that is those bacteria that can cause infection in vulnerable people, is much less clear cut. AMR *E. coli*, including *E. coli* resistant to critically important antimicrobial agents are detected in food producing animals and they have been detected in food including foods of non-animal origin. The evidence for transfer of AMR *E. coli* to humans from food animals has been reviewed by Muloi and colleagues in 2018. They concluded that some studies suggest transmission of AMR from food animals but it is difficult to draw robust conclusions (Muloi, Ward, Pedersen et al 2018). However, given the unequivocal evidence for the role of food as a vehicle for transfer of AMR salmonella and Shiga-toxin producing *E. coli* to humans there is little reason to doubt that that food also serves as a vehicle for transfer of AMR commensal *E. coli* and other commensal Enterobacterales to people.

It is likely that many AMR bacteria and MGE in food producing animals were introduced from humans to animals and that such bacteria circulate in both directions. The potential human origin of many AMR bacteria established in animals does not diminish the potential of food producing animals and food to play an important role in amplifying and disseminating AMR. It is difficult to estimate the relative importance of food in amplification and spread of commensal AMR organisms when compared with other factors such as global population movement, person-to-person spread and acquisition from healthcare environments. It may be that the role of food is relatively more important in those countries with effective systems to limit spread by other pathways.

Another aspect of the relationship between food and AMR is the potential for certain foods or food supplements to influence the extent to which people have gut colonization with AMR. There is limited research in this area. A recent paper reported people antimicrobial resistant genes were detected less frequently detected in the gut of those who had diverse diets that were high in fiber and low in animal protein (Oliver A, Xue Z, Villanueva YT, 2022). The authors speculate that dietary intervention may have a role to play in reducing colonization with AMR bacteria.

Actions needed to address this wicked problem - mitigation

Reducing manufactured antibiotics in the biosphere.

The most obvious element of response is to reduce manufacture and use of antibiotics. The scale of manufacture and use is phenomenal. In the 29 EU/EEA countries 4 264 tons of antimicrobials were used in humans and 6 358 tons were used in animals in 2018 (Tiseo, Huber, Gilbert et al 2020). Tiseo *et al* (2020) estimated the global consumption of antimicrobials in food animals was 93 309 tons in 2017 (compared with estimate of 63 151 in 2010 by the same group). The authors project an increase to 104 079 tons in 2030. Of note Tiseo and colleagues do not address the aquaculture sector or the use of antimicrobials in production of plant based foods. Schar and colleagues estimate the annual use of more than 10 000 tons of antimicrobials in aquaculture and project that this will increase by 2030 (Scharl, Klein, Laxminarayan et al 2020). Antimicrobial use in plant production is generally a focus of much less attention however three classes of antimicrobial agents (aminoglycosides, tetracyclines, and quinolones) which are categorized as either critically important or highly important by WHO are used in food plant production. This issue is comprehensively reviewed by Miller and colleagues (2022). The authors also draw attention also to the use of resistance genes in genetic modification of plants and to the issue of acquired resistance to azoles in molds related to use of azoles in some crops. The issue of acquired azole resistance in *Aspergillus species* is now a significant human health concern in the care of people with profoundly impaired immune function (Miller, Ferreira and LeJeune 2022).

These data are useful as a general indicator of the scale of manufacture and use of antibiotics. Changes in a country over time and comparisons between countries need to be interpreted with caution for a number of reasons. Antimicrobial agents differ widely in relation to potency (for example 1kg of a fluoroquinolone is equal to several kilograms of a quinolone in terms of antibacterial effect). They also differ in relation duration of action, discharge, persistence in the environment. Furthermore, antibiotic classes differ with respect to the importance of the class for healthcare. Thus while reduction in tons of antimicrobial used are desirable, the metric must be considered carefully. A reduction in tons used achieved by switching to more potent, more persistent or more important antimicrobial is likely to be counterproductive. For example a switch from using a ton of tetracycline to 0.5 tons of a fluoroquinolone would be counterproductive.

In human medicine the unit applied to measurement of antibiotic consumption is usually the Defined Daily Dose (DDDs) (https://www.who.int/tools/atc-ddd-toolkit/about-ddd). This takes account of differences in potency and duration of action of antibiotics. There is a broad consensus that human health and healthcare globally could be improved and costs reduced by improving practice with respect to antibiotic use. There is very marked variation between countries in patterns of consumption. Much of the variation is unlikely to be justified by differences in patterns and causes of infection. In 2020 the mean consumption for the EU/EEA was 16.4 DDD per 1000 inhabitants but the range was from 8.5 in the Netherlands to 28.9 in Cyprus (https://www.ecdc.europa.eu/sites/default/files/documents/ESAC-Net%20AER-2020-Antimicrobial-consumption-in-the-EU-EEA.pdf).

Many countries have established national plans to address the challenge of AMR including initiatives intended to reduce the quantity and improve the quality of antibiotic prescribing. These programs are referred to as antimicrobial stewardship programs. Antimicrobial stewardship supports the use of antibiotics where they are likely to result in therapeutic benefit. In some settings, for example in some low-income or remote settings with poor access to treatment for infection, an increase in consumption of some antibiotics may represent good antimicrobial stewardship. In many parts of the world, there is very good reason to believe that antibiotics are frequently used when they are not needed and are not useful. This is related to unregulated use of antibiotics in places where they can be purchased without prescription and to prescription of antibiotics without a good reason in places where access is regulated by prescription. Use of antibiotics when they are not needed is more likely to do harm than to do good. Antibiotics, like all medicines, can have harmful side effects. A key role of antimicrobial stewardship programs is to reduce unnecessary and potentially harmful use of antibiotics to improve healthcare and to control AMR. Overall there has been useful progress towards improved antibiotic use in human healthcare in many countries but it remains inconsistent and slow.

There is a broad consensus that there is scope for major reduction in antibiotic use in food production without loss of productivity. This centers on using approaches that promote biosecurity and animal health thus reducing the requirement for antibiotics (Levy 2014). As with use in humans there has been very useful progress on this in some countries but globally progress remains slow. Opinion leaders in the food industry can play an important role in driving change by preferential use of products from producers who have reduced antibiotic use.

In addition to reducing manufacture and use of antibiotics there may be an opportunity to reduce the impact of those used by better control of discharge of biological material such as feces and urine from

humans and animals that are receiving antibiotics. Antibiotics in active form are excreted in feces and urine. Hospitals are intensive users of antibiotics. Monitoring and control of discharges in effluent of hospitals and similar settings presents opportunities to reduce environmental contamination with antibiotics agents (Morris, Harris, Morris et al 2015). There are proprietary systems to remove antibiotic from hospital effluent but they are not widely deployed. There are also concerns regarding the potential of feces and bio-solids derived from feces of animals consuming antibiotics to increase contamination of environment and of food with antibiotic residues. Although the application of bio-solids to land has significant benefits this potentially harmful effect must be managed (Food Safety Authority of Ireland 2015, Healy, Fenton, Cummins *et al*. 2017, Monahan, Harris, Morris *et al*. 2022,).

An important element in reducing harmful use of all antimicrobial agents in all sectors is the acceptance that microorganisms will always be present in open systems. Many such organisms are harmless and may be beneficial. There is often excessive application of antibiotics and other antimicrobial agents such as disinfectants in the misguided pursuit of sterility. In humans and animals the goal in relation to skin, gastrointestinal tract and other open surfaces is a healthy and balanced microbiome rather than sterility except in very specific circumstances. Although disinfection has a valuable role in many environmental settings, including food producing settings, thorough cleaning is more important than application of disinfectants. One cannot disinfect dirt. Attempts to maintain sterility in open systems, animate or inanimate, by application of chemical antimicrobial agents almost inevitably lead to the dominance of organisms that have either intrinsic or acquired resistance to the agent used.

Reducing dissemination of AMR

Microorganisms and MGEs are everywhere. They move continuously and rapidly through the environment and across species boundaries (animal to human and human to animal). This reality is reflected in the One Health approach to AMR referred to above. Microorganisms also move across political boundaries. Global mobility of people, animals and goods contribute to the rapid spread of any new emerging AMR phenomenon. In the context of this bulletin the potential spread of AMR associated with trade in food, food ingredients, food packaging and food animals is particularly relevant.

The global dissemination of *K. pneumoniae* resistant to the Carbapenem class of antibiotics is well described and is an illustrative example (Munoz-Price, Poirel, Bonomo et al., 2013). Acman et al (2022) describe the role of MGEs in the global dissemination of the NDM carbapenemase enzymes. MGE coding resistance may already be widely disseminated by the time they are identified. For example the *mcr*-1

gene coding for resistance to the antibiotic colistin was first reported in China in 2016. It quickly became apparent that it was already disseminated (Zhang, Huang and Chan 2016). While globalization is likely to be a major driver of dissemination of AMR it is unlikely that changes in this trend will be acceptable as part of the policy response to AMR.

Adoption of patterns of behavior, in particular hand hygiene, that reduce person-to-person spread of organisms in healthcare, food service and general settings can help to reduce spread. Control and treatment of effluent from centers of intense antimicrobial use including hospitals and many intensive animal production facilities can be expected to slow dissemination of AMR organisms and MGEs.

In relation to food production, control of the dissemination of AMR bacteria is similar to the control of dissemination of potentially pathogenic microorganisms. Unprocessed or minimally processed products that are expected to contain viable *Enterobacterales* are likely to contain AMR *Enterobacterales.* This is particularly the case if they originate from regions where AMR is widespread, where untreated fecal material is used as fertilizer and untreated water is used for irrigation or washing of food products. Foods and animal feed that has been subject to an effective thermal or radiation control point intended to eliminate *Enterobaterales* are unlikely to contain significant quantities of viable pathogens or commensals with acquired AMR. If foods are subsequently processed, packaged, and distributed in line with best practice AMR organisms are unlikely to be reintroduced to the product or to proliferate in the product.

There is more uncertainty regarding AMR carried by certain species of organisms that are more tolerant of physical critical control points such as heat or radiation. Such organisms may survive and could potentially transfer MGEs coding resistance to commensal or pathogenic bacteria in the gut after consumption. Likewise, there are questions about MGE that may remain intact after a critical control point that has inactivated the organism that carried the MGE. Intact MGEs from inactivated organisms could potentially be assimilated by commensal or pathogenic bacteria in the gut after the food is consumed. These issues have not been established as significant for public health or food safety at present however there is a recent report suggesting that MGE's contribute to the ability of *L. monocytogenes* to persist on dairy farms (Castro H, Douillard FP, Korkeala H et al. 2021).

Actions needed to address this wicked problem - adaptation

Discovery of new antimicrobial agents was for decades expected to provide a cornerstone of our ability to manage AMR. This is emphasized in the recent G20 statement on AMR. However in recent years the

pipeline for new classes of antibiotic has yielded very little to compare with the “silver bullets” of the early days of antibiotic discovery (Al-Tawfiq JA, Momattin H, Al Ali AY 2022). There are many initiatives in this area but there have been limited gains. Phage therapy is frequently raised as an option but it does not appear likely to provide a viable alternative to antibiotic treatment for most infections in the medium term.

Our dependence on antibiotics in human and animal healthcare can be reduced to some degree by measures to reduce the occurrence of infections that drive the dependence on antibiotics. These include improved access to drinking water and sanitation, improved nutrition, housing and education, better use of vaccination and other measures to reduce spread of infection and vulnerability to infection.

Overall however strategies for adaptation to provide alternative treatments to existing antibiotics or reduce the need for antibiotic treatment do not seem likely to be implemented effectively in the medium term. It would be unwise to expect that we can develop adaptation strategies to compensate for failure of effective action to mitigate AMR.

Conclusions

AMR has been described as the silent pandemic. The dissemination of AMR is largely invisible most of the time. Most people who acquire AMR organisms experience no illness at the time of acquisition. They cannot be aware that they are shedding and disseminating AMR organisms. They do not know that they may pose a risk to other people. For some people the AMR organisms they acquired and have carried for some time impact on their health months or years later if they become more vulnerable and develop and infection with that organism. The silent nature of spread and the difficulty of linking long term serious consequences for an individual with the specific actions or omissions of individuals, business or agencies is a key part of why AMR is a “*super wicked problem*”.

It is encouraging that AMR is well understood and is universally acknowledged as a major global challenge. It is accepted that it AMR mediated by human activity and that can be mitigated effectively by human activity. It has not been the subject of campaigns of denial to anything like the extent that global warming has been subject to denial. Some countries have taken exemplary action. However the global response remains inadequate. The impact on us as individuals, families and societies is likely to grow until we begin to apply what we know in a manner that is proportionate to the challenge. There is no reason to believe that food and food production should be singled out as the key driver of the most critical AMR challenges to human health such as resistance to carbapenems. It is clear that food and

food production contributes to amplification of AMR and that actors in this domain have an important role to play in the One Health response required to address this challenge. Beyond the role in our professional work every citizen can play a part also by being aware of and by raising awareness that many common infections get better equally quickly without antibiotics and that, quite apart from the societal issue of AMR, taking antibiotics when they are not needed is more likely to do harm than good.

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About the authors:

Antimicrobial Resistance: A Food Safety Concern *was prepared by Prof. Martin Cormican, Established Professor of Bacteriology, University of Galway, Ireland and former National Clinical Lead for HCAI and AMR, University of Galway, and Prof. Dearbháile Morris, Professor of Antimicrobial Resistance and One Health, School of Medicine, University of Galway.*

Prof. Martin Cormican graduated from NUI Galway Medical School in 1986. He trained in Ireland (Galway), UK and USA (University of Iowa). He is director of the GUH National Microbiology Reference Laboratory services which include services for Carbapenemase Producing Enterobacteriaceae. He is former National Clinical Lead for HCAI and AMR. His research interests include antibiotic resistance and food borne infection. He is director of the Centre for One Health at University of Galway and Chair of the Scientific Committee of the Food Safety Authority of Ireland.

Prof. Dearbhaile Morris, graduated from DCU with a B.SC. in Biotechnology in 1997 and went on to complete a Ph.D. in Bacteriology at University of Galway in 2002. Dearbháile is Professor of Antimicrobial Resistance and One Health at the School of Medicine, University of Galway. Dearbháile established the Antimicrobial Resistance and Microbial Ecology Group in 2010 and her research group works closely with national and international research groups focusing on antimicrobial resistance mechanisms and epidemiology, food and water borne pathogens and other contaminants, the wider societal impact of infection, One Health and Astro-microbiology. Affiliation: Centre for One Health and School of Medicine, University of Galway, Ireland.

Prof. Dearbhaile Morris, graduated from DCU with a B.SC. in Biotechnology in 1997 and went on to complete a Ph.D. in Bacteriology at University of Galway in 2002. Dearbháile gained postdoctoral experience at The Children's University Hospital, Temple Street, Dublin before returning to take up a lecturer post at the Discipline of Bacteriology, University of Galway in 2004. Dearbháile is Director of the Ryan Institute Centre for One Health at University of Galway, and established the Antimicrobial Resistance and Microbial Ecology Group in 2010. Dearbháile's research group works closely with national and international research groups focusing on antimicrobial resistance mechanisms and epidemiology, food and water borne pathogens and other contaminants, and the wider societal impact of infection. Affiliation: Centre for One Health and School of Medicine, University of Ireland, Galway.

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