

Bracing for Superbugs

Strengthening environmental action
in the One Health response to
antimicrobial resistance



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Authors:

Teresa M. Coque, Ramón y Cajal Health Research Institute-IRYCIS., Madrid (Spain); Centro de Investigación Biomédica en Red de Enfermedades Infecciosas-CIBERINFEC, Instituto de Salud Carlos III, Madrid, (Spain)

David W. Graham, Newcastle University, Newcastle upon Tyne (United Kingdom)

Amy Pruden, Virginia Polytechnic Institute and State University, Virginia (United States)

Anthony D. So, Johns Hopkins University, Baltimore, Maryland (United States)

Ed Topp, Agriculture and Agri-Food Canada, University of Western Ontario, Ontario (Canada)

UNEP: Susan Vaughn Grooters, Achim Halpaap, Nada Hanna, Miguel Salazar.

Coordinator and author: Aitziber Echeverria (UNEP)

Contributors:

David Bass, Johann Bengtsson-Palme, Carlos Bezuidenhout, Ariel Brunn, Pranab Chatterjee, Eddie Cytryn, Benjamin C. Davis, Monika Dolejska, Gail Hansen, Peiyong Hong, Rai Kookana, Arshnee Moodley, Marcos Quintela-Balujá, Prateek Sharma, Phil Taylor, David Verner-Jefferies, Jeff Waage.

UNEP: Haosong Jiao, Tapiwa Nxele, Ambre Zwetyenga.

In consultation with or reviewed by:

Esteban Abad, Ruth Atkinson, Fernando Baquero, Stefan Berggren, Niketha Bhandekar, Amelia Breeze, Steve Brooks, Naomi Bull, Sandra Castro Scarone, William Calero Cáceres, Kimberly Cook, Solveig Danielsen, Sally Davies, Steven Djordjevic, Gunilla Eklund, Sabiha Essack, Marinella Farre Urgell, Bart Fraaije, William Gaze, Lidija Globevnik, Thomas Harrison, Alwyn Hart, Rene Hendriksen, Ryo Honda, Amit Khurana, Manish Kumar, Joakim Larsson, Stephanie Lyon, Sunita Narain, Kaare Magne Nielsen, Jose Luís Martínez, Janet Midega, Jochen Mueller, Indumathi Nambi, Colín Nunan, Jorge Olivares Pachecho, Ingvild Riisberg, Laetitia Sieffert, Rajeshwari Sinha, Hasmita Stewart, Joan Tell, Pablo Tsukayama, Jayavignesh Viayan, Maria Wallin, Caroline Whalley, Sian Williams, Tong Zhang, Yong-Guan Zhu.

FAO: Marlos DeSouza, Omar Elhassan, Jeffrey LeJeune, Jorge Pinto Ferreira, Ambra Gobena, Sasha Koo-Oshima, Junxia Song, KimAhn Tempelman, Jing Xu.

UNEP: Dina Abdelhakim, Sheila Aggarwal-Khan, Jacqueline Álvarez, Kevin Helps, Andrea Hinwood, Monika MacDevette, Susan Mutebi-Richards, Steven Stone, Kakuko Nagatani-Yoshida.

WHO: Bruce Gordon, Kate Medicott, Elizabeth Tayler, Suzanne Young.

WOAH: Elisabeth Erlacher, Ólafur Valsson.

Design and layout: Lowil Espada.

Editorial support: Amanda Lawrence-Brown (UNEP), John Smith.

Media and launch support: UNEP: Daniel Cooney, Nicolien De Lange, Maria Vittoria Galassi, Moses Osani, Keishamaza Rukikaire, Laila Saada and other members of the UNEP Communication Division.

Acronyms and Abbreviations

ADI	Acceptable daily intake	JEFCA	Joint FAO/ WHO Expert Committee on Food Additives
AMC	Antimicrobial consumption	LIC	Low Income Country
AMR	Antimicrobial resistance	LMIC	Lower Middle-Income Country
AMS	Antimicrobial stewardship	MRL	Maximum residue limit
AMU	Antimicrobial use	MDR	Multidrug resistance
AOP	Advanced oxidation processes	MGE	Mobile genetic element
API	Active pharmaceutical ingredient	MIC	Minimum inhibitory concentration
ARG	Antimicrobial resistance gene	MPTF	Multi Partner Trust Fund
ATLASS	FAO Assessment Tool for Laboratory and Antimicrobial Resistance Surveillance Systems	MRSA	Methicillin-resistant Staphylococcus aureus
BAT	Best Available Technology	MSC	Minimum selective concentration
CABI	Centre for Agricultural Bioscience International	MSW	Municipal solid waste
CARICOM	Caribbean Community	NAP	National Action Plan
CBD	Convention on Biological Diversity	NBSAP	National Biodiversity Strategies and Action Plans
COP	Conference of the Parties	NCBI	National Centre for Biotechnology Information
CPE	Carbapenemase-producing Enterobacteriaceae	OECD	Organisation for Economic Co-operation and Development
DNA	Deoxyribonucleic acid	OHHLEP	One Health High-Level Expert Panel
EPPP	Environmentally Persistent Pharmaceutical Pollutants	PCR	Polymerase chain reaction
ERA	Environmental Risk Assessment	PNEC	Predicted No Effect Concentration
ESBL	Extended Spectrum Beta-lactamases	QMRA	Quantitative Microbial Risk Assessment
EUCAST	European Committee on Antimicrobial Susceptibility Testing	R&D	Research and Development
FAO	Food and Agriculture Organization of the United Nations	RNA	Ribonucleic acid
G7	the Group of Seven	SCHER	Scientific Committee on Health and Environmental Risks
G20	the Group of Twenty	TrACSS	Tracking AMR Country Self-assessment Survey
GAP	Global action plan on Antimicrobial Resistance	UNEA	United Nations Environment Assembly
GARDP	Global Antibiotic Research & Development Partnership	UNEP	United Nations Environment Programme
GBF	Kunming-Montreal Global Biodiversity Framework	UNGA	United Nations General Assembly
GDP	Gross Domestic Product	UV	Ultraviolet
GLASS	Global Antimicrobial Resistance Surveillance System	VICH	Veterinary International Conference on Harmonization
GLG	One Health Global Leaders Group on AMR	WASH	Water, Sanitation and Hygiene
HGT	Horizontal gene transfer	WEF	World Economic Forum
IACG	Interagency Coordination Group on Antimicrobial Resistance	WGS	Whole genome sequencing
IMI	Innovative Medicines Initiative	WHA	World Health Assembly
		WHO	World Health Organization
		WOAH	World Organisation for Animal Health
		WWTP	Wastewater treatment plant

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Foreword

Antimicrobials are an essential part of modern life. Yet, the more we use them inappropriately, the more the microbial world adapts. There is strong evidence that bacteria, parasites, viruses and fungi are becoming resistant to antimicrobials. Infections in humans, animals and plants are becoming difficult, sometimes impossible, to treat. Antimicrobial resistance (AMR) has therefore emerged as a principal public health problem.

AMR was, directly and indirectly, responsible for an estimated five million or so deaths in 2019. By 2050, up to 10 million deaths could occur annually – on par with the 2020 rate of cancer deaths. If unchecked, AMR could shave US\$ 3.4 trillion off GDP annually and push 24 million more people into extreme poverty in the next decade. AMR is a global problem, and the risks are shared by all countries. However, it is closely linked to poverty, lack of sanitation, poor hygiene and pollution. Therefore, low-income and lower-middle-income countries are the worst affected by AMR.

This report provides evidence that the environment matters in the development, transmission and spread of AMR. It offers solutions to address the development and spread of AMR in the environment, particularly by preventing and managing chemical and biological pollution from the pharmaceuticals, agriculture and healthcare sectors and municipal waste. Changes to reduce the risk of superbugs include solid regulation of discharges, strengthening wastewater treatment, realigning incentives to reduce the use of antimicrobials and the private sector stepping up corporate responsibility.

The report shows the need for a more ambitious and systemic approach, rather than working sector by sector. AMR represents a major global threat across human, animal, plant and environmental health. Using the 'One Health' approach – which recognizes that the health of people, animals, plants and the environment are interdependent – can address AMR. Simply put, tackling AMR will require all hands-on deck: government, civil society, international organizations and the private sector.

While more research and development are pivotal to fighting AMR, sufficient information is already available for stakeholders to act on AMR as an issue of environmental, health and economic concern. Significant momentum has developed. But we must do more. We need to leverage high-level political engagement, financial resources and technical expertise, with a focus on country-level needs and demands.

UNEP is committed to tackling this crisis. As part of the Quadripartite Alliance with the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO) and World Organisation for Animal Health (WOAH), UNEP works to strengthen environmental action as part of a 'One Health' response to AMR.

This report shows that solutions exist and can be implemented through international commitment. If we take proactive action, we can reduce the harm and risks of AMR.



INGER ANDERSEN



Executive Summary

Antimicrobials have been essential in reducing the burden of infectious disease in humans, animals and plants for decades. However, their effectiveness is now in jeopardy because several antibiotic, antiviral, antiparasitic and antifungal treatments no longer work because of antimicrobial resistance or AMR.

The World Health Organization considers AMR in humans and animals to be one of the top ten threats to global health. Estimates suggest that by 2050 up to 10 million deaths could occur annually affecting economies and shifting more people into poverty. If not dealt with, AMR could also significantly affect agricultural production, again affecting economies and food security, and low-income and lower middle-income countries will bear most of the burden.

Global attention to AMR has mainly focused on human health and agriculture sectors, but there is growing evidence that the environment plays a key role in the development, transmission and spread of AMR. The environmental dimensions of AMR are complex and characterized by dynamic interactions, cyclic interrelationships, complexities and multiple causalities and dynamics in multi-dimensional media that impact global planetary health.

AMR can occur naturally or can be acquired. Increased use and misuse of antimicrobials and other microbial stressors, such as pollution, create favourable conditions for microorganisms to develop resistance both in humans and the environment from sources such as sewage. Bacteria in water, soil and air for example can acquire resistance following contact with resistant microorganisms.

The environmental dimensions of AMR include pollution from hospital and community wastewater, effluent from pharmaceutical production, run-off originating from plant and animal agriculture and other forms of waste and releases. These matrices may contain not only resistant microorganisms, but also antimicrobials, various pharmaceuticals, microplastics, metals and other chemicals, which all increase the risk of AMR in the environment. Polluted waterways, particularly those that have been polluted for some time, are likely to harbour microorganisms that increase AMR development and distribution in the environment. With increasing pollution and lack of management of sources of pollution, combined with AMR in clinical and hospital settings and agriculture, risks are increasing.

The key economic-sectors contributing to the environmental dimensions of AMR can be broadly classified as: pharmaceutical and other chemical manufacturing and uses including a range of different chemicals, such as antibiotics, antivirals and fungicides as well as disinfectants; agriculture including animal production, aquaculture, food crops or those providing inputs such as feed, textiles, ornamental plants, biofuels and other agricultural commodities; healthcare delivery in hospitals, medical facilities, community healthcare facilities and in pharmacies where a broad range of chemicals and disinfectants may be used.

While the relationship between environmental pollution and AMR and the reservoir of resistance genes in the environment has been established, the significance and its contribution to AMR globally is still unclear. Even so, there is enough knowledge to implement measures to reduce the factors that influence AMR from an environmental perspective; this will also address the triple planetary crisis by addressing sources, sinks and waste.

Using the 'One Health' approach, which recognises that the health of people, animals, plants and the environment are closely linked and interdependent, can successfully address AMR. Some countries have already adopted this approach and have included environmental-related aspects into their National Action Plans on AMR. Agriculture, health and environmental agencies have in place many policy and regulatory frameworks and controls addressing some of the drivers and factors with an impact on environmental dimensions of AMR. Voluntary industry initiatives have established a common framework for managing discharge of antimicrobial compounds and apply it across manufacturing and supply chains among their members. International organizations and bodies are taking decisions and have initiatives such as the joint efforts of the Quadripartite Alliance (FAO, UNEP, WHO and WOA) for strong and coordinated action.

Yet still more needs to be done.

This report calls for priority action to address key pollution sources from poor sanitation, sewage; community and municipal wastes; healthcare delivery; pharmaceutical manufacturing; intensive crop, and terrestrial and aquatic animal production sectors. There are many co-benefits of preventing and managing pollution in these sources to address biological wastes that contain resistant microorganisms that spread AMR, and chemical wastes that select for AMR. To prevent and reduce such pollutants it is crucial to:

- create robust and coherent national level governance, planning, regulatory and legal frameworks, as well as establish coordination and collaboration mechanisms
- increase global efforts to improve integrated water management and promote water, sanitation and hygiene to limit the development and spread of AMR in the environment as well as to reduce infections and need for antimicrobials
- increase integration of environmental considerations into National Action Plans on AMR, and AMR into environmental-related plans such as national chemical pollution and waste management programmes, national biodiversity and climate change planning
- establish international standards for what are good microbiological indicators of AMR from environmental samples, which can be used to guide risk reduction decisions and create effective incentives to follow such guidance
- explore options to redirect investments, to establish new and innovative financial incentives and schemes, and to make the investment case to guarantee sustainable funding, including the allocation of sufficient domestic resources for tackling AMR.

Prevention is at the core of the action and environment is a key part of the solution. Implementing comprehensive and coordinated strengthening of environmental action in the 'One Health' response to AMR will not only help reduce the risk and burden of AMR on societies but will also help address the triple planetary crisis.

Introduction

Global attention to antimicrobial resistance (AMR) has been dominated by a focus on the human health and agriculture sectors. However, evidence is mounting that environmental drivers play a significant role in the development, transmission and spread of AMR, including back to humans and animals.

Many human activities create pollution that promotes the emergence of AMR in the environment. AMR in the environment can cause human, animal or plant diseases or soil biodiversity loss that can lead to further use of antimicrobials (a negative feedback from initial use) that only exacerbates AMR.

The issue of AMR and the environment was recognized by the third session of the United Nations Environment Assembly (UNEA-3) in 2017, which requested this report on the environmental impacts of AMR and the causes of the development and spread of resistance in the environment, including gaps in understanding of those impacts and causes (United Nations Environment Programme [UNEP] 2018). Environmental impacts of AMR include pollution, both biological and chemical, that affect human, animal and plant health, as well as ecosystem services.

While causal pathways are still being established and researched to demonstrate how environmental

factors contribute to resistance in human and animal pathogens, there is already sufficient knowledge to implement measures to reduce the factors that influence AMR from an environmental perspective.

This report reviews the available evidence on environmental dimensions of AMR. It was prepared through a consultative and extensive review process that engaged more than 50 experts and stakeholders from countries around the world, including from the Quadripartite organizations: the Food and Agriculture Organization of the United Nations (FAO), the United Nations Environment Programme (UNEP), the World Health Organization (WHO) and the World Organisation for Animal Health (WOAH).

Given the potential cost and high-impact risks of inaction (O'Neill 2016; World Economic Forum [WEF] 2021), this report calls for urgent, comprehensive and coordinated strengthening of environmental action in the 'One Health' response to AMR.

Increase of AMR has severe consequences

2.1 Antimicrobials are essential and their effectiveness must be preserved

Antimicrobials play an essential role in protecting the health of people, animals and plants (Hernando-Amado *et al.* 2019; Joint Programming Initiative on Antimicrobial Resistance 2019). For many decades, antimicrobials have been effective in treating or preventing a wide range of infectious diseases. However, their effectiveness is now in jeopardy (Levy and Marshall 2004). A number of antibiotic, antiviral, antiparasitic and antifungal treatments that once worked no longer do so because microorganisms have become resistant to them (Allen *et al.* 2010; Topp *et al.* 2018; Graham *et al.* 2019; Murray *et al.* 2022).

There is strong evidence that antimicrobials are increasingly failing to cure infections and the research and development pipeline of novel antimicrobials is lacking (Figure 1). Therefore, AMR poses a significant threat to human, animal and plant health, food security and economic development by reducing the ability to respond to common infectious agents.

Failing to address the global burden of AMR, including its environmental dimensions, could take humanity back to an era when even mild infections could become deadly.

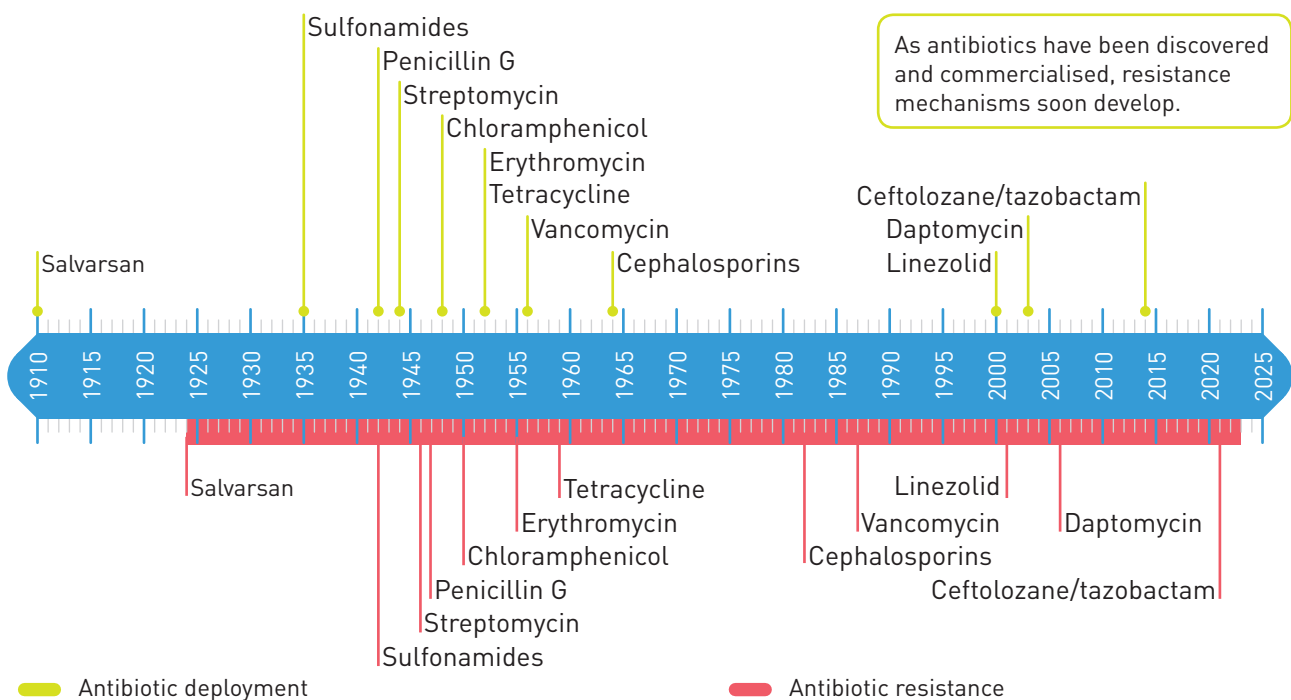


Figure 1

Commercial deployment of antibiotics and emergence of antibiotic resistance – a timeline

Box 1

What is antimicrobial resistance (AMR) and how does it develop?

Antimicrobials are agents intended to kill or inhibit the growth of microorganisms. They include antibiotics, fungicides, antiviral agents and parasiticides. Some heavy metals, disinfectants, antiseptics, many other pharmaceuticals and some natural products may also have antimicrobial properties (Karpanen *et al.* 2012; Pal *et al.* 2017; Almoudi *et al.* 2018; Jones and Joshi 2021; Mendes *et al.* 2022). Antimicrobials are widely used in healthcare for humans and animals, and in agriculture for crop and animal production.

AMR occurs when microorganisms such as bacteria, viruses, parasites or fungi become resistant to antimicrobial treatments to which they were previously susceptible.

AMR can be intrinsic or acquired; the latter can occur through mutations, or in the case of bacteria by the acquisition of deoxyribonucleic acid (DNA) from different microorganisms, via horizontal gene transfer (HGT) of mobile genetic elements (MGEs) (Levy and Marshall 2004; Martínez, Coque and Baquero 2015). Acquired resistance is an evolutionary response by microorganisms, via mutation or HGT, such that they are no longer inhibited or killed by antimicrobials.

Increasing use and misuse of antimicrobials and other microbial stressors (e.g. the presence of heavy metals and other pollutants) creates favourable conditions for microorganisms to develop resistance (Levy and Marshall 2004; Wales and Davies 2015). This can happen in the digestive tracts of humans and animals or in environmental media (e.g. water and soil) and from sources such as sewage (Wales and Davies 2015; Baquero *et al.* 2019; Zhu *et al.* 2019; Figure 1 in Larsson and Flach 2022). Consequently, the likelihood of AMR developing in microorganisms infecting humans, animals and plants is increasing.

2.2 The health, social and economic impacts of AMR

Increasing AMR in human and animal pathogens is among the top ten threats compromising global health (WHO 2021a). According to recent estimates, in 2019, 1.27 million deaths were directly attributed to drug-resistant infections globally, and 4.95 million deaths were associated with bacterial AMR (including those directly attributable to AMR) (Murray *et al.* 2022). Some estimates indicate that by 2050 it could cause up to 10 million deaths globally per year - on par with the 2020 death toll from cancer (O'Neill 2016).

Left unchecked, the economic impact of AMR is also likely to be significant. In the next decade, it could result in a gross domestic product (GDP) shortfall of US\$ 3.4 trillion annually and push 24 million more people into extreme poverty (World Bank 2017).

These World Bank estimates do not cover all the direct and indirect costs of AMR, which could increase these amounts (Morel *et al.* 2020). A recent World Economic Forum report (2021) points out that disease causes worktime and productivity losses, and it estimates that if current trends continue unchecked, AMR could increase animal mortality rates by one per cent, an equivalent loss of US\$13 billion in livestock value (US\$3 billion of which is attributed to waterborne AMR) and US\$3 billion in aquaculture value.

Although the risks of AMR to human, animal and plant health and the environment are shared by all countries, Low-Income Countries (LICs) and Lower-Middle-Income Countries (LMICs) bear a significant burden of infectious disease and will be

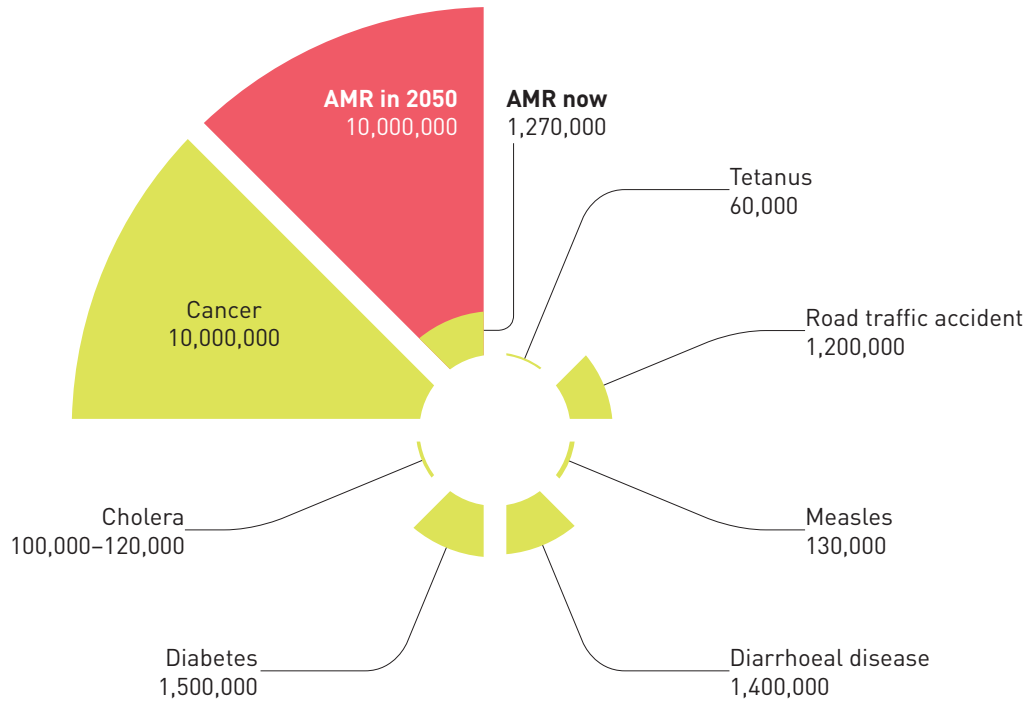


Figure 2

Predicted mortality from AMR compared with common causes of current deaths (adapted from O'Neill 2016; Murray *et al.* 2022)

more adversely affected by AMR. Examining projected global deaths by continent (Figure 3), also indicates where we are seeing problematic levels of AMR

particularly in Asia and Africa (O'Neill 2014; Murray *et al.* 2022).

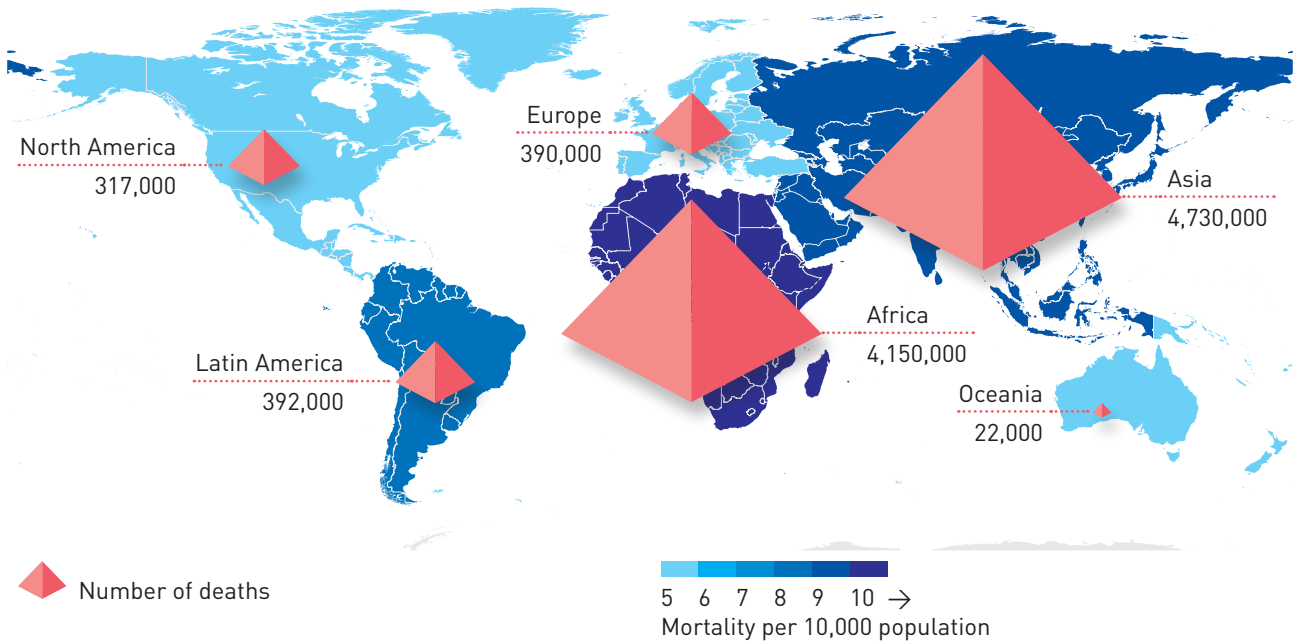


Figure 3

Predicted global deaths from AMR in 2050 (O'Neill 2014)

AMR also exacerbates inequities within societies. Groups including women, children, migrants, refugees, people employed in certain sectors (e.g. agriculture or healthcare) and those living in poverty may be particularly vulnerable and/or more exposed to drug-resistant infections (WHO 2007; Bhopal and Bhopal 2020; WHO *et al.* 2021). Moreover, in several countries, women are largely responsible for the collection of water, and the lack of access to water and sanitation on premises not only limits the time women

can invest in education, income generation activities or leisure but also exposes them to a higher risk of suffering gender-based violence (Travers, Khosla and Dhar 2011; House *et al.* 2014; UNEP and International Union for Conservation of Nature [IUCN] 2018, p. 25) More research on the gender- and age-differentiated impacts and outcome of resistant infections is required to understand how to target policies and assist the most vulnerable populations who remain at risk of being left furthest behind (WHO 2018a).

2.3 Summary

- The effectiveness of antimicrobials is now in jeopardy as certain microorganisms, such as bacteria, viruses, parasites or fungi, become resistant to antimicrobial treatments to which they were previously susceptible.
- AMR is a significant threat to human and animal health, food security, economic development and equity within societies.
- Unless the world acts urgently in addressing the global burden of AMR, including its environmental dimensions, AMR will have disproportionate and devastating impacts, especially to LICs and LMICs. Policy setting that is informed by the collection of disaggregated data (e.g. on gender, age and socioeconomic status) can help to address inequalities from AMR.

Environmental dimensions of AMR

Environmental dimensions of AMR are complex. To view the environment as a single entity – perhaps as a reservoir, or in terms of rural or urban sectors, or describing all waters, soils and air as if their groupings are static – does not properly capture the broader, shared environment and how everything is linked (Figure 4). To understand the development, transmission and spread of AMR in the environment, it is imperative to view it through a multi-dimensional lens.

Microorganisms (particularly bacteria) in water, soil and air can acquire resistance following contact with resistant microorganisms that may have originated in the environment over evolutionary time or have been introduced through human and/or animal waste streams (Cantón, González-Alba and Galán 2012; Perry, Waglechner and Wright 2016).

Resistance can develop due to selective pressures from antibiotics, fungicides, antiviral compounds, parasiticides, certain disinfectant chemicals

(e.g. quaternary ammonium compounds, triclosan and chlorine) and other co-selecting compounds (e.g. biocides and metals such as zinc and copper), which are released into the environment by human activity, poor sanitation or from contaminated land and water. Resistant microorganisms can spread and be transmitted to humans, animals, food animals, plants and wildlife because of complex interconnections across nature (Graham *et al.* 2019; Larsson and Flach 2022).

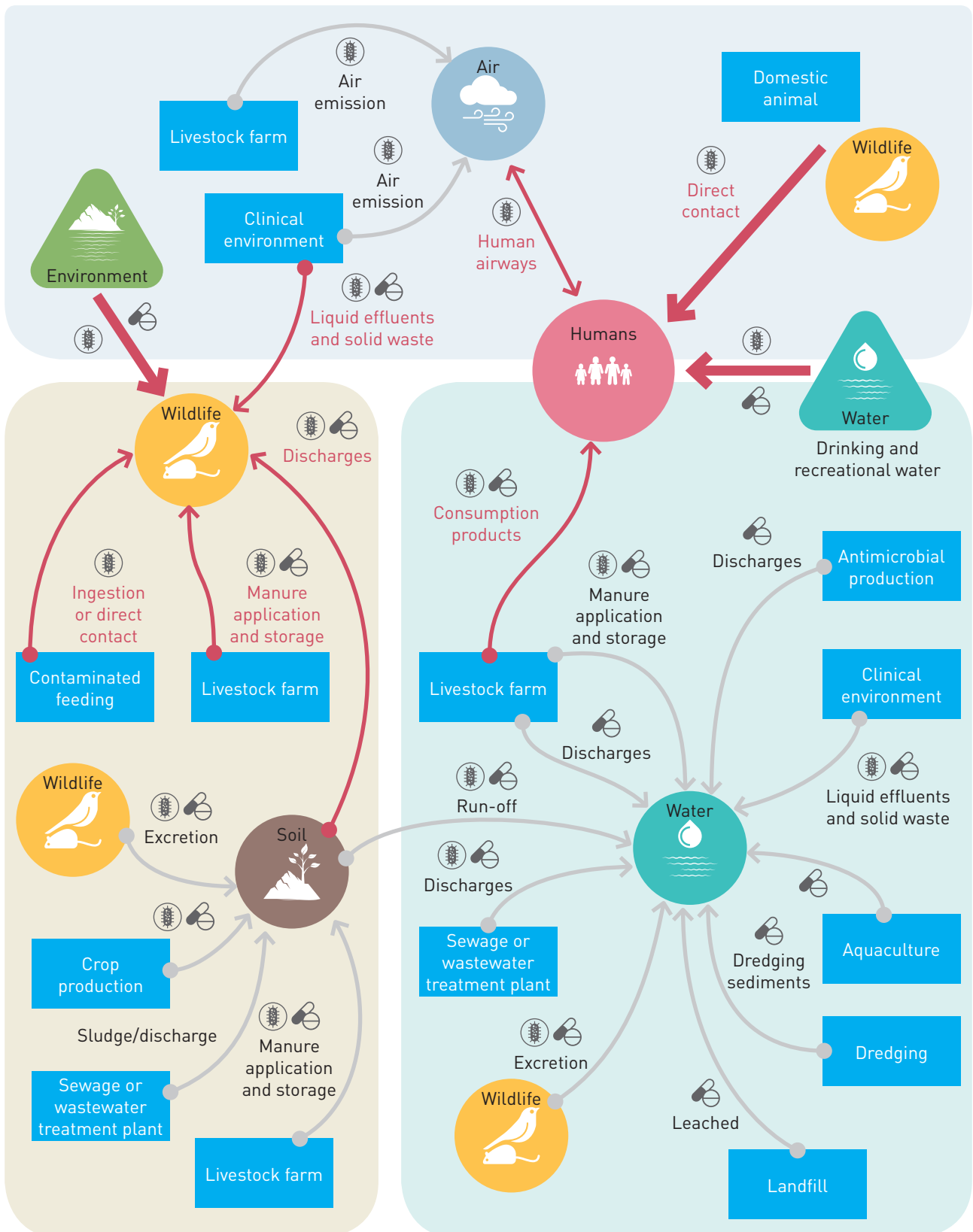
3.1 AMR development in the environment

AMR is an evolutionary phenomenon exacerbated since the beginning of the industrial age by human activities, biological and chemical pollution sources (Rodgers *et al.* 2019). When antimicrobials are released into the environment, they can select for resistant microorganisms and/or new AMR can develop. This may happen by spontaneous mutation, acquisition and transmission by mobile genetic elements (MGE), or through horizontal gene transfer (HGT) events (Figure 5) between environmental and plant, animal or human associated bacteria (Kumar and Pal 2018; Larsson and Flach 2022).

Antimicrobial resistance genes (ARGs) are portions of DNA that encode resistance to one or more antimicrobial compounds (Martínez, Coque and Baquero 2015). ARGs are either intrinsic, developed through mutations that occur in evolutionary processes, or can be acquired from adjacent microorganisms in a process of HGT (e.g. conjugation,

transduction or transformation). The group of all intrinsic and acquired ARGs collectively carried by microorganisms inhabiting a given environmental niche, is referred to as that environment's resistome (Perry, Waglechner and Wright 2016).

Locations such as rivers, lakes and oceans, which over time receive pollution, are more likely to harbour microorganisms with ARGs and MGEs that can fuel AMR development and provide a source of AMR spread within the environment (Kristiansson *et al.* 2011; Chen, H. *et al.* 2019). The microorganisms comprising these aquatic and sediment microbiomes may be of indigenous environmental origin that have evolved AMR over evolutionary time (Waglechner, Culp and Wright 2021), or they may represent invasive species of resistant microorganisms introduced into the environment, such as in animal and human waste streams.



References

- Resistant microorganisms
- Antimicrobial residue
- Activities
- Environmental aspects

Figure 4

Environmental complexities in transmission and spread of AMR

In the environment, not all transmission networks and connections spread AMR equally, but inland water sources are considered a critical vehicle (Fondi *et al.* 2016). River sediments in the vicinity of wastewater sources, may increase the potential for selection, co-selection and HGT. Longer contact times between chemicals and wastewater with indigenous microorganisms increase the likelihood of AMR selection and transmission events (Kristiansson *et al.* 2011), although other factors such as the specific environmental sources and microorganisms, that are carrying the ARGs, also are important to AMR fate in such locations (Quintela-Baluja *et al.* 2019; Wu *et al.* 2022).

3.1.1 Selection pressure

Selection, co-selection and cross-selection of resistance

Pollution from hospital and community wastewater, effluent from pharmaceutical production, run-off

originating from plant and animal agriculture and other forms of waste are frequently composed of, or are deposited into, nutrient rich environments containing complex mixtures of chemicals and biological substances. These matrices may contain not only resistant microorganisms, but also antimicrobials, various pharmaceuticals, microplastics, metals and other chemicals. Physiochemical properties such as oxygen content, pH, nutrient availability and temperature are also known to influence AMR (Jiang *et al.* 2022).

Pollutants in the environment have several important ramifications. In the presence of selective agents, the evolutionary processes of selection, co-selection and cross-selection favour proliferation of resistant bacteria. Co-selection refers to when resistance to a given antimicrobial is selected for by another, different antimicrobial or chemical. This happens when genes conferring resistance to different antimicrobials are in the same microorganism or

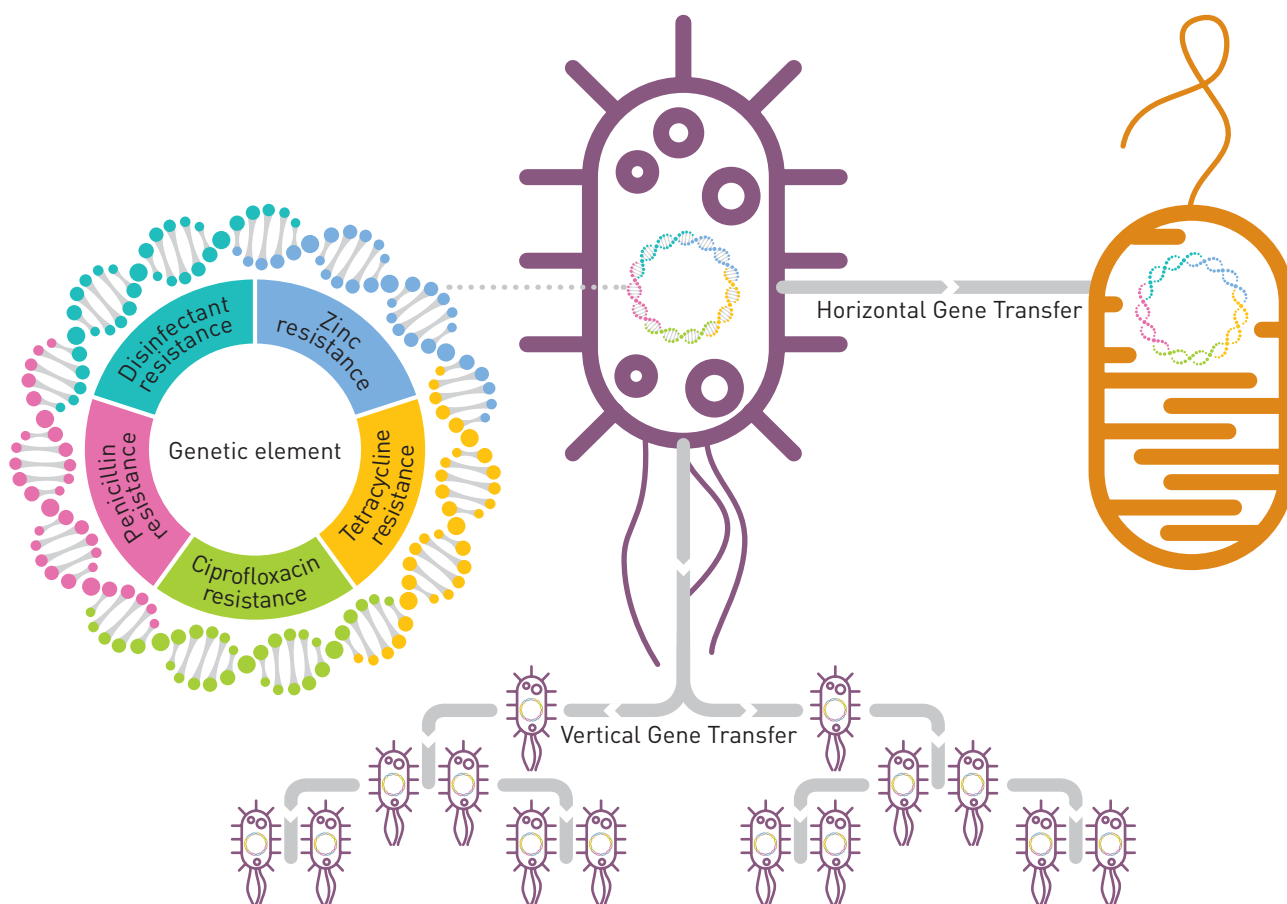


Figure 5

Horizontal and Vertical Gene Transfer

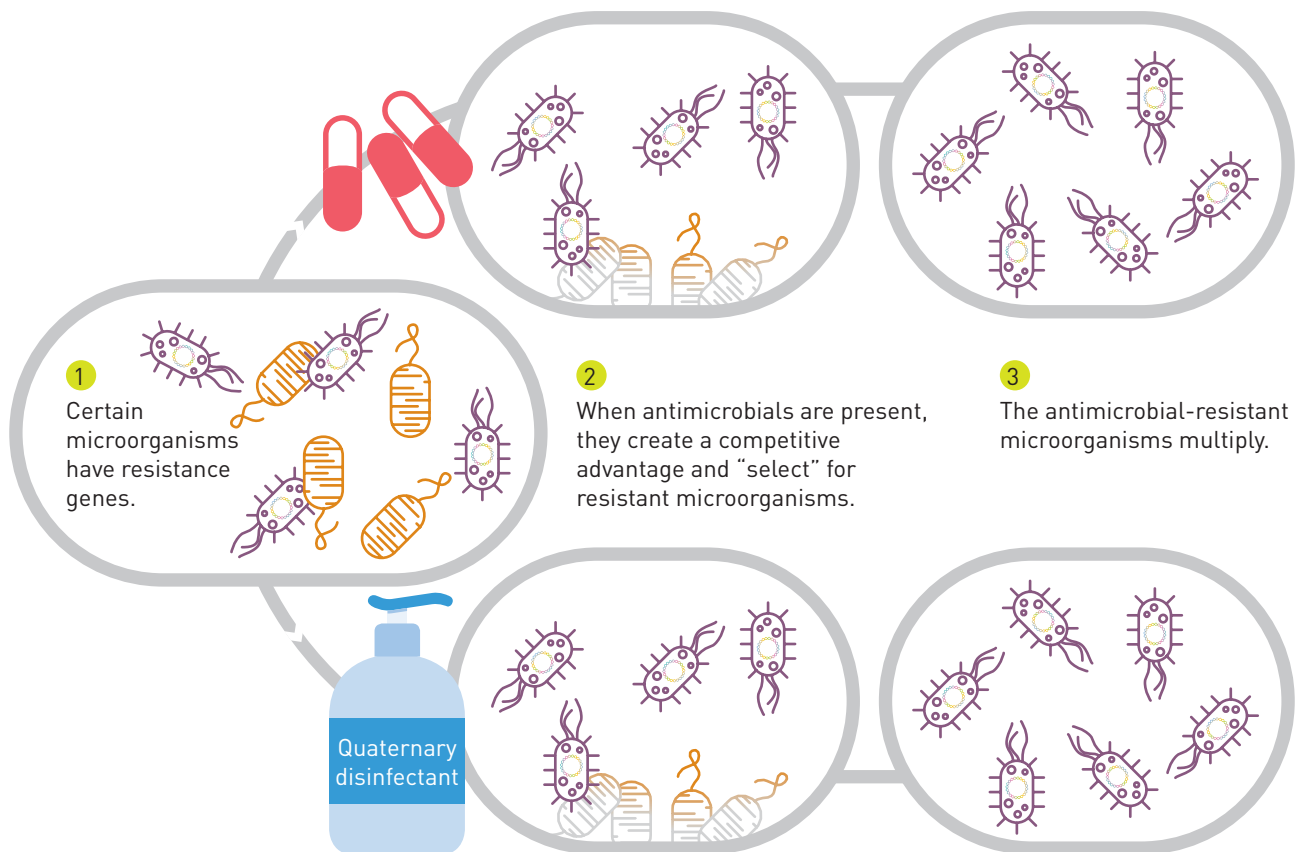


Figure 6

Selection pressure and antimicrobial resistance (United States Centers for Disease Control and Prevention [US CDC] n.d.)

DNA segment. Cross-selection can occur when a single resistance mechanism confers resistance to multiple antimicrobials or other chemicals (e.g. efflux pumps in bacteria). Also, co-regulatory mechanisms can result in co-selection of AMR. Many pollutants also increase the rate that resistance genes are exchanged (e.g. HGT from conjugative plasmids, transformation, and transduction by bacteriophages) among bacteria.

Resistance transmission can take place when the concentration of the antimicrobial (or other chemical agents) are 10 to 1,000 times lower than the concentrations used in human and animal medicine as during clinical treatment (Bengtsson-Palme and Larsson 2016). Wastewater treatment infrastructure can significantly reduce antimicrobials and other co-selecting chemicals in effluent (Murray *et al.* 2020), and is key to environmental pollution management. However, the concentration of antimicrobials and other selective agents present in sewage, even when diluted, may exceed predicted no effect concentrations (PNECs) for resistance development in aquatic

environments (Haenni *et al.* 2022; Bengtsson-Palme and Larsson 2016). Environmental risk assessments, that take into consideration the likelihood for resistance development and seek consolidation of terminology, have been suggested (Murray *et al.* 2021). Although further field validation is needed to determine minimal selective concentrations (MSCs) and to evaluate how well PNEC values reflect the potential for AMR development and transmission in environmental media (e.g. water and soil).

In considering antimicrobial residues and food, the Joint FAO/ WHO Expert Committee on Food Additives (JECFA) has recommended maximum residue limits (MRLs) of antimicrobials in foods of animal origin to provide an acceptable daily intake (ADI) that considers not only toxicity, but for some agents a microbiological ADI for the likelihood of development of AMR in the human gut microbiome, using a model that is based on concentrations of antimicrobials that are known as minimally inhibitory concentrations (MIC) (Codex Alimentarius 2021). Currently, some MRLs for antibiotic

residues in food, recommended by JECFA and adopted by Codex, can select for resistant bacteria. There has been academic discussion on the need to re-evaluate these limits so that they instead consider MSCs of antimicrobials (Subirats, Dominques and Topp 2019), which is a more conservative measurement. This is because when concentrations of antimicrobial residues exceed the MSCs, then selection for resistance may occur. These concentrations may be below the established MRLs that have been mostly established to prevent an allergic response or toxicity (Andersson and Hughes 2017). Likewise, if the ingestion of contaminated food results in a concentration of antimicrobial which exceeds the MSCs, selection for resistance may occur in the human gut microbiome.

When quaternary ammonium compounds, other biocides and some heavy metals (e.g. zinc and copper) are found in waste streams, they can have adverse effects on aquatic and terrestrial species. These chemicals can create a co-selective pressure when bacterial species have multiple genes that confer resistance to these agents and other antimicrobials (Wales and Davies 2015). When the resistance genes co-occur in the same microorganisms, the presence of one agent may co-select for resistance of the other, even in its absence (Pal *et al.* 2015). Thus, one antimicrobial can co-select for resistance to other antimicrobials, which is commonly seen in environmental systems. For example, zinc and copper are used extensively as supplements in animal feed for nutritional purposes and disease control and this may select for improved environmental survival of drug-resistant bacteria in environments containing metals such as in the gastrointestinal tract of animals fed these elements (Bearson *et al.* 2020).

The use of disinfectants in healthcare facilities and food animal production is widespread. Sublethal concentrations of disinfectants (e.g. chlorine, chloramine and hydrogen peroxide) can promote the exchange of ARGs between bacteria (Zhang *et al.* 2017). Further research is needed to better understand the significance of disinfectants and bacterial response governing this phenomenon.

In an agricultural context, herbicide use to control weeds in agriculture may enrich ARGs and MGEs by altering soil microbiomes and may contribute to

further AMR development in agricultural environments (Li *et al.* 2022; Liao *et al.* 2021). Microplastics also pose a problem, as they harbour resistant microorganisms (Liu *et al.* 2021; Bartkova *et al.* 2021; Kaur *et al.* 2022). Use of plastics in agriculture settings creates microplastic pollution of soils (He *et al.* 2018) and is concerning because current uses are unsustainable (FAO 2021a). When microplastics are found in water there is an increase in gene transfer frequency in bacteria attached to the plastic surface (Arias-Andres *et al.* 2018). Microplastics polluting rivers show that urban settings are correlated with increased abundance and dissemination of ARGs, and that polypropylene is more associated with AMR acquisition and spread (Li *et al.* 2021).

Resistant microorganisms on microplastics, found in wastewater treatment plants (WWTPs), water, soil and air have been studied to understand the mechanisms and dynamics of transport and transfer of resistant microorganisms harboured in biofilms (Piergiacomo, Brusetti and Pagani 2022). However, most literature investigating environmental transport and transfer of AMR with microplastics describes studies in a controlled laboratory setting and there is a need to better understand the processes in more complex environmental media and matrices (Liu *et al.* 2021).

As natural environments normally contain complex chemical mixtures resulting in different selective pressures, a future challenge will be to determine the frequency and the effects of such interactions to assess an environment's selective potential more comprehensively (O'Neill 2016). An important, but difficult task, might include the re-evaluation and harmonisation of data and terminology for several safety measures. These include microbial safety limits for the environment to consider AMR, MRLs set for antibiotics in food and established PNECs for resistance development in aquatic environment, and to also include measures for assessing risk of AMR development in soil and other environmental media (Le Page *et al.* 2017). Furthermore, both environmental risks of resistance development and ecotoxicity need to be assessed. The role of individual bioactive and mixtures of chemicals in diffuse and point source discharges should be evaluated in the context of environmental risk assessments. The pharmaceutical manufacturing industry has begun this kind of approach in establishing voluntary discharge

standards (Tell *et al.* 2019). Additionally, more research into the gender- and age-differentiated impacts of these individual chemicals and mixtures of chemicals is required (Strategic Approach to International Chemicals Management [SAICM] 2018).

Antimicrobial use and environmental pollution

A major public health challenge is the extremely context-dependent effect of antimicrobial pollution (Danner *et al.* 2019). Antimicrobial agents are widely used in human medicine, aquaculture, livestock and crop production, and are also put into the feed and water of food animals. They are excreted in significant quantities into the environment as active molecules, or partially degraded, from various sources. The concentration of antimicrobials excreted unmetabolized in the faeces and urine of humans and animals is highly variable and is dependent upon the antimicrobial drug class, formulation, the route of administration, animal species and health status (Kümmerer and Henninger 2003; Giguère, Prescott and Dowling 2013). Where provision of wastewater treatment is not adequate, close contact with polluted waters can result in a consumption-excretion cycle (WEF 2021).

The consumption-excretion cycle occurs when containment, controls or barriers for these pollutants are lacking, such as pit latrines without confining

barriers, or when inadequately treated or untreated wastewater is used to irrigate farmland, or animal manure or human waste is used to fertilize crops. This results in functional antimicrobials entering the environment unless waste management measures to address AMR development and spread are applied. Such releases transmit antimicrobial resistant microorganisms and ARGs, which can conditionally promote AMR, into the environment (Bengtsson-Palme, Kristiansson and Larsson 2018; Bürgmann *et al.* 2018; Karkman, Pärnänen and Larsson, 2019; Berendes *et al.* 2020). Environmental releases can also occur when unused or expired antimicrobials are not properly disposed (e.g. take-back programmes) (Bashaar *et al.* 2017; Nepal *et al.* 2020).

A technical report was prepared for the World Economic Forum (Vivid Economics 2020) assessing the costs and risks of water pollution globally. It gathered available data on emissions from clinical use of antimicrobials, agricultural uses, as well as antimicrobial manufacturing. These measures combined make up part of a measured score for pollution emitted into water. As having wastewater treatment infrastructures in place can reduce environmental pollution, this also factors into a country's overall pollution score. Therefore, a pollution score can be determined by combining water discharge sources against connections to

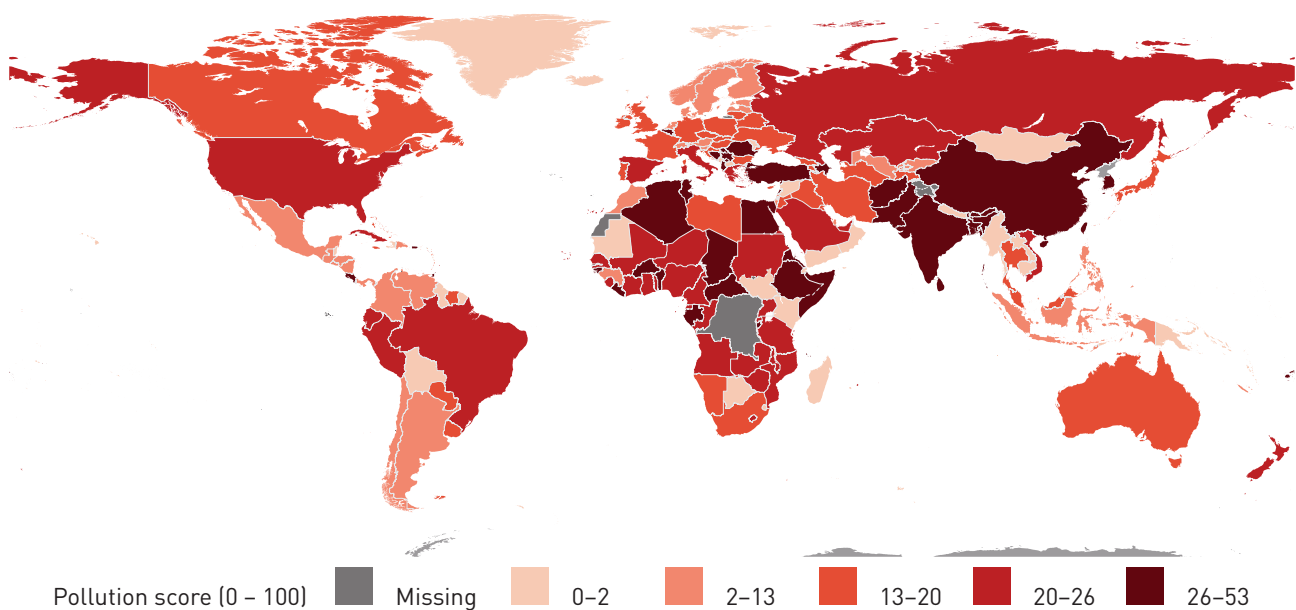


Figure 7

Estimated global environmental water contamination and pollution from antimicrobials
(Vivid Economics 2020)

available wastewater treatment infrastructure (Figure 7). Regions with higher scores indicate there are opportunities for further pollution management.

Wastewater from different geographic regions has comparatively different AMR burden and gene profiles; with Africa and South America having the highest per capita levels in their wastewater, and Europe and Oceania having the least (Hendriksen *et al.* 2019; Munk *et al.* 2022). Such regional variations in AMR are best explained by antimicrobial usage, microbial diversity and anthropologic factors, such as the extent of sanitation infrastructure and availability of quality healthcare (Collignon *et al.* 2018).

Collectively, chemical pollutants can influence the selection of ARGs in the environment and alter the relative abundance of resistant pathogens of human, plants and animals (Kumar and Pal 2018). Pollution by chemicals with antimicrobial activity (e.g. pharmaceuticals, certain metals, biocides and other compounds) may influence the genetic mobilisation of ARGs in certain microorganisms or

enhance AMR in microorganisms in the environment (Murray *et al.* 2021), although the relative importance of such drivers to actual AMR selection is uncertain.

Factors that influence the magnitude of effects of antimicrobial pollution on environmental AMR include the physical and chemical properties of an antimicrobial (i.e. antimicrobial drug class) and the amount (i.e. concentration), the presence of other antimicrobials and/or contaminants, the duration of exposure and the physio-chemical properties of environmental media (e.g. water or soil) (Almakki *et al.* 2019). In addition, the potential for antimicrobials to select for AMR at environmentally relevant concentrations varies dramatically (Bengtsson-Palme and Larsson 2016; Stanton *et al.* 2020). Antimicrobials have been detected in water bodies and other landscapes at concentrations that can provide selection pressure for AMR development (Haenni *et al.* 2022). In some rare cases the detected concentrations are greater than the therapeutic blood concentrations used to treat diseases (Kristiansson *et al.* 2011; Brack *et al.* 2022; Wilkinson *et al.* 2022).

3.2 AMR and the triple planetary crisis

AMR challenges cannot be understood or addressed separately from the triple planetary crisis of climate change, biodiversity loss and pollution and waste because they are all driven by unsustainable consumption and production patterns (Cavicchioli *et al.* 2019; UN 2022). Fuelled by population growth, urbanization and growing demand for food and healthcare, we can expect an increase in the use of antimicrobials and in pollutant releases into the environment.

Unsustainable consumption and production patterns are of particular concern to agri-food systems, but also other sectors such as chemicals, including antimicrobials, which as noted above are now in jeopardy of losing their effectiveness.

3.2.1 Climate change

The climate crisis has numerous impacts on ecosystems, human health, animal health and food

production, which also affect AMR (Global Leaders Group [GLG] on AMR 2021a). Higher temperatures can be associated with increased frequency of horizontal gene transfer, especially those associated with conjugation (Lerman and Tolmach 1957; Kim, Kim and Kathariou 2008; Vegge *et al.* 2012), as well as an increase in antimicrobial resistant infections (MacFadden *et al.* 2018; McGough *et al.* 2020; Pepi and Focardi 2021). The climate crisis also contributes to the emergence and spread of AMR in the environment due to the continuing disruption of the environment due to extreme weather patterns (Burnham 2021).

Additionally, the frequency, composition and amounts of pollution containing biotic and abiotic agents may be increasing due to the climate crisis. Temperature, oxygen and carbon dioxide concentrations in the environment can also influence the survival and proliferation of bacteria, and the rate at which they acquire resistance (Liao, Chen and Huang 2019; Gupta, Laskar and Kadouri 2016; Jong *et al.* 2020).



Flooding contributes to the spread of AMR in the environment
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Antimicrobial impacts on microbial biodiversity may in turn affect biogeochemical cycles such as the carbon and methane cycles, which are directly involved in regulating earth's climate (Bollinger *et al.* 2021).

3.2.2 Biodiversity loss

Human activity and climate change have altered soil microbial diversity in recent decades, which may also promote the circulation of antibiotic resistance genes in the environment (Zhu and Penuelas 2020). Natural microbial communities provide important ecosystem functions, and the ecotoxicological effects of antimicrobials on environmental microbiomes may also impact broader ecosystem services such as those related to biogeochemical cycles and plant health (Brandt *et al.* 2015). Even treating cattle with certain antibiotics changes dung beetle microflora, which can interrupt the essential ecosystem service that dung beetles provide (Hammer *et al.* 2016).

Biodiversity and fully functional ecosystems are critical for planetary health, and antimicrobials potentially threaten the health of ecosystems (Grenni, Ancona and Barra Caracciolo 2018; Banerji *et al.* 2019). High microbial diversity can act as a biological barrier to resist the spread of AMR (Chen, Q. *et al.* 2019); conversely, antimicrobial use can threaten to diminish microbial diversity (Chen, J. *et al.* 2019), and microbiological biodiversity preservation is essential to maintain a diverse molecular reservoir for future pharmaceutical discovery. Microbes inhabiting natural environments have long been,

and will continue to be, sources of pharmaceutical discovery for wellness, disease prevention and health care use (Neergheen-Bhujun *et al.* 2017). Since soil biota is an essential component of planetary health (Zhu *et al.* 2019; Zhu and Penuelas 2020), maintaining soil microbial diversity and identifying the forces that shape soil microbial diversity is crucial in preserving this soil-borne legacy (Neergheen-Bhujun *et al.* 2017; Zhu and Penuelas 2020).

Shifts in microbial diversity in natural habitats are a bioindicator of change in ecosystem functions (Grenni, Ancona and Barra Caracciolo 2018; Jørgensen *et al.* 2018; Banerji *et al.* 2019). Human activities, such as the generation of wastewater, elevate ARGs in affected environments, but few studies have examined how the microbes carrying these ARGs persist and interact with other microbial species in their surroundings (Rodriguez-Mozaz *et al.* 2015; Bengtsson-Palme, Kristiansson and Larsson 2018; Smalla *et al.* 2018; Banerji *et al.* 2019). While the impacts to ecosystem services and biodiversity loss from antimicrobial use and pollution are being better elucidated, there remains very limited evidence for a causal link between AMR and impacts to biodiversity loss.

3.2.3 Pollution and waste

Antimicrobial resistance genes are increasingly recognized as emerging contaminants, with the magnitude of their occurrence correlating with anthropogenic inputs (Pruden *et al.* 2006; Sanderson *et al.* 2016; UNEP 2017), and contaminated

environments can become sources of AMR. Of particular concern is the release of biological AMR pollutants originating from discharges of both treated and untreated human and animal excreta into

the environment. Discharges of chemical wastes, including from pharmaceutical manufacturing and disposal of unused and expired antimicrobials, add to pollution concerns.

3.3 AMR transmission and spread in the environment

Resistant microorganisms are found in humans, animals, plants and the environment (in water, sewage, soil and air), and spread can occur from all these media (Ferguson *et al.* 2016; Price *et al.* 2017; Hernando-Amado *et al.* 2019).

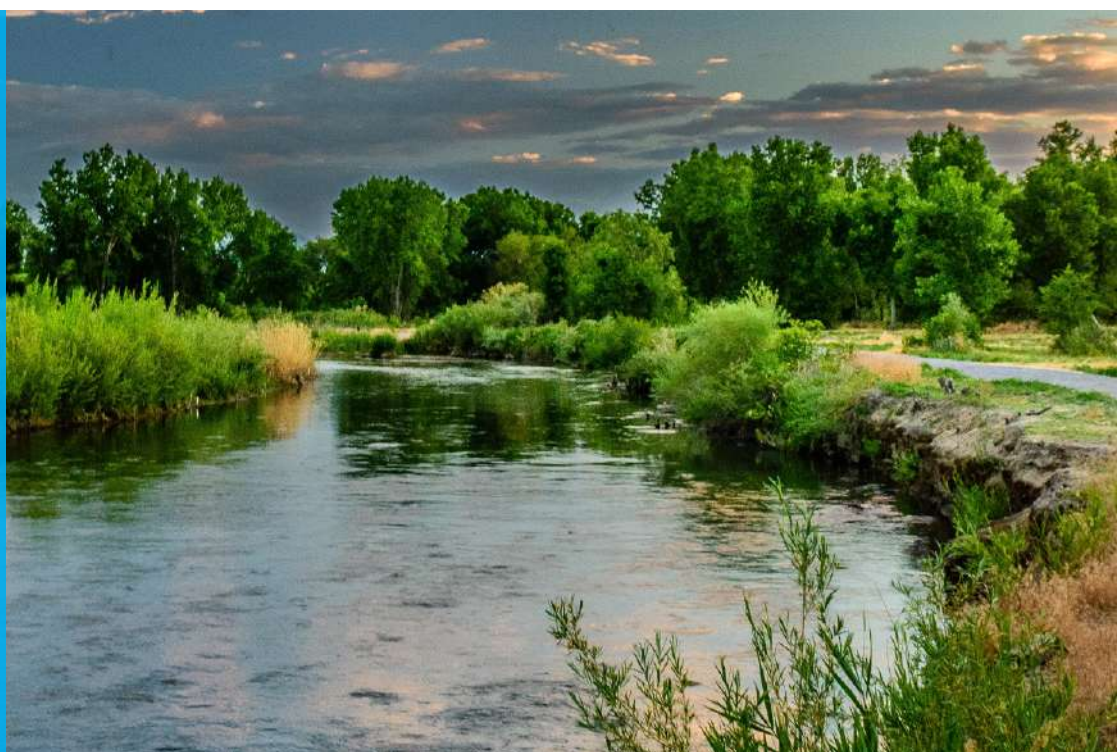
Environmental media transmit and spread antimicrobial resistant microorganisms within and between humans, animals and environment (Baquero *et al.* 2019; Hernando-Amado *et al.* 2019). The presence and relative abundance of specific resistant and susceptible microorganisms, particularly in domestic wastewater, can indicate what is circulating in society, including in healthcare facilities (Pruden *et al.* 2021).

Identified sources of resistant microorganisms, genes and antimicrobials initiate their spread from specific or relatively local points of release. However,

the actual path of AMR spread includes places within the environment that temporarily harbour AMR, which can then be transmitted onwards to humans or animals (Figure 8). Such locations are transient or conditional sources of AMR and are often influenced by hydrological and anthropogenic events in the environment.

Human exposure to AMR can also take place following consumption of food that has become contaminated with resistant microorganisms from the production environment, food animal microbiomes or the processing environments, or when water contaminated with faecal matter is ingested (Hölzel, Tetens and Schwaiger 2018; Leonard *et al.* 2018; FAO and WHO 2019; Koutsoumanis *et al.* 2021). When wastewater treatment and waste management is insufficient, there are higher exposures and greater chances

Rivers, lakes and sediment can be transient sources of AMR © Matthew Montrone



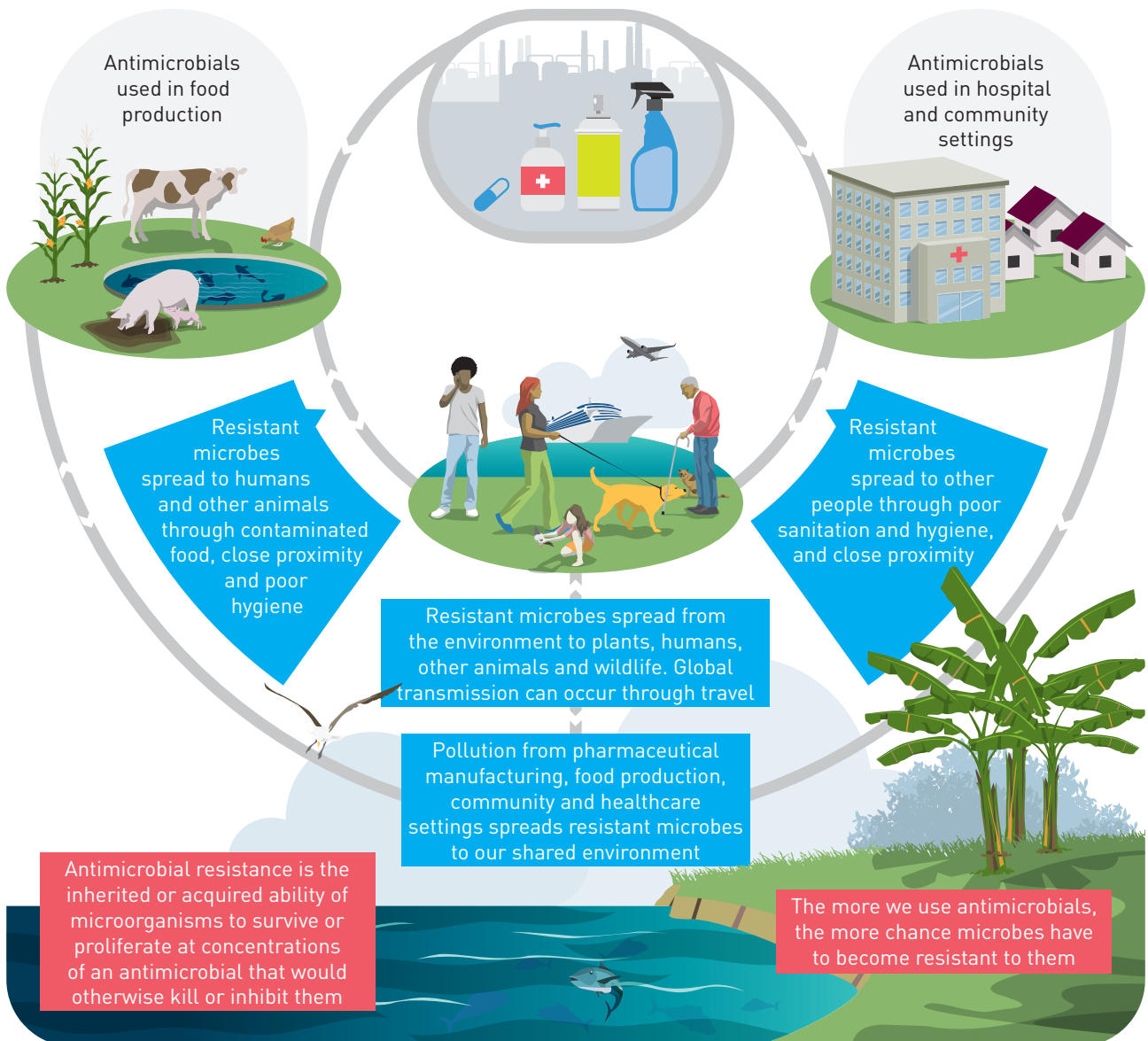


Figure 8

How antimicrobial resistance can spread (adapted from Australia, Department of Health and Aged Care 2017)

for spread (Bürgmann *et al.* 2018). In low-resource settings, clinically important multidrug resistant bacteria are often widespread in the environment, increasing the probability of AMR transmission between humans and animals (Iskandar *et al.* 2020).

Exactly how bacteria and other microorganisms acquire ARGs and the specific transmission routes are difficult to trace, but spread in water systems seems to play an important role in both processes (Baquero, Martínez and Cantón 2008; Lupo, Coyne and Berendonk 2012; Fondi 2016).

3.3.1 Transient and diffuse spread of AMR in the environment

The transmission and spread of AMR are not confined to point-sources, such as wastewater emitted from a pipe or agri-food system drainage outlets. Diffuse or non-point source pollution can also be important because it is often an unbounded phenomenon that can overlap across ecological scales. Transient and diffuse sources include rivers, lakes and sediments, overflows, agricultural runoff, soil, airborne transmission and wildlife migration. Globalization, international trade and migration of both people and

wildlife makes it important to consider non-point spread of AMR because it occurs irrespective of borders.

Water – rivers, lakes and sediments

River and lake sediments can be a transient source of AMR (Pruden *et al.* 2006) that readily accumulates resistant microorganisms and genes, MGEs and chemical pollutants that have been deposited in transit (Lu and Lu 2020). Such deposition makes such locations ‘new’ sources for AMR spread, which can have different resistant microbial hosts than original sources, having transformed during transit. Sediment is also a location where in situ AMR evolution and transmission can occur. Sediments can be pseudo-static for long periods, slowly accumulating AMR from wastewater and other releases. However, they become sources during extreme weather events, and remobilise AMR en masse into the wider environment.

A study of the Cache-La Poudre River, which emanates from a pristine origin in the Rocky Mountains, was the first to demonstrate a gradient in magnitudes of ARGs in water and sediment as there were more WWTPs and agricultural runoff inputs to the river (Pruden *et al.* 2006). Studies on the Almendares River in Cuba showed that although untreated wastewater releases occur year-round and accumulate near waste outfalls in the dry season (Graham *et al.* 2011), over 98 per cent of associated ARGs are transported downstream during the wet season (Knapp *et al.* 2012). Similar phenomena have been seen in other locations, including the Ganges, where the summer monsoon washes accumulated sediment with resistant microorganisms and genes downstream (Ahammad *et al.* 2014).

Similar effects were seen in a river-lake continuum in China where ARGs in downstream lake sediments resembled upstream river sediments, suggesting AMR spread with sediment transport (Chen *et al.* 2020). The genetic signature (ARGs) in river sediments resembled upstream wastewater sources, implying harboured AMR originated from human waste sources to the river and then the lake, probably in a series of steps. Notably, ARG concentrations did not increase during sediment transport, although AMR diversity did increase, implying minimal in situ microbial growth,

but increased AMR potentiation of ARGs between human and environmental microorganisms.

A catchment scale study in the River Thames showed strong associations between wastewater treatment plants and the prevalence of AMR in sediments, with the proximity to, size and type of treatment plant being the most significant predictor of AMR levels in sediments (Amos *et al.* 2015).

Combined sewer overflows spread treated and untreated waste into the environment.

Untreated wastewater contains diverse and elevated concentrations of resistant microorganisms and genes. In places with wastewater collection networks (i.e. sewers or drains), the wastewater flows in pipes or channels to WWTPs or receiving environments in combined or sanitary sewers. Sanitary sewers only transport wastewater, whereas combined sewer drains receive both wastewater and surface runoff, which means flow rates can vary widely depending on precipitation events (Nappier *et al.* 2020). Combined flows can sometimes exceed the design capacity of sewers and impair WWTP operations. As a result, combined sewers have outfalls that release blended but untreated wastewater during major weather events (United States Environmental Protection Agency 2019; Dittmer, Bachmann-Machnik and Launay 2020).

Combined sewer overflows exist around the world and may be a significant source for environmental AMR in countries of all income levels because they essentially are sources of raw sewage entering the environment (i.e. bypassing wastewater treatment systems) (Honda *et al.* 2020). Unplanned overflows of sewers, or open drains during precipitation events, can result in wastewater flooding, which can be most dramatic in places with limited infrastructure (Figure 9). Such releases can also result in untreated wastewater leaching into groundwater, wells and water sources, especially if the sewers or drains are poorly maintained (Paul *et al.* 2004).

In many cases, combined sewer overflows are designed to bypass WWTPs resulting in flows containing abundant resistant microorganisms and resistance genes entering downstream receiving waters. The effects of combined sewer overflows are sometimes misconstrued as being from the WWTP

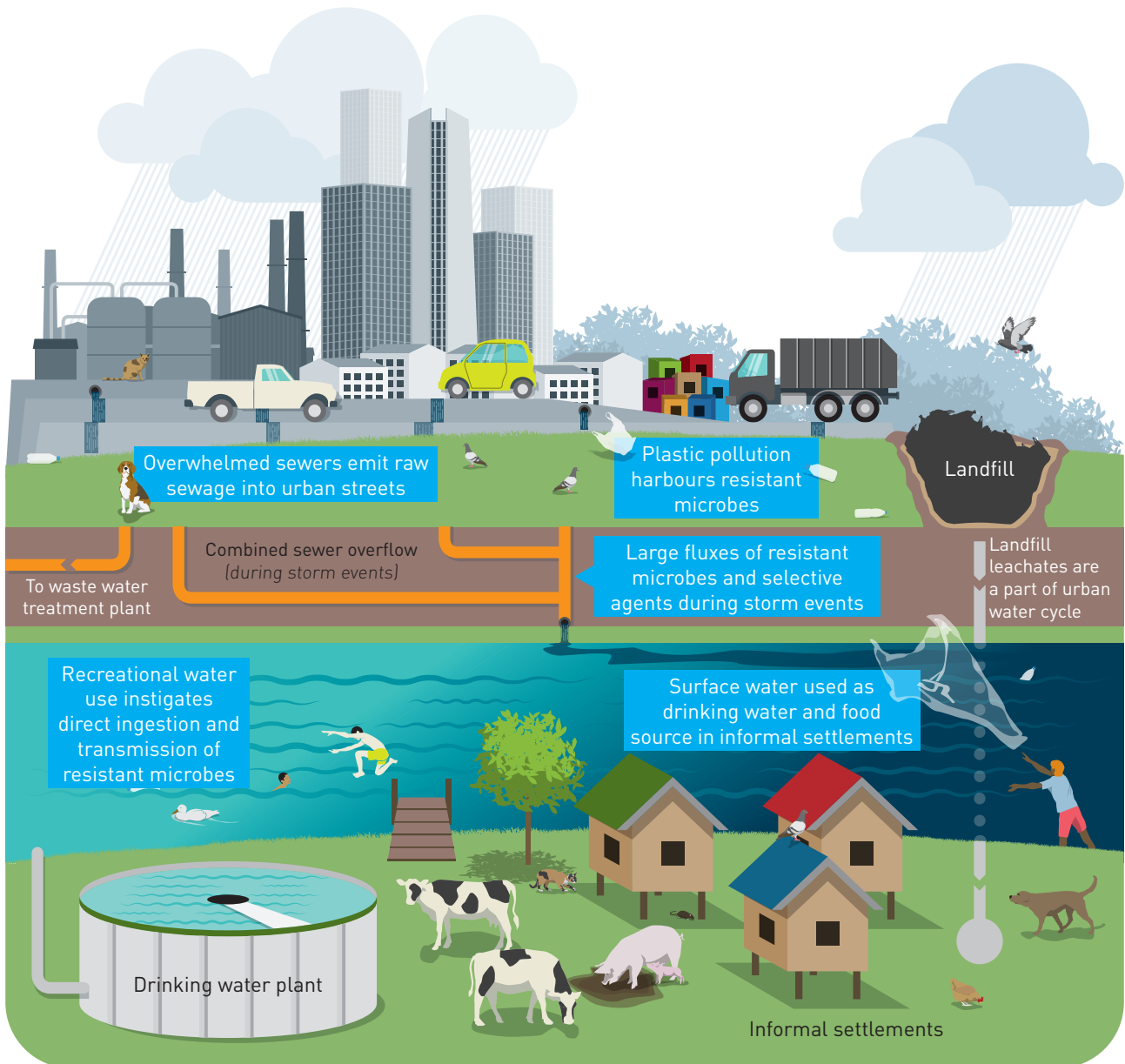


Figure 9

AMR Spread from flooding and urban storm runoff

itself (Quintela-Baluja *et al.* 2019), whereas elevated resistant microorganisms and ARG levels may be legacies from previous combined sewer overflow events. As an example, resistant *E. coli* abundances can be 5,000 times greater in combined sewer overflow than in WWTP releases (Honda *et al.* 2020).

Combined sewer overflows are especially difficult to monitor as AMR sources because they are driven by local weather events and landscapes. A recent study on urban stormwater, which looked specifically at ARGs and MGEs, and metagenomics to characterise resistomes, found AMR within stormwater was

highly variable between storms and locations, and elevated during storm events (Garner *et al.* 2017). Sediment also fuels AMR spread during major weather events, such as flooding, which is exemplified by the consequences of Hurricane Maria in Puerto Rico (Davis *et al.* 2020). Human faecal and genetic anthropogenic AMR markers were quantified in three watersheds six months after the hurricane, and relative ARG abundances and diversity increased downstream of all impacted sites, probably due to flooding.

Although combined sewer overflows cannot be directly linked to some environment AMR exposure

scenarios, they might partially explain observations, such as elevated levels of cephalosporin-resistant *E. coli* in English and Welsh coastal surface waters (Leonard *et al.* 2015). There was evidence of increased colonisation by resistant strains in frequent recreational water users that suggests wastewater releases can translate into carriage of AMR strains in exposed people (Leonard *et al.* 2018), which again may be in part due to combined sewage overflows within catchments, which are common in the United Kingdom. This example shows that wastewater releases influence AMR in exposed individuals, but delineating the root cause, i.e. routine wastewater treatment plant releases versus combined sewer overflows, is a critical knowledge gap.

Soils

Another transient source of AMR is soil, yet not as physically mobile a source as water. Nevertheless, soil is analogous to a sediment, as it harbours ARGs and can act as a transient source of AMR spread. Soils retain their previous exposure history to pollutants and AMR. Certain pollutants are retained and others not, depending upon the soil itself, water (e.g. leaching) and air (e.g. wind) circulation. Soils as sources are especially important relative to agricultural practices and locations where solid or industrial wastes have been placed (Manyi-Loh *et al.* 2018), or where antimicrobials or other bioactive compounds have been employed are important to consider. This includes legacy industrial and disposal locations, where ARGs have been noted in estuarine sediments (Rodgers *et al.* 2019).

Airborne transmission

The potential for airborne exposure is also gaining attention and is increasingly recognized as an environmental transmission pathway (Chen, Kumari and Achal 2020). Air is a particularly dynamic medium that can allow the transmission and spread of AMR (Jin *et al.* 2021; Kormos *et al.* 2022). Transient airborne spread of AMR can occur at different scales, ranging from seasonal and international to incidental and local, and include bacterial, fungal and viral pathogens. ARGs and resistant bacteria are present in biological aerosols from windborne dust, water vapour from wastewater treatment plants and landfills (Miaśkiewicz-Pęska and Szyłak-Szydłowski 2015; Breza-Boruta 2016; Behzad, Mineta and Gojobori 2018;

Kraemer, Ramachandran, and Perron 2019; Li, L. *et al.* 2020). These movements can be exacerbated by air pollution and climate change impacts, particularly severe weather events and wildfires (Kobziar *et al.* 2018).

Atmospheric particulate matter, which comes from many sources, has been shown to carry AMR *Klebsiella* and *Aeromonas* strains, especially at warmer temperatures (Zhang *et al.* 2021). In a Hong Kong study, the majority of ARGs associated with airborne particulates in the inhalable range (PM_{2.5}) were associated with WWTP sources (Xie *et al.* 2022). Similar observations have been made for various ARGs and resistant pathogens on dust particles and aerosols, using metagenomic, high-throughput qPCR and other methods. Scenarios include indoor dust in buildings (Ben Maamar *et al.* 2020), regional dust storms (Gat *et al.* 2017), global urban air quality (Li, J. *et al.* 2018) and food animal production operations (Davies and Wales 2019).

Dust-associated methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected downwind of swine production facilities (Ferguson *et al.* 2016). Proximity to swine production and MRSA infection has also been shown to be associated (Beresin *et al.* 2017). Another example is the transport of antifungal-resistant strains of *Phakopsora pachyrhizi*, the causative agent of soybean rust, one of the most economically devastating fungal diseases of soybeans (Furlan, Carvalho and Antuniassi 2018).

The extent of microbial spread depends upon dilution, dispersion and mixing, and primary modes of transmission, bacterial survival in different environments, probability of colonisation and infective doses, which differs among bacterial pathogens and hosts (Zhai *et al.* 2018). There is a need to address knowledge gaps surrounding airborne AMR transmission and spread especially given its transient nature and association with relative levels of ventilation and weather and climatic conditions. The relative impact of airborne transmission and spread of AMR to human, animals and plants is a 'One Health' issue that deserves more research focus (Jin *et al.* 2021). Air quality standards could be further developed to consider ARGs, which may better protect public health (Li *et al.* 2018).

Wildlife

In parallel to the loss of natural landscapes, increasing livestock and human population densities have been suggested as important drivers for AMR transmission and carriage in exposed wildlife. Birds, small mammals and insects are frequent carriers of resistant microorganisms (Zurek and Ghosh 2014; Ho *et al.* 2015; Furness *et al.* 2017; Rogers *et al.* 2018; Onwugamba *et al.* 2020; Ahlstrom *et al.* 2021).

Some of the main sources of AMR transmission to wildlife include landfills, insufficiently treated wastewaters draining into rivers and lakes that then affect aquatic species, as well as waste from intensively managed livestock farms (Dolejska and Papagiannitsis 2018; see Figure 10). Landfills also provide accessible, consistent and nearly limitless food sources for scavenging animals. Gulls, storks and small mammals feeding on

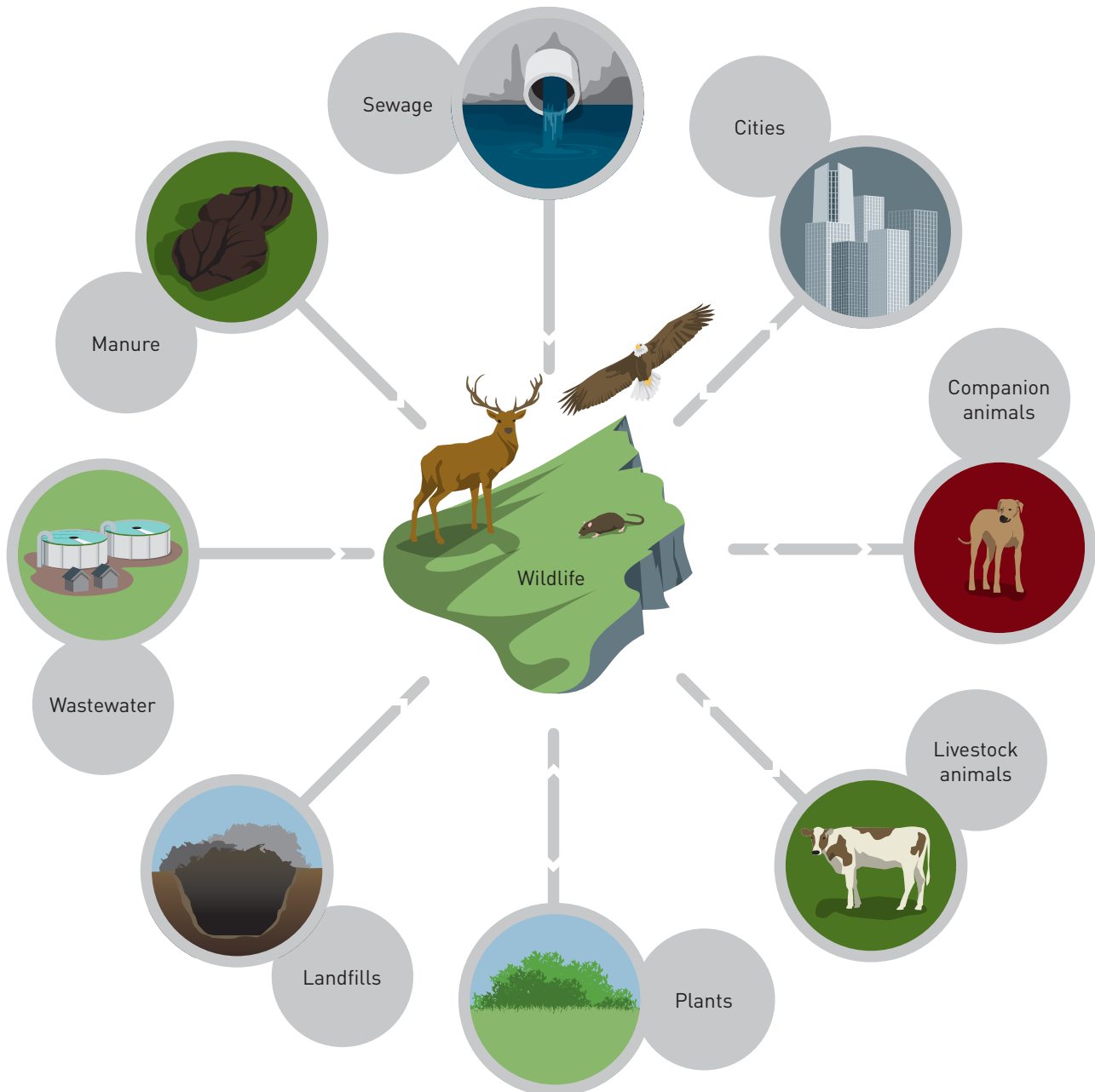


Figure 10

Transmission and spread of AMR to and from wildlife (adapted from Dolejska and Papagiannitsis 2018; reprinted with permission from Elsevier)

landfills have been identified to carry antimicrobial resistant bacteria including those with significant clinical importance (Allen *et al.* 2011; Ahlstrom *et al.* 2018; Martín-Maldonado *et al.* 2020). However, AMR spread via wildlife is not exclusive to specific anthropogenic settings.

At local and regional scales, wild animals frequently reside near animal operations, pastures, urban environments and reservoirs of drinking or recreational waters, and in this way transmit AMR back to humans, plants and animals (Arnold, Williams and Bennet 2016). Globally, seasonal migration of wildlife, especially wild birds that are capable of long-range travel, represent an important pathway for the transmission of infectious diseases including from resistant pathogens (Reed *et al.* 2003).

Bird migration has contributed to the global spread of AMR in ways similar to international tourism. Mass migratory patterns of wildlife allow the spread of resistant organisms from the regions with high levels of environmental AMR contamination to regions with even prudent AMR stewardship. For example, the first reported occurrence of carbapenemase-producing bacteria (NDM-1 enzyme in *Salmonella enterica*) in

a wild animal were isolated from black kites (*Milvus migrans*) in Germany in 2013 (Fischer *et al.* 2013).

Migrating birds, because of long-range movements, can spread resistance globally (Dolejska and Literak 2019). For example, black kites seasonally migrate between Europe and Africa by way of the Balkan States where NDM-1 producing bacteria are common (Nordmann *et al.* 2011). Clinically relevant resistance, such as production of extended spectrum beta-lactamases (ESBL), AmpC cephalosporinases, carbapenemases and colistin-associated resistance, have now been isolated from migratory birds from around the world (Guenther *et al.* 2012; Guenther *et al.* 2017; Wang, J. *et al.* 2017).

There has shown to be an increased risk of AMR carriage in water-associated species, such as mallards, that commonly forage downstream of WWTPs or directly on partially treated wastewater lagoons (Cole *et al.* 2005; Hessman *et al.* 2018). Antibiotic resistant *E. coli* with highly similar genomic profiles have been detected in wild birds and wastewater, suggesting their potential role in the spread of AMR (Varela *et al.* 2015). Urban rodents in domestic wastewater systems also frequently carry AMR (Swift *et al.* 2019).

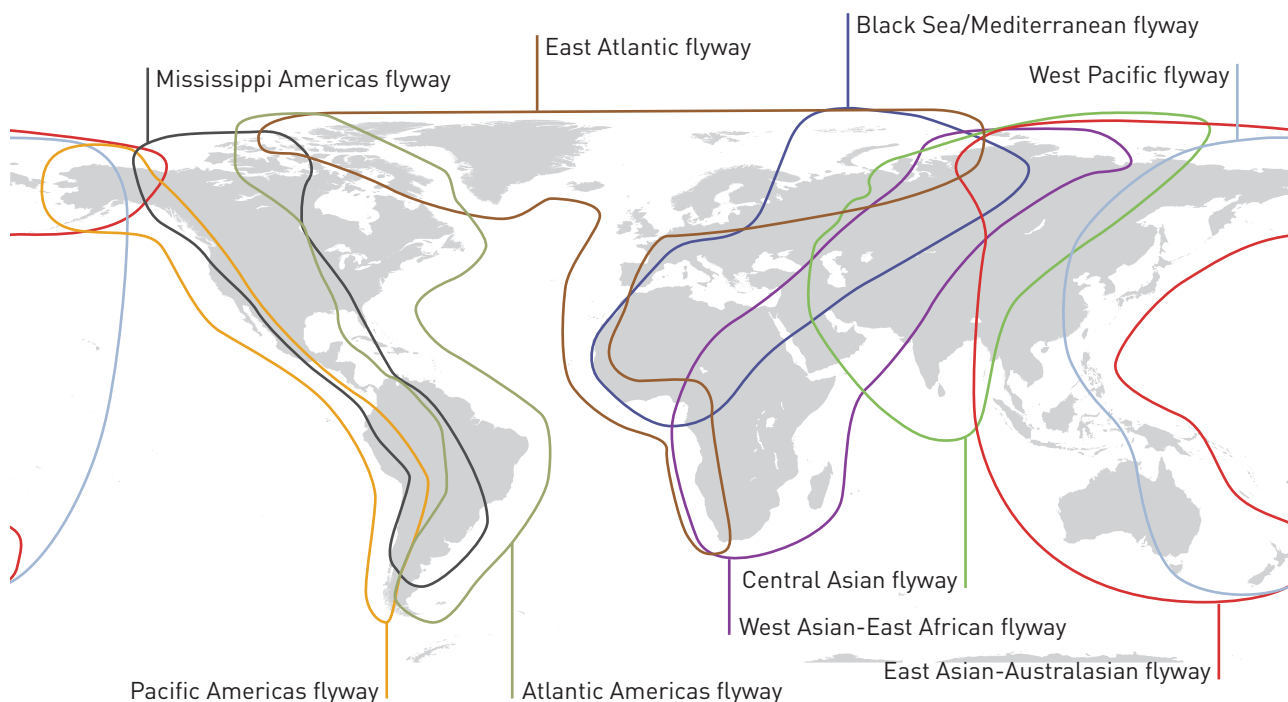


Figure 11

Migration of wildlife – transmission pathway (East Asian-Australasian Flyway Partnership Secretariat n.d.)

Box 2

The environment matters in zoonotic diseases and pandemic spread

The COVID-19 pandemic highlights the importance of the environmental dimensions of zoonotic infectious diseases, especially the potential for antimicrobial resistant microorganisms to be transmitted from the environment to humans (UNEP and International Livestock Research Institute [ILRI] 2020). Around 400 emergent disease events have occurred since 1940, and 14 global outbreaks caused by microorganisms have been reported since 2000, including COVID-19 (SARS-CoV-2) (Jones *et al.* 2008; Morse 2012; Smith *et al.* 2014; LePan 2020; Stephens *et al.* 2021; Destoumieux-Garzón *et al.* 2022; Larsson and Flach 2022). Most of these events were related to the emergence of pathogens from the environment. While they were low-probability events, such events can have highly significant adverse impacts.

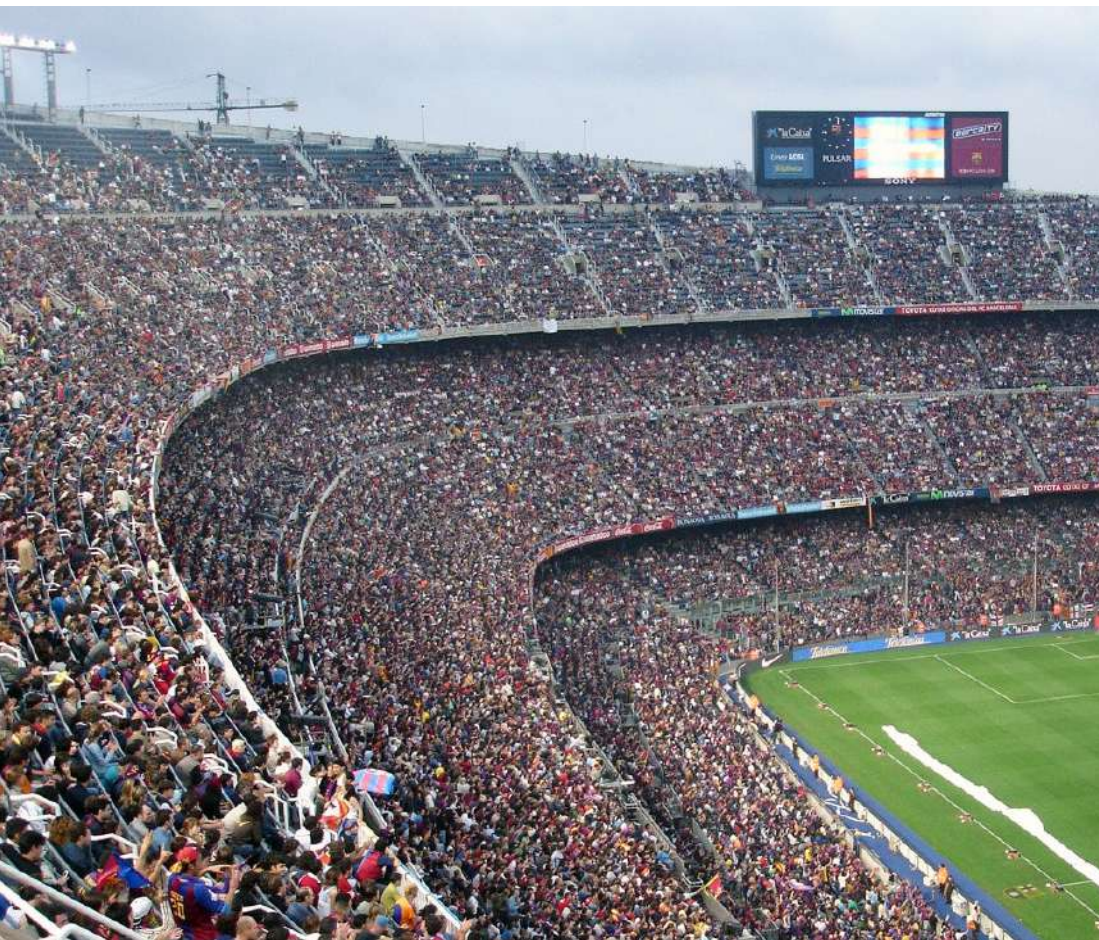
The origin of the great majority of antimicrobial resistant genes (ARGs) is not well known. However, it is thought many novel forms of resistance observed in the clinic today originated from a low-probability transfer of a novel ARG from a bacterium of environmental origin (Humeniuk *et al.* 2002; Yu *et al.* 2022). The taxonomy of species that contain ARGs, many of which are now mobile, need to be further identified and sequenced to determine their environmental origin potential. Further inclusion of newly sequenced origin species in reference databases would be important, as many databases currently attribute ARGs to pathogens, and this may represent only recent HGT events and selection pressures (Ebmeyer, Kristiansson and Larsson 2021).

The world has not taken the threat of zoonotic diseases and pandemics and their environmental dimensions seriously enough. Prevention and control measures such as timely notification, a closer science-policy interface, adequate co-operation within and among countries, systematic data collection and sustainable and predictable funding and logistics in LICs and LMICs must be taken (Sachs *et al.* 2022). Further, an understanding of the gender- and age-differentiated susceptibilities to zoonoses is crucial (Bhopal and Bhopal 2020).

Farm sites (water, soil, feeds, wastewater, sewage, lagoon, manure and treated sludge) serve as key points for potential AMR pollution. Wild animals can easily pick up bacterial pathogens and antimicrobial resistant bacteria when moving and feeding in the farm environment or surrounding contaminated areas including fertilized fields. Antimicrobial resistant bacteria have been reported in different groups of farm-associated animals, including insects (Literak *et al.* 2009; Poudel *et al.* 2019), poultry (Wang, Y. *et al.* 2017) and mammals (Nhung *et al.* 2015). For example, small wild mammals living on farms or in their vicinity were found several times more likely to carry *E. coli* isolates with tetracycline resistance determinants and multidrug resistance strains than animals living in natural areas (Kozak *et al.* 2009). Management of livestock waste is therefore crucial to limit transmission of AMR to wildlife populations.

To gain a deeper and more comprehensive insight into the resistomes carried by wildlife microbiota, laboratory approaches, such as qPCR or metagenomics exist but need to be applied in a standardized manner to improve comparability of data (Martiny *et al.* 2011; Marcelino *et al.* 2019; Miller *et al.* 2020; Skarżyńska *et al.* 2020; Hu *et al.* 2021). Future research should focus more on the human-animal-environment interface to clearly identify sources of AMR transmission pathways involving wildlife.

Many of the strategies to prevent, prepare and respond to pandemics have co-benefits to the actions to address AMR. Combining efforts for pandemic and AMR prevention, preparedness and response will improve synergies thus increasing impact, effectiveness and harmonization in the human,



Mass gatherings of people include sporting events such as the FIFA World Cup © Pixabay

animal, plant and environment interface, food safety and security and water, sanitation and hygiene (GLG on AMR 2022). This lack of pandemic preparedness cannot be allowed to happen again. The COVID-19 pandemic is a wake-up call to better understand and improve all areas of prevention of and preparedness for infectious diseases, including their environmental dimensions (Pachauri *et al.* 2021). It can also provide lessons learned. One of these is the need to benefit from synergies through preventing and tackling various disease threats concurrently, especially mitigating environmental pathways of spread.

Mobility of people and goods

Transnational and intercontinental transport and movements of goods and people have been growing steadily in the past 100 years (Zhu *et al.* 2017), and the rapid globalization of AMR and ARGs follows the interconnectedness of trade and movement across borders. Through these movements, resistant microorganisms spread from one side of the world to the other, particularly through human travel and shipments of crops and animals (Saker *et al.* 2004).

To place the scale of human travel into context, in 2019 the total number of passengers carried on scheduled airline services rose to 4.5 billion (ICAO 2019), and there were 29.7 million ocean cruise passengers, with most ships stopping in several countries (Statista 2021). It is reported that resistant strains and genes carried by human individuals can be retained for up to 12 months after travel (Arcilla *et al.* 2017) further contributing to potential spread.

AMR spread can occur due to waste releases during travel too, such as from ships or airplanes. The International Convention for the Prevention of Pollution from Ships stipulates that sewage from a ship can only be discharged after it is treated by the treatment plant onboard and discharged four nautical miles from the nearest land (Wankhede 2019). However, ships are allowed to discharge untreated wastewater 12 nautical miles away from the land. Similar international conventions do not exist for cross-border air flights and management of waste.

Commercial shipping moves diverse microorganisms in ballast water from around the globe. More than 80 per cent of commercial trade is transported internationally by the world's oceans (United Nations Conference on Trade and Development [UNCTD] 2017; Hess-Erga *et al.* 2019). Since 1970, marine traffic has increased at an average rate of 2.1 per cent per year, reaching 11 billion tons of cargo in 2021 (UNCTD 2022). An estimated 100 million metric tons of ballast water is discharged each year into US ports alone (Lv *et al.* 2018).

Food products are yet another source of cross-border transportation of AMR. Foodborne outbreaks of drug-resistant pathogens linked to imported food products have been reported from multiple countries. Global meat production in 2020 was forecasted to be 333 million tons, only about 6 million tons lower than 2019 (FAO, UNDP and UNEP 2021). Given such trends, it is unsurprising to see that several notable examples of drug resistance have proliferated internationally (Sarno *et al.* 2021).

Mass gatherings result in the congregation of millions of people at a single location. Such congregations of individuals require mass travel from different geographic places and socioeconomic backgrounds, which can spread regional AMR in the host location, and to and from traveller destinations (Bokhary *et al.* 2021). Without precautions, such places can become potential 'super-spreader' locations of AMR and infectious disease. Attendees can also acquire resistant pathogens after gatherings and carry them back to their points of origin (Leangapichart *et al.* 2016).

Displacements due to political unrest, war and changes in resources or opportunities can all drive the mass movement of people and impact AMR (Baltay 2020). Displacement and migration almost certainly increase the risk of overloaded water, wastewater and hygiene capacities enroute and at destinations, and equitable access to and appropriate use of antibiotics by refugees and migrants is important to address AMR (WHO 2022a). Often displaced individuals lack access to basic rights including proper housing, healthcare, water and sanitation, which are all factors with demonstrated inverse correlations with AMR (Collignon *et al.* 2018) and increase its possible spread.

Delineating how such transport, movements and events impact AMR spread is a major knowledge gap.

3.3.2 Examples of global dissemination of resistance genes

In examining cases of AMR dissemination, it can be difficult to determine how resistance spreads globally, but genomic and epidemiologic evidence illustrate how this can be possible. Of the many examples, *mcr-1*, *bla_{CTX-M}* and *bla_{NDM-1}* represent global spread of ARGs in the 'One Health' sectors.

First detected in 2015, *mcr-1* produces an enzyme that confers resistance to colistin, a polymyxin, considered a critically important antibiotic (Liu *et al.* 2016; WHO 2019). Colistin is one of the last remaining clinically effective options against carbapenem-resistant *Enterobacteriaceae*, and is used as a last-resort, life-saving treatment in human medicine for multidrug-resistant bacterial infections. Within a few years of the gene's discovery, rapid global dissemination was documented as *mcr-1* spread across five continents (Liu *et al.* 2016; Wang *et al.* 2018; Ling *et al.* 2020). Indeed, *mcr-1* is now detected around the world in different environments.

An analysis of globally available sequenced isolates containing *mcr-1* suggest that food animals and colonized or infected humans were the primary mechanism of global dissemination, with aquatic organisms now recognized as primary reservoirs of *mcr-1* ARGs (Grami *et al.* 2016; Wang, Y. *et al.* 2017; Cabello and Godfrey 2018; Zhang *et al.* 2019; Anyanwu, Jaja and Nwobi 2020). Healthy individuals, without prior exposure to colistin, but colonized by bacteria carrying *mcr-1* after international travel bolster the evidence that such cross-border traffic contributes to its rapid global spread. Targeted metagenomic analyses of the faeces of healthy Dutch travellers to Southern Africa, and South and Southeast Asia found that almost five per cent of them acquired the *mcr-1* gene while on travels (von Wintersdorff *et al.* 2016; Wang *et al.* 2018). A systematic review that pooled data from over 632,000 travellers documented 30,060 isolates of resistant microorganisms, with most being acquired by travellers to low- and lower-middle-income countries (Bokhary *et al.* 2021).

Bacteria that produce extended spectrum beta-lactamases (ESBL) are resistant to some of the most important and common antibiotics used in human medicine, such as penicillin and cephalosporin, but not carbapenem – all antibiotics sharing a common beta-lactam ring chemical structure. The global epidemiology of the plasmid associated CTX-M-type ESBL is complex given that there are over 50 allelic variants; however, they have been noted to have become increasingly common in all regions of the world in the last two decades (Bevan, Jones and Hawkey 2017). Given that CTX-M enzymes are linked to microbial species originating from microbiomes of the rhizosphere, around the roots of plants, the associated genetic backgrounds (clonal and mobile genetic platforms) also speak to the importance of environmental origins of their dissemination and spread. In addition, the role of poor sanitation, carriage in the human gut microbiota and through food animals have also been considered to have contributed to the rapid global spread of *bla*_{CTX-M} genes.

Carbapenems are used to treat life-threatening infections caused by ESBL-producing bacteria. New Delhi metallo-beta-lactamase-1 (NDM-1 coded by *bla*_{NDM-1} gene) causes multidrug-resistance in bacteria and confers resistance not only to carbapenems, but also to other beta-lactam antibiotics, which complicates the treatment of common infections. Travel, either human or wildlife, is evident in the spread of *bla*_{NDM-1}. First documented from a traveller, *bla*_{NDM-1} was found in 2008 in Sweden in a patient previously hospitalized in India (Yong *et al.* 2009), in a German hospital patient in 2009 (Pfeifer *et al.* 2011) and in surface waters in Delhi in 2010 (Walsh *et al.* 2011). The *bla*_{NDM-1} gene apparently was moving both with people and due to environmental pollution (Walsh *et al.* 2011).

As an example, the gene was detected in the Ganges in 2012 where relative *bla*_{NDM-1} prevalence was highest during the pilgrimage season when visitors increased at specific sites that had inadequate sanitation

ARGs have been found in many remote areas of the world, including in Arctic regions
© Pixabay



(Ahammad *et al.* 2014). Such transient exposures are especially problematic because initial AMR exposure might occur along the river, but then exposed individuals return to their primary residence spreading AMR from the gathering points (Kantele *et al.* 2015). This environmental association of bla_{NDM-1} has been recognized, along with concerns on how to manage it (Shahid 2011; Walsh *et al.* 2011). By 2011, bla_{NDM-1} was noted to have spread to all continents, except Antarctica (Nordmann *et al.* 2011), and was even found

in High Arctic soils of Norway's northern most islands in 2013 near remote human and wildlife congregation points (McCann *et al.* 2019).

The bla_{NDM-1} spread is best explained by human travel, dissemination in migratory wildlife or both. The rapid and global spread of certain ARGs, such as $mcr-1$, bla_{CTX-M} and bla_{NDM-1} , make a compelling case for coordinated local and global action.

3.4 Summary

- Environmental dimensions of antimicrobial resistance are numerous and interconnected, and to understand the development, transmission and spread of AMR in the environment, it is imperative to view it through a multi-dimensional lens.
- AMR challenges are closely linked to the triple planetary crisis of climate change, biodiversity loss and pollution and waste, all of which are driven by human activity, including unsustainable consumption and production patterns.
- When antimicrobials are released into the environment, they can select for resistant microorganisms and resistance emergence. Biological and chemical pollution sources containing antimicrobials contribute to resistance development.
- Resistant microorganisms can spread and be transmitted to humans, companion animals, food animals, plants and wildlife because of complex interconnections across nature.
- Human exposure to AMR from the environment can take place following consumption of food and/or water that have become contaminated by resistant microorganisms.
- The transmission and spread of AMR are not confined to point-sources. Transient and diffuse sources, which include water (rivers, lakes and sediments), overflows, agricultural runoff, soil, airborne transmission and wildlife migration can also be important. Other critical factors are globalization, climate change and the mobility of people and goods, and wildlife.
- Improved understanding of the associations between AMR and different population groups (e.g. gender, age and occupation) is crucial.

4

Management to Prevent and Respond to AMR

4.1 Recognise the environment is key to advancing a 'One Health' response to AMR

Actionable evidence of the importance of the environmental dimensions of AMR has been mounting. As such, AMR requires a response based on a

concerted systems approach, such as 'One Health', at global, regional and country levels from all sectors, stakeholders and institutions.

Box 3

The 'One Health' approach

"One Health' is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development."

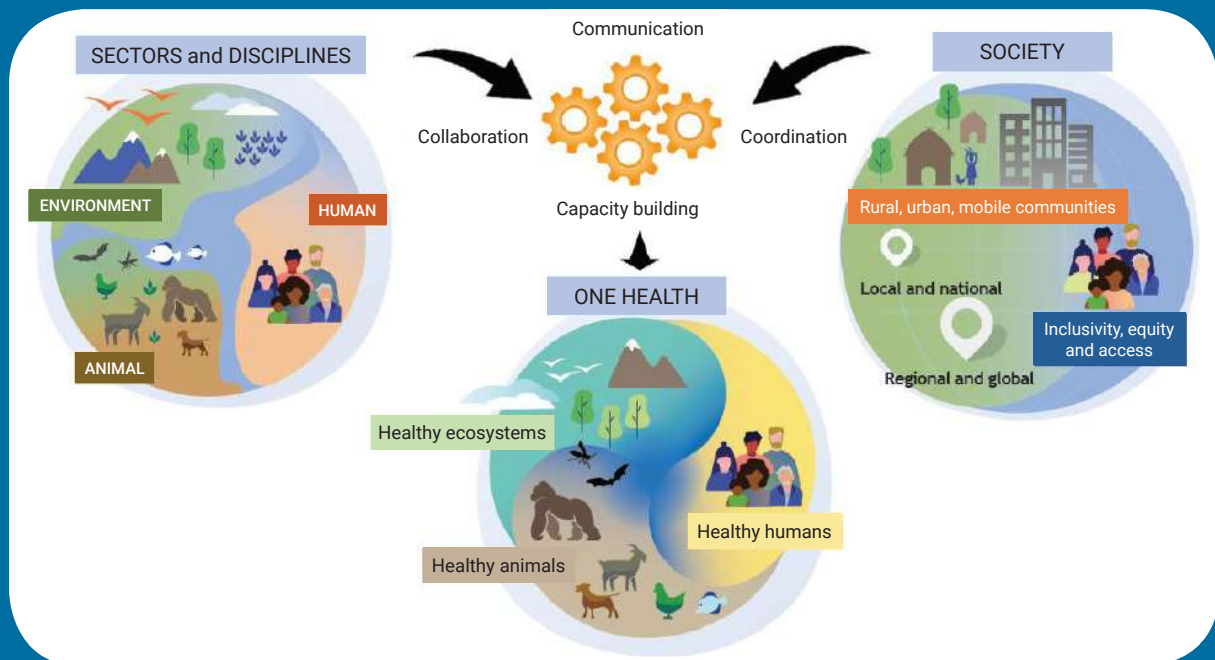


Figure 12

One Health definition developed by the One Health High-Level Expert Panel (WHO 2021b)

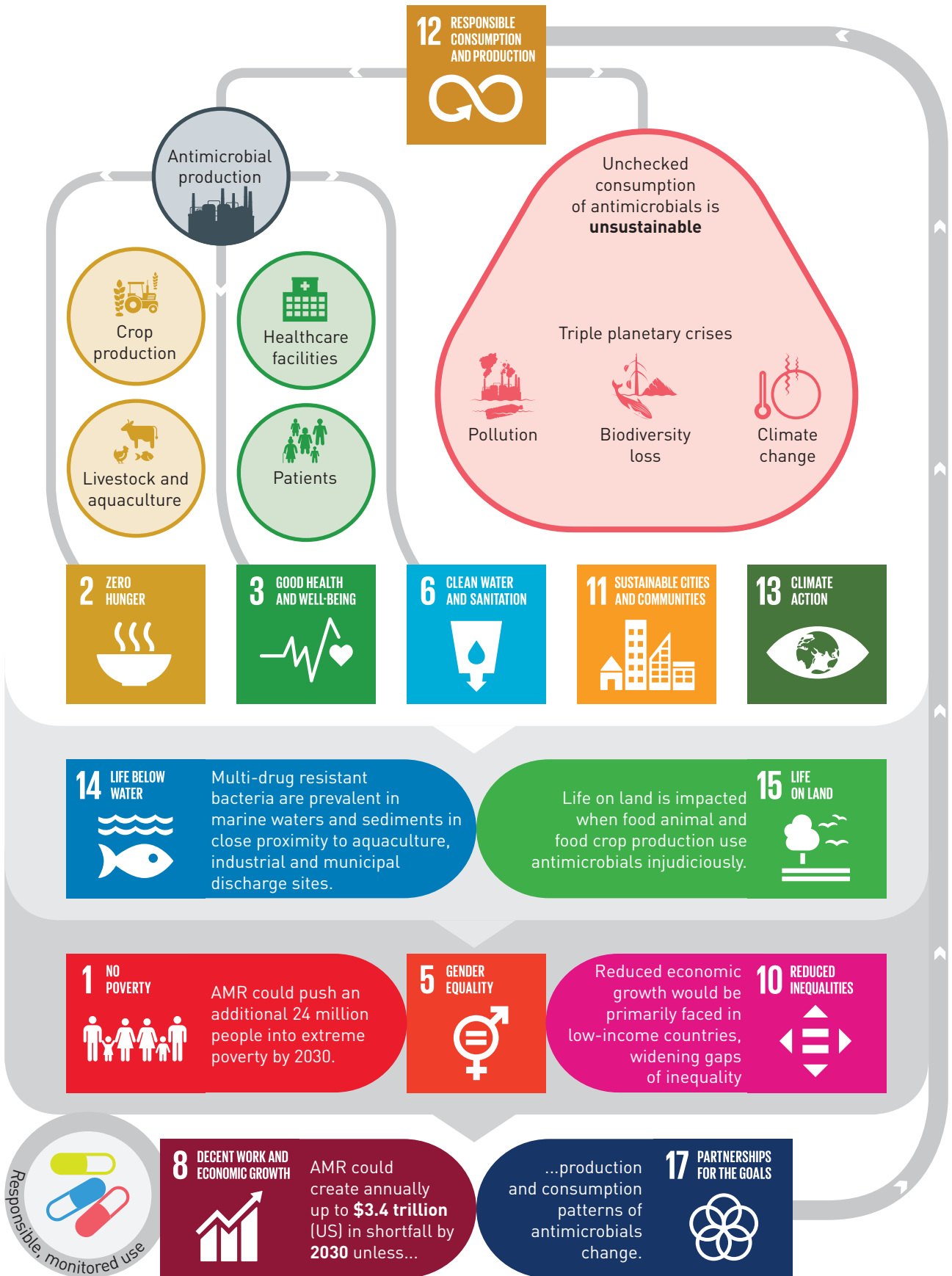


Figure 13

Sustainable production and consumption of antimicrobials can impact many other SDGs

A 'One Health' approach, which considers the health of people, animals, plants and ecosystems in unison, is urgently needed to reduce the burden of AMR and prevent deaths. Reducing the need for antimicrobials, leads to less use and therefore less AMR development, thus creating a positive net effect across sectors.

The 'One Health' approach has many benefits, including cost savings due to addressing multiple threats at the same time (Hernando-Amado *et al.* 2019; Brack *et al.* 2022). Therefore, solutions need to further be addressed in the context of achieving several

Sustainable Development Goals (SDGs) such as SDG 2, SDG3, SDG 6, SDG 11, SDG 12 and SDG 13.

For humans, vulnerability to AMR is further heightened based on one's sex, age and socio-economic status (Yoshikawa 2002; Collignon *et al.* 2018; WHO 2018a). Therefore, approaches and plans that align with the SDGs are highly recommended as these are underlined by the principle of 'leave no one behind', which embeds the indivisible dimensions of sustainable development: social, economic and environmental (UN 2021a).

4.2 Address key economic-sector value chains affecting AMR in the environment

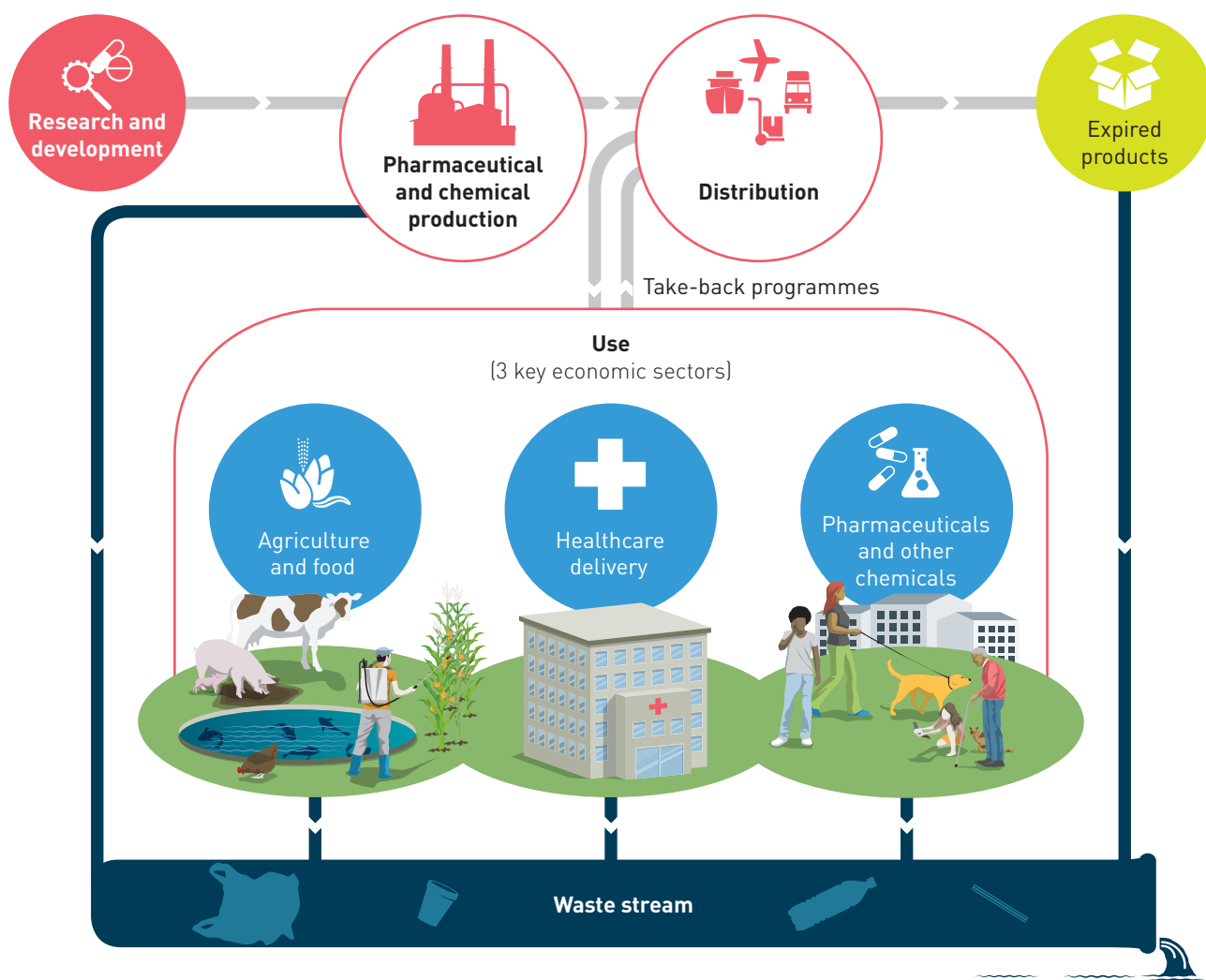


Figure 14

Key economic-sector value chains affecting AMR in the environment

A value chain describes the inputs and outputs needed to bring a product or service to market. From a sustainability perspective, a value chain approach can serve to “identify key points of intervention within economic systems to reduce natural-resource use and environmental impacts caused by production and consumption, and to define a common agenda for action” (UNEP 2021a).

Three economic sectors and their value chains are key drivers of AMR development and spread in the environment: pharmaceuticals and other chemicals, agriculture and food, and healthcare. Effective monitoring, disclosure and transparency are needed in each value chain to understand when and where antimicrobials are used and where AMR is likely to occur. It is equally important to better understand the governance structures and key actors in these value chains to target interventions, realign incentives to minimize AMR and forge partnerships.

Together with pollutants from poor sanitation, sewage and waste effluent in municipal systems, the inputs and outputs from these three key economic-sector value chains profoundly influence the development and spread of AMR, and consequently the overall long-term value of antimicrobials for promoting human, animal, crop and environmental health.

4.2.1 Pharmaceutical and other chemical value chains

Production from this sector includes a range of different chemicals, including antibiotics, antivirals and fungicides, as well as disinfectants. Their use, application and environmental fate may vary significantly.

Pharmaceutical production starts with the processing of raw materials, the manufacture of active pharmaceutical ingredients, drug formulation, packaging and distribution and the consumption and management of expired ‘end-of-life’ products. Often the different parts of this value chain are in separate countries. Curbing antimicrobial pollution from manufacturing and keeping production costs low to ensure affordable access to antimicrobials creates policy tensions that require careful global and national coordination, policy and regulation to resolve (Nijsingh, Munthe and Larsson 2019).

Inadequate management of pharmaceutical manufacturing discharges can lead to negative impacts on the environment (AMR Industry Alliance 2022). Recent evidence suggests sub-minimal inhibitory concentration of antimicrobials from pharmaceutical manufacturing, municipal and livestock wastewater discharges may influence AMR transmission (Bengtsson-Palme and Larsson 2016; Murray *et al.* 2021). However, the relative importance of low concentrations of antimicrobials in driving AMR emergence versus more acute factors, such as faecal waste releases, is still debated. Environmental field data are lacking and selection is also known to be driven by other ecological factors (Knapp *et al.* 2008). In addition, increasing the transparency of relevant chemical and pharmaceutical production, sales, use and disposal, as well as data on environmental releases, is needed to help address these knowledge gaps (Larsson and Fick 2009; Årdal *et al.* 2021).

Effluent and waste from pharmaceutical manufacturing

Pharmaceutical production can periodically release resistant microorganisms and genes, which in combination with chemical releases, can impact the transmission and spread of AMR in the environment as noted above (Larsson, de Pedro, and Paxeus 2007; Fick *et al.* 2009). This can occur through manufacturing operations and effluent generation.

Implementing measures to prevent and control pharmaceuticals such as antimicrobials in effluent is crucial to minimize the selection and spread of AMR in the environment but also to minimise the ecotoxicity effects on aquatic organisms (e.g. bacteria and alga) (Isidori *et al.* 2005; Larsson, de Pedro and Paxeus 2007; Bengtsson-Palme and Larsson 2016). Less than a tenth of antimicrobials have been tested for in wastewater and environmental samples, with no environmental toxicity data being available for most medicines (OECD 2019).

The untreated discharge of pharmaceutical wastes is a key example of where antimicrobial and other selective agents in the environment are sufficiently high to select for resistant microorganisms and ARGs in situ and increase abundance of resistant microorganisms (Kookana *et al.* 2014; Bielen *et al.* 2017; Binh *et al.* 2018; Marathe *et al.* 2018; Bengtsson-Palme *et al.* 2019; González-Plaza *et al.* 2019).

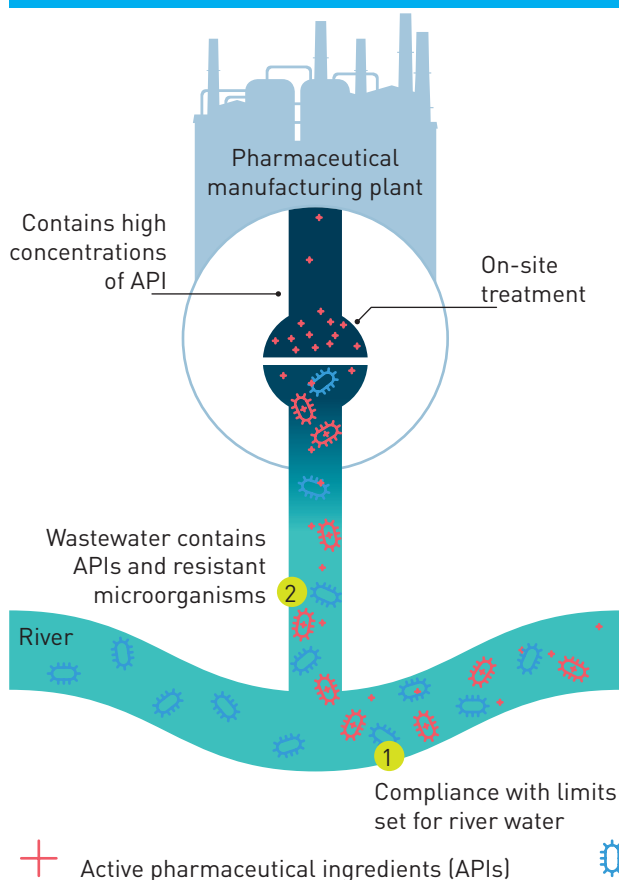
The pharmaceutical industry is considered largely an unregulated sector in terms of environmental pollution (Larsson and Fick 2009; Bengtsson-Palme, Gunnarsson and Larsson 2018; Nijsingh *et al.* 2019). This could be due to the absence of criteria for individual pharmaceuticals and their impacts including AMR (see section 3). Untreated discharge has resulted in high levels of antimicrobial mixtures in exposed surface waters (Larsson, de Pedro and Paxeus 2007; Graham *et al.* 2011) and detection of novel forms of AMR from such environments (Kristiansson *et al.* 2011).

Treatment of wastewater from active pharmaceutical ingredient (API) production should reduce the concentrations of APIs to below levels that select for AMR (Bengtsson-Palme and Larsson 2016; Tell *et al.* 2019).

Addressing pollution from antimicrobial manufacturing has consistently been identified as a priority area of intervention.

Sterilization of effluent from the production of active pharmaceutical ingredients is an option for minimizing pollution with resistant microorganisms, that may have been selected during production, from escaping the treatment facility. Treatment technologies that might achieve this criterion include advance oxidation process (AOPs), incineration and filtration with activated carbon, but new and more sustainable technologies are needed. AOPs and incineration are highly energy consuming, whereas activated carbon would require vast amounts of carbon filters for larger volume waste streams. Carbon filtration also creates filter waste that needs to be incinerated and may not be adequate to reduce all types of APIs to safe levels.

Option 1: Wastewater is directly discharged into the environment



Option 2: Wastewater is sent to a municipal wastewater treatment plant, before being discharged into the environment

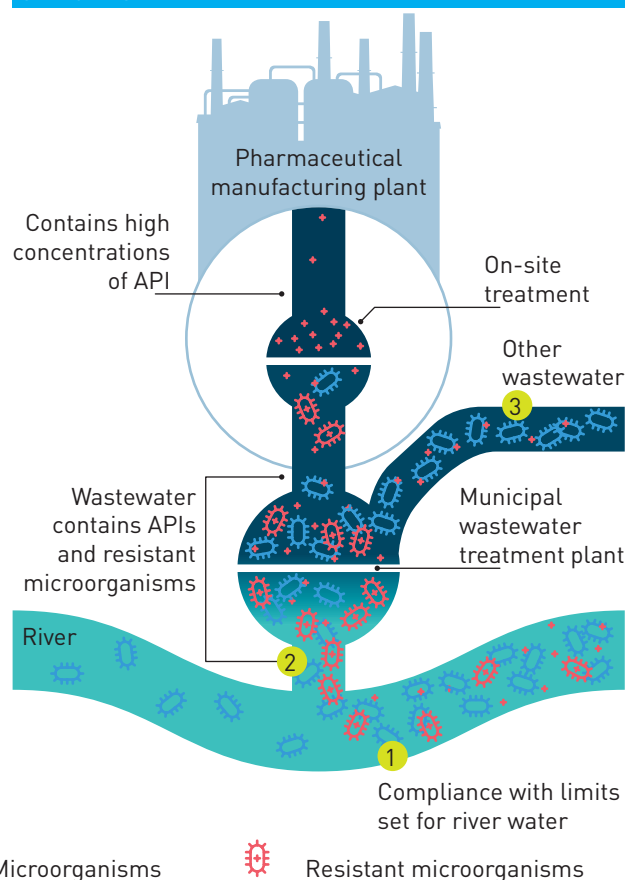


Figure 15

Wastewater discharges from pharmaceutical manufacturing

Another solution that has been proposed to deal with APIs production waste is to use advanced catalysts to generate oxidants, which then neutralizes the APIs. This latter technology has the potential to be less energy-demanding than an AOP while performing at similar removal levels, but current options are expensive. Therefore, green engineering of in-factory production processes to reduce waste releases should also be part of the solution.

There are limited proven treatment options for pharmaceutical wastewater before release to the environment. For example, activated sludge biological treatment has been used, such as in China (Li *et al.* 2009; Li *et al.* 2010) and India (Kristiansson *et al.* 2011; Marathe *et al.* 2016), but high levels of antibiotics in such waste provide a strong selection pressure towards AMR strains (Johnning *et al.* 2013). This results in 'treatment' that produces AMR rather than a system that reduces APIs and the exposure and possible risks associated with them (Larsson 2014).

In general, emissions of APIs are also not regulated globally (Larsson 2010; AMR Industry Alliance 2022; Tracking AMR Country Self-assessment Survey 2022, Question 6.2.8), and the global regulatory landscape for the control of pharmaceutical releases varies widely. A critical knowledge gap that needs to be addressed to effectively inform regulations is identifying reasonable and effective discharge limits (Bengtsson-Palme, Gunnarsson and Larsson 2018; Topp *et al.* 2018; Nijsingh *et al.* 2019; Årdal *et al.* 2021). Voluntary industry initiatives are establishing a common framework for managing discharge of antimicrobial compounds and applying it across manufacturing and supply chains among their members (FAO, WOH and WHO 2020; AMR Industry Alliance 2022) and have developed an antibiotic manufacturing standard.

Concerns about the supply chain resilience and drug prices have so far prevented the demand for specific discharge limits as part of their procurements of medicines, although this has been discussed in several fora (Sustainable Procurement in the Health Sector Secretariat and UNDP 2015; Access to Medicine Foundation 2018). Contributing to this problem is the price pressure for inexpensive drugs, particularly antibiotics, which have made environmental concerns and AMR development and spread a lower priority to cost cuts (Laxminarayan *et al.* 2016; Bengtsson-Palme, Gunnarsson and Larsson 2018; Nijsingh *et al.* 2019).

More action is still needed, and environmental regulators should strengthen the framework to protect the environment from AMR and antimicrobial pollutants. It is important to effectively control API emissions from manufacturing both in production of the API itself and its formulation into drug products for patient use (AMR Industry Alliance 2022). Environmental regulators should also be empowered and funded to enforce regulations and legislation related to pharmaceutical releases distinguishing products that are manufactured under good emission control and prioritize them in for example procurement decisions. These activities should be implemented in ways that do not add additional cost to the consumers, as antimicrobials need to be kept affordable.

The Group of Seven (G7) countries requested WHO to include pharmaceutical waste streams as part of quality controls in standard operating procedures (G7 2021a). The current lack of consistent regulatory oversight and coordinated global action makes it challenging to resolve this source of AMR risk.

Management options to address effluent and waste from pharmaceutical manufacturing



Develop and enforce standards to reduce antimicrobial discharges/emissions that prevent AMR emergence in the environment, including strengthening of regulatory frameworks and inspection systems, incentives and subsidies for implementing upgrades in the manufacturing process, and ensuring stability of fragile generic supply chains critical to maintaining affordable, low-cost antimicrobials for healthcare.



Introduce environmental and social risk management strategies, gender impact assessments, and implement cost and energy-efficient Best Available Technologies (BAT) for the management of effluent and waste and social safeguards.



Set discharge targets for antimicrobial manufacturing waste and wastewater such that more appropriate waste management technologies are employed, which balance PNEC aspirations and the need for local sustainability.



Monitor antimicrobial residues, resistant microorganisms, ARGs and MGEs in the environment in the vicinity of pharmaceutical production plants.



Incorporate waste management into standard operating procedures used in the production of antimicrobials with a lifecycle approach.



Improve supply chain transparency (e.g. sharing data regarding emission levels, site of APIs production and formulation).



Put in place and promote sustainable procurement and reimbursement systems for manufacturers adhering to environmental standards and good emission control.



Develop incentives to utilize and design degradable antibiotics. Consider research and development of new antimicrobials, as replacements and substitutes are needed as resistance develops. Resistance mechanisms exist in all approved antimicrobial classes, whether derived from natural, semi-synthetic, or synthetic compounds. Therefore, approaching how antimicrobials are designed needs to be thought about differently.



Ensure appropriate labelling (including information about the correct use, dosage, pharmaceutical expiration dates, environmental impact of antimicrobials and special instruction on proper disposal of unused antimicrobials) and packaging suitable for intended use, such as in single capsules for oral administration in humans or other sized units for use in different species of animals.



Increase understanding and improve prescription patterns (e.g. stewardship programmes in healthcare and veterinary medicine).



Enhance controls for marketing and sale of antimicrobials (e.g. advertising, internet sales, over-the-counter sales without a prescription and the black market).

4.2.2 Agricultural and food value chains

Agriculture production entails raising food animals, engaging in aquaculture, producing food crops or providing inputs such as feed, textiles, ornamental plants, biofuels and other agricultural commodities. The pathways along the agri-food value chains vary, but all begin with the production of plants or animals including the procurement and provision of nutrients (such as feed or fertilizer rich in antimicrobials or essential minerals), source water, growing crops/ animals, administering medicine (e.g. antimicrobials) and waste management. Storage, processing, packaging and distribution for sale and consumption are also important aspects of value chains, along with the storage, disposal and management of inputs (e.g. pesticides, fertilizers and medicines) and waste. Several points in the agriculture value chain serve as entry points for antimicrobials and antimicrobial resistant organisms into the environment such as the use of antimicrobials to treat infection and promote growth, use of reclaimed wastewater for irrigating crops, use of manure as fertilizer and inadequate waste management.

Population growth and increased demand for food has resulted in an increase in demand and consumption

of animal protein (Tiseo *et al.* 2020). Aquatic animals currently provide 20 per cent of animal protein to the human diet for over 40 per cent of the world (FAO 2020; FAO, UNDP and UNEP 2021). This has led to the intensification of agriculture, and land and water use in livestock production systems, as well as small-scale, backyard and aquaculture farms in some low- and middle-income countries that are subject to minimal regulatory oversight (Smil 2011; Coyne *et al.* 2019; FAO, UNDP and UNEP 2021; Schar *et al.* 2021). In general women face inequalities in terms of accessing resources, services, employment opportunities, taking part in decision-making and other aspects related to food loss and food waste from aquatic food production systems (Grever 2021). Unless broader steps are taken towards making food systems more sustainable and curbing the use of antimicrobials in animal husbandry practices, the use of antimicrobials in food production will continue to grow (Tilman *et al.* 2011). Examples of countries that have meaningfully reduced antimicrobial use in food animal husbandry include Belgium, China, Denmark, the Netherlands and Thailand (Baudoin, Hogeveen and Wauters 2021; Hog *et al.* 2021; Global High-level Ministerial Conference on Antimicrobial Resistance 2022; WOA 2022).



Vegetables for sale at market, an end point in Agriculture and Food Value chains. © Davide Provolo

Use of antimicrobials and manure in crop production

Fungicides, antibiotics and other chemicals applied in crops may affect AMR development

Unlike antimicrobials used in humans and animals, pesticides are applied directly into the environment and could result in higher local concentrations of these pollutants with subsequent effects on AMR. Pesticides with antimicrobial properties such as antibiotics, fungicides (including metal-based plant protection products such as those containing copper) are used to maintain plant health. These agents should be used, stored and disposed of in ways that limit environmental contamination.

Country self-reported estimates of fungicides and bactericides used in agriculture were 605,986 tons in 2020 (FAO 2022a). This global use in agriculture shows an overall increasing trend over the past thirty years (Figure 16), and of particular concern is the use of fungicides in crop production. Increasing resistance to fungicides used on crops has wide implications, including for human and veterinary medicine, as triazole fungicides are widely used in crop production but are also used to treat fungal infections

in humans (Fisher *et al.* 2018; Schoustra *et al.* 2019; Jørgensen *et al.* 2021).

Widespread use of fungicides in agriculture is linked to a growing number of azole-resistant lung infections in humans, acquired from inhalation of *Aspergillus fumigatus* fungal spores (Meis *et al.* 2016). Increased azole-resistant aspergillosis (Brauer *et al.* 2019) has been partially fuelled by triazole fungicide use in crop production (Snelders *et al.* 2012). Moreover, disruption of soil and changing weather and climate may affect valley fever (coccidioidomycosis), caused by *Coccidioides*, and these infections, as well as those from *Candida auris*, have been documented as severe and multi-drug resistant (Toda *et al.* 2019; US CDC 2019). Underlining the importance of airborne exposures, aspergillosis and coccidiomycosis are typically acquired via inhalation.

The volume of antibiotics used in horticulture in countries where legislation governing their use is strong represents only a small fraction of total antimicrobial use in agriculture. However, in LICs and LMICs, the amounts of antimicrobials used on crops is unknown, but likely widespread (Taylor and Reeder 2020). Unlike antimicrobials used in

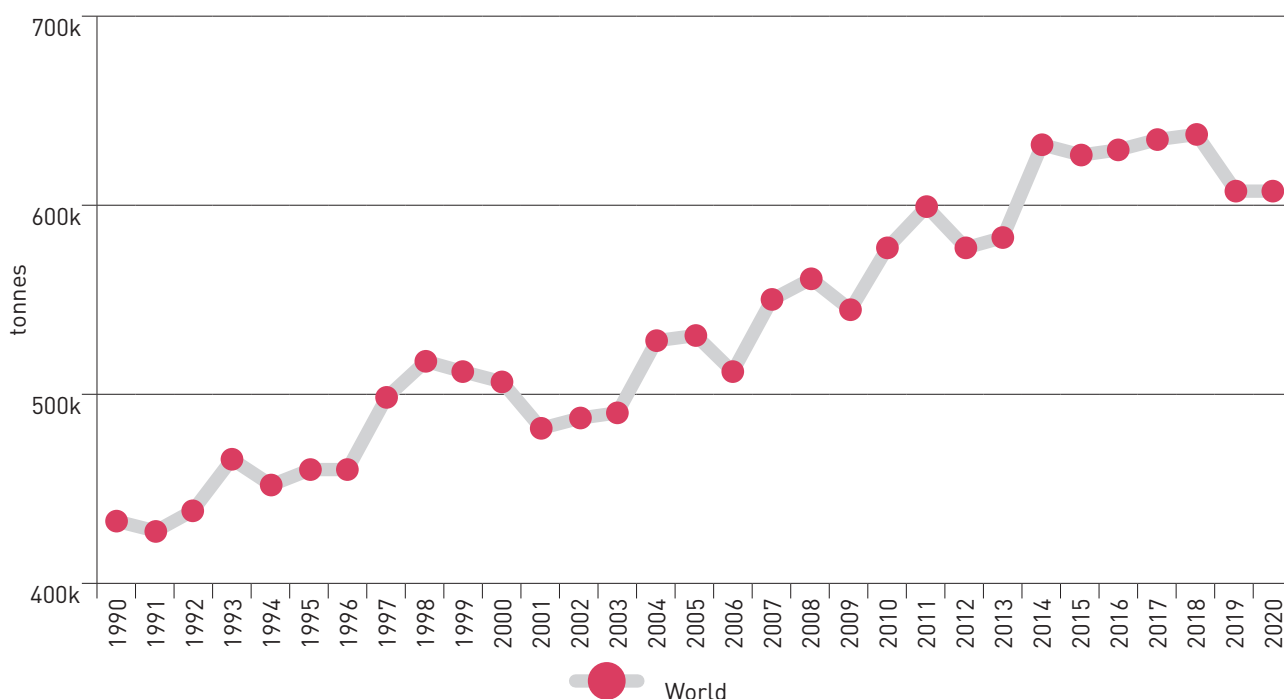


Figure 16

Trend in fungicide and bactericide use in agriculture (FAO 2022a)

humans and animals, pesticides are applied directly into the environment and could result in higher local concentrations of these pollutants with subsequent effects on AMR. Soil amendments with fertilizer of a biological or chemical nature can contribute directly to AMR or antimicrobial residues in water. Eutrophication, as measured by total nitrogen, total phosphorus and chemical oxygen demand, may select for or enrich AMR in aquatic systems (Li, X.D. *et al.* 2020).

Use of wastewater, sewage and manure in crop production can develop and spread AMR

When manure or wastewater biosolids (sewage sludge) are used to fertilize or condition soil, or when untreated wastewater is used for irrigation, antimicrobial residues, ARGs and resistant microorganisms are released into the environment (Marti *et al.* 2013; Li *et al.* 2015). Irrigation water is a known source of produce contamination with antimicrobial resistant microorganisms and associated risks to human health (Gekenidis *et al.* 2018; Rahman

et al. 2021). An estimated 11 per cent of irrigated croplands receive inadequately treated wastewater (Kookana *et al.* 2020), which almost certainly means AMR releases occur. This source may be particularly significant because waste management in animal systems tends to be much less sophisticated than with human wastes (Graham *et al.* 2019). Furthermore, there is an overlap between antimicrobials used in human and veterinary medicine, which result in mutually relevant AMR development (Scott *et al.* 2019).

However, nutrients excreted by farm animals and poultry are an extremely important fertilizer for crop production and volumes of manure generated by animal production systems are enormous. For example, in Europe it is estimated to be 1.4 billion tons per year (Foged *et al.* 2011; Zhang and Schroder 2014). Therefore, utilizing these valuable nutritional sources for crop production must be balanced with the potential consequences of AMR transmission and spread.



Integrated pest management programmes reduce the need for antimicrobial pesticides in plant production
© Tim Mossholder

AMR in crop production spreads via food chains

Contamination of food crops with antimicrobial residues and antimicrobial resistant microorganisms from environmental sources during primary production has implications for public health. Use of antimicrobials in crop production, often as pesticides can also cause direct pollution to the environment (e.g. soils) impacting microbial biodiversity and ecosystem services (Jørgensen *et al.* 2018). Selection pressure from antibiotic use in a crop production environment is a concern, and therefore it has been recommended that the use of antibiotics in integrated pest management should not be registered as pesticides when the antimicrobials are also used in human and animal medicine (FAO and WHO 2019).

Residues of antimicrobial agents exceeding safety limits may be present in foods that have been inappropriately treated and/or harvested without respecting recommended instructions and pre-harvest intervals. Perhaps more importantly, fruits and vegetables may be a source of ingestion of antimicrobial resistant pathogens when consumed raw. Furthermore, farm workers may be exposed to hazardous amounts of antimicrobials if they are not applied appropriately or without the use of proper personal protective equipment.

Employment in the agricultural sector may inform gender-based risks and exposure hazards. As certain antimicrobials are used as pesticides in agriculture, women are more exposed and vulnerable. Although women account for 37 per cent of the rural agricultural workforce worldwide, and up to 48 per cent for LICs, women are usually the workers who apply pesticides (FAO 2022b). While the division of labour among genders in pesticide handling and spraying varies globally, in some countries, 85 per cent or more of all pesticide applications on commercial farms and plantations are made by women – often working while pregnant or breastfeeding. Women also reportedly make less use of personal protective equipment and have more frequent injuries from pesticides than men (Caterbow and Hausmann 2016). Moreover, social and economic factors contribute to women being more exposed to pesticides than men. These factors can include unequal gender roles and responsibilities; women working more in informal agricultural sectors; and personal protective equipment not being adequately designed for women (International Labour Organization 2021).

Using faecal material as a source of crop fertilizer comes with human and animal health risks, notably through exposure to pathogenic or resistant enteric

Farm workers without adequate personal protective equipment may be exposed to antimicrobial residues © Quang Nguyen Vinh



microorganisms via consumption of contaminated plant-based foods or water. Antimicrobial residues may be hazardous if consumed even at low concentrations (e.g. anaphylaxis), and there is growing concern that even low levels of consumed residues may negatively impact the gut microbiome (Zhou and Zhao 2021). Fresh fruits and vegetables, contaminated from irrigation water, soil and fertilizers, unsanitary equipment and workers, may all contaminate food with antimicrobial resistant bacteria (Hölzel, Tetens and Schwaiger 2018; Koutsoumanis *et al.* 2021). Although this is more problematic in LIC and LMIC food systems due to the frequent use of inadequately treated wastewater for irrigation and limited barriers between the waste and food product (Samtiya *et al.* 2022).

In times and locations of water scarcity, wastewater use for irrigation purposes can be viable, providing that the wastewater is treated to achieve a quality that is fit-for-purpose and does not compromise the safety of the food (FAO and WHO 2021). However, there is evidence that resistant microorganisms and ARGs can be selectively enriched in soils irrigated with reused wastewater (Wang *et al.* 2014; Marano *et al.* 2021), although this depends on the nature of the local soil, climatic factors and the crop types (Marano *et al.* 2019). Considerations of AMR would ideally be used to determine a fit-for-purpose use, such as whether a food product is likely to be eaten raw.

Management options to govern the use of antimicrobials and manure in crop production



Implement the International Code of Conduct on Pesticide Management to optimize the regulatory and technical measures required in the lifecycle of pesticides. Utilise a gender-responsive approach to ensure that women are included as key stakeholders in the discussions and implementation.



Optimize the monitoring and evaluation system for antimicrobials used in plant protection at regional and country level.



Reduce discharges and improve run-off management to protect water sources from pollutants and resistant microorganisms and antimicrobial residue contamination.



Apply nature-based solutions as part of Integrated Pest Management to minimize the use of antimicrobials.



Improve the management of fertilizers of faecal origin (e.g. use fertilizers of faecal origin according to codes of hygienic practice for the protection of food safety).



Raise awareness and strengthen capacity of smallholder farmers with respect to ecological pest management and growing healthy crops, including through farmer education programmes and other extension and capacity building activities that target both female and male farmers.



Increase barriers between the waste source (where reused or other wastewater is used for irrigation) and the final product that might be consumed.

Effluent and waste in terrestrial animal production

Many antibiotics used in animal production are either identical or share similar chemical structure as those used in human medicine. Use of these drugs not only has implications for management of waste with resistant microorganisms and antimicrobial residues, but also because of their potential selective and co-selective properties for resistance against antibiotics used in human medicine.

In intensive animal production systems, antimicrobials are frequently relied upon to maintain livestock health, welfare and productivity, including for control of diseases. In some jurisdictions, antimicrobials are still used as growth promoters. A sustainable global food system would phase out antibiotic use in livestock for growth promotion and routine use of antimicrobials in food animal production, and instead focus on best practices in the production of healthy animals. Confined animal feeding operations have been examined for abundance of resistance markers, including ARGs, in downstream surface waters emanating from faecal waste lagoons. Such studies show that use of antimicrobials for any purpose impacts abundance and distributions of ARGs (Peak *et al.* 2007) highlighting AMR as a water quality issue.

Use of antibiotics in agriculture that correspond to those used as a last resort in human medicine is of special concern and should be discouraged. This was apparent in the emergence of plasmid-mediated resistance against colistin, a last-resort drug for managing multi-drug resistant, Gram-negative bacterial sepsis in humans (Liu *et al.* 2016). In Europe and North America, the use of critically important antibiotics for human medicine are not permitted for use in agriculture except as a last resort.

In addition, zinc and copper are often added to animal feeds as micronutrients and have antimicrobial properties (Højberg 2005; Jensen 2006). These elements can act as co-selective agents for resistance (Yazdankhah, Rudi and Bernhoft 2014). Co-selection can take place in animal digestive tracts, and since unabsorbed metals are excreted in the faeces can also select for resistance in the environment (Berg, Tom-Petersen and Nybroe 2005; Medardus *et al.* 2014). Although co-selection effects are often transient and disappear if exposures are removed, and the use and dosage of zinc in food

animal production is being reconsidered (Shurson, Urriola and Hung 2022).

Risks from food products of animal origin include multi-drug resistant *Salmonella* spp., which are known to be associated with poultry and pork products (Zhang *et al.* 2018; Kipper *et al.* 2022) and can cause foodborne illness outbreaks (Xiong *et al.* 2020). Foodborne infection pathways of globally dispersed AMR clones, including bacteria acquired from consuming chicken, have been identified as the agent of urinary tract infections (Singer 2015; Liu *et al.* 2018), which is the third most common infectious condition and is predominantly suffered by women (ReAct 2020). Collectively, antimicrobials and other co-selective agents (e.g. zinc and copper) used in animal agriculture, along with resistant microorganisms and ARGs, are released together to the environment from various agricultural sources. The mixture of these chemical and biological contaminants (such as in manure) impact AMR selection, transmission and spread in affected environments (Topp *et al.* 2018).

Environmental application of antimicrobials in aquaculture

Aquaculture is predicted to supply more than 50 per cent of aquatic protein globally by 2050, equating to more than 8 per cent of global animal food proteins (Jennings *et al.* 2016; FAO 2020). More than 500 different species are cultured in a range of associated production systems, ranging from small backyard freshwater ponds to the highly-mechanized and capital-intensive salmon seawater net pen operations in Northern European countries (Stentiford *et al.* 2020). Antimicrobials are used worldwide in aquaculture, particularly in intensive-rearing systems, to control disease (Smith 2008; Brunton *et al.* 2019). Due to genetic exchange in aquaculture farms from the persistent use of antimicrobials, these have been designated as possible 'genetic hotspots' (Watts *et al.* 2017). Dissemination of AMR to surrounding environments occurs because of spatiotemporal variables with fish feed usage and varying regulations (Han *et al.* 2017; Raza *et al.* 2022).

Use of antimicrobials in aquaculture can result in environmental contamination. Antimicrobials may be added directly to a pond or tank where fish, crustaceans and molluscs are held for treatment purposes, which can contaminate the sediments

and surrounding water. If treated with a dip or bath procedure, antimicrobial-contaminated water used for the treatment is often released into the environment after use. When antimicrobials are added to feed, unconsumed feed may drop to the bottom of the pen or pond. However, estimating the amounts and types of antimicrobials used in aquaculture is challenging because sales and use records are often not publicly available, particularly in many of the Asian countries where most of the production takes place (Henriksson *et al.* 2018; Lulijwa, Rupia and Alfaro 2020; Schar *et al.* 2021). Despite uncertainty about the exact amounts of chemicals used in aquaculture, they represent a significant component of all use in animals farmed for food (Rico *et al.* 2013; Henriksson *et al.* 2018; Thornber *et al.* 2020).

Antimicrobials excreted by aquatic animals also contaminate the surrounding environment. This imposes a selection pressure on off-target bacteria within the aquatic microbiome. Studies have demonstrated altered biodiversity resulting from antimicrobial use in aquaculture (Fang *et al.* 2021). The rate of absorption and the percentage of unchanged antimicrobials excreted by fish was found to be temperature dependent (Rigos, Alexis and Nengas 1999).

When inappropriate antimicrobial treatments are employed and/or post-antimicrobial withdrawal periods are not observed, hazardous residues of antimicrobials may occur in harvested commercially produced fish and shellfish for human consumption

Antimicrobials may be used in open and closed aquaculture systems © Alexey Komissarov



(Watts *et al.* 2017). Residue standards are set by Codex Alimentarius to limit dietary exposures and informed by microbiological and toxicological risk assessment of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (FAO 2022c).

Aquaculture rearing facilities may also act as sinks or reservoirs for resistant microorganisms and genetic elements, discharged into the aquatic environment (Taylor, Verner-Jeffreys and Baker-Austin 2011). These factors pose risks of transmission of resistant

Management options to address releases, effluent and waste from animal production



Reduce antimicrobial use in food animals by improving animal health through implementing biosafety, biosecurity, vaccination and good animal husbandry programmes.



Avoid antimicrobial usage in open systems where the drugs can be rapidly transported away from treated fish or crustacea.



Consider targeted pre-treatment of waste across the farm to slaughterhouse continuum to remove AMR microorganisms and to reduce antimicrobials before discharge into the environment or general sewerage systems.



Promote disease prevention in aquaculture, including vaccination, nutritional interventions, immune stimulation with feed additives and UV application for water systems, to reduce the need for antimicrobials and parasiticides in aquaculture and animal husbandry.



Improve efficient disease identification and management, including rapid diagnostics, such as antimicrobial sensitivity testing, and biosecurity measures.



Recirculate water in aquaculture that could facilitate the management of waste and decrease the risk of antimicrobials present in influent and effluent from these closed systems.



Nutritional interventions to maintain and improve stock health and for prevention of disease and need for antimicrobial use.



Develop market incentives that would help motivate aquaculture producers to invest and adopt alternative management practices that curb the use of antimicrobials.



Provide barriers or treatment of water entering aquaculture facilities where local water quality is poor due to faecal and other pollution, to reduce transmission into the food system.



Undertake multidisciplinary research to better understand the gender-differentiated risks and diseases associated with consumption and production of food products of animal origin, which will better inform public health responses.

bacteria and elements to consumers. Other chemicals, such as disinfectants or chemicals used to prevent, reduce or eliminate fouling (antifoulants), are also widely used in aquaculture (Boyd and McNevin 2015), further contributing to risks of co-selection in the aquatic environment. However, in some scenarios, AMR can spread from the surrounding environment into aquaculture facilities, due to water pollution outside of the operations as seen in certain shrimp farms (Thongsamer *et al.* 2021).

As the food sourcing from aquaculture increases, identifying the sources and sinks of AMR is essential. Monitoring and analysing AMR transfer between microbial communities, the environment and farmed aquaculture products can help better understand the implications to human and environmental health (Watts *et al.* 2017).

4.2.3 Healthcare value chains

Healthcare delivery occurs in many locations including hospitals, medical and community healthcare facilities, aged care homes and prisons, research and teaching facilities and in pharmacies where a

broad range of chemicals and disinfectants may be used directly, influencing the microenvironment of a particular setting (Lasek *et al.* 2018). At the system level, this value chain is focused on providing health care to people, procuring, stocking and storing quality antimicrobials and ensuring their proper distribution, control and use. At the patient level, healthcare providers diagnose, prescribe, dispense, counsel and monitor the effectiveness of and response to treatment with antimicrobials.

In healthcare delivery, pharmaceuticals enter a given setting or facility as part of patient treatment and any antimicrobials that are administered will largely be excreted and end up in a facility's associated wastewater. The amount of antimicrobials excreted in faeces and urine is highly variable, for many of the commonly used antimicrobials in human medicine, 60 to 90 per cent of the administered dose may appear in excreta as an active metabolite (Kümmerer and Henninger 2003, Table 3, p. 1208-1209).

In addition to antimicrobials administered to patients, disinfectants, sterilants and biocides are used in clinical and community settings (e.g. due to hygiene



Antimicrobials are used in healthcare delivery © Pixabay

and sanitation protocols in hospital settings) and are present in waste, in wash water and wastewater systems (Kumari, Maurya and Tiwari 2020). Adequate treatment of hospital discharges can minimize contaminating the local water and wastewater systems. An important strategy to reduce overuse of antimicrobials in healthcare settings is to employ stewardship programmes (Schuts *et al.* 2016; Davey *et al.* 2017; Organisation for Economic Co-operation and Development [OECD] 2018; Al-Omari *et al.* 2020), including guidelines on proper diagnostics, choice of antimicrobial and prudent use. These programmes are plausible options to reduce outputs to the environment.

Successful mass drug administration programmes, which are increasingly used as both prevention and treatment of neglected tropical diseases and severe childhood diseases at the population level in LICs and LMICs, could have serious environmental impact (Konopka *et al.* 2022).

As antimicrobials are frequently used in healthcare, effluent from healthcare facilities is an important source of discharges of antimicrobial resistant microorganisms, ARGs and antimicrobials into the environment, particularly from hospitals. Although the total amount of antimicrobials used in primary care exceeds the amount used in hospitals, a higher proportion of antimicrobials used in hospitals are more often critically important based on WHO classifications (WHO 2019). Moreover, untreated wastewater discharges from hospitals contain significantly more resistant microbes, ARGs and antimicrobial compounds and their metabolites, particularly related to 'last resort' antimicrobials (Quintela-Baluja *et al.* 2019; Buelow *et al.* 2020). Effluent from hospital wastewater systems can be considerably higher in antimicrobial concentration than from community settings (Kraupner *et al.* 2021). Hospital sources also contain more diverse and abundant resistant microorganisms and genes than typical domestic wastewater, especially multidrug-resistant strains

Management options to address effluent and waste from healthcare facilities



Educate and train hospital personnel on hygiene, sanitation and safe medicine disposal practices.



Implement high-quality hygiene and infection prevention in healthcare operations.



Ensure the safe and sustainable disposal and treatment of antimicrobial medicines and hazardous waste from healthcare facilities by, for example, creating, strengthening and promoting take-back programmes.



Consider AMR-targeted, on-site treatment of hospital wastewater with vigorous treatment to prevent spread into the environment.



Leverage hospital stewardship and infection prevention control programmes to limit environmental contamination by AMR pollutants.



Encourage sustainable procurement and sound management and disposal of antimicrobials by healthcare systems.

and pathogens (Hassoun-Kheir *et al.* 2020). Overall antibiotic concentrations are also higher in hospital wastewater than domestic wastewater.

Hospital environments may also create conditions conducive to the survival of resistant microorganisms (Lamba, Graham and Ahammad 2017; Proia *et al.* 2018). Genomic studies of hospital plumbing surfaces have revealed their potential to provide a favourable environment for the formation of biofilms in which resistant microorganisms may thrive (Weingarten *et al.* 2018). Given hospitals typically have higher levels of AMR, direct releases to the environment increase AMR exposures to surrounding human and animal populations, resulting in consequential AMR spread beyond the walls of the hospital (Islam *et al.* 2017). When comparing AMR sources in an Ethiopian city, untreated hospital wastewater releases had the highest levels of antimicrobial resistant bacteria, relative to animal rearing, community wastewater and other local sources (Geta and Kibret 2022).

Installing hospital-specific wastewater treatment systems may be beneficial (e.g. advanced oxidation process with ozonation, nanofiltration and reverse osmosis), and because AMR in hospital waste is more concentrated and volumes much smaller than community settings, such technologies can be used (Carraro *et al.* 2016).

Hospital wastewater treatment is especially important in locations without modern community WWTPs because wastewaters are often released directly into the environment. In some countries, there are laws pertaining to healthcare/biomedical waste management (WHO 2015; Datta, Mohi and Chander 2018). For example, there is a requirement for wastewater treatment for hospitals and medical centres with no access to a community WWTPs. The treatment process may include a multi-chamber septic tank with primary sedimentation tank and digestive chamber followed by aeration and sedimentation then a final treatment consisting of passing through a micro filter and chlorine disinfection.

4.3 Prevent and manage wastewater and solid waste as AMR sources

In addition to the key sectors outlined above that comprise the main sources of AMR in the environment, other important sources are human faeces and wastewater effluent, especially if untreated, and municipal and solid waste.

The level of pollution or exposure from these sources and different types of environments is varied, and hence the risks for selection differ with many orders of magnitude depending on the source and environment (Hanna, Tamhankar and Lundborg 2023).

4.3.1 Poor sanitation, wastewater and related waste effluent

Improved water, sanitation and hygiene (WASH) can prevent AMR spread

Among the most important sources of resistant microorganisms and antimicrobial resistance genes to the environment is human waste, including faecal, skin and urogenital tract microorganisms (e.g. bacteria) that end up in sewage and wastewater.

Over 56 per cent of wastewater globally is released into the environment with little or no treatment (United Nations Human Settlements Programme and WHO 2021). About 616 million people use poor or basic facilities (e.g. pit latrines without a slab or platform, hanging latrines or a bucket latrine) and at least 494 million people practice open defecation, including into street gutters, behind bushes or near open bodies of water (WHO and United Nations Children's Fund [UNICEF] 2021). Even with the traditional wastewater treatment used in high-income countries (HICs), ESBL-producing microorganisms can be found in treated effluent; although levels are much lower compared with untreated sewage discharges (Marano *et al.* 2020).

Inadequate WASH implementation is of primary concern in many LICs and LMICs, particularly in rural environments and urban informal settlements, where lack of sanitation can lead to water contamination, waterborne illnesses and AMR transmission and spread (Graham, Giesen and Bunce 2019; Nadimpalli



Figure 17

Environmental AMR pollution sources and areas for prevention and management

et al. 2020). Maintaining a stable supply of clean water and optimizing the use of chemical disinfectants, or applying effective alternatives, is essential to ensure improved water quality at the point of use while minimizing the potential for AMR transmission through water supplies (Bürgmann *et al.* 2018).

The specific type and amount of antimicrobial used, and the effectiveness of local waste infrastructure in reducing pollutants governs antimicrobial and AMR releases into the environment via human waste. There is a range of infrastructure including no containment of faeces (e.g. open defecation); no faecal waste collection; fragmented sewerage collection systems; combined (stormwater and wastewater) or sanitary (only wastewater) sewers; and centralized or decentralised networks. The extent of wastewater treatment varies widely, ranging from primary (solids settling), secondary (carbon biodegradation, physical settling and removal) to highly advanced treatment technologies. As technological sophistication increases, antimicrobials and relative improvements in resistant microorganism reductions progressively improve, with the ‘best buy’ treatment option in any scenario dependent on existing local context, infrastructure and resources (Graham, Giesen and Bunce 2019). As we learn more about the selective effects of complex mixtures of antimicrobials and other chemicals, PNECs for individual compounds in mixtures may change and with it our understanding of the probability of selection for AMR occurring in wastewater polluted environments (Hayes *et al.* 2022).

Occurrence and transmission of AMR has been exacerbated by rapid urbanization and increasing population density (Zhu *et al.* 2022). This is particularly evident in emerging and developing economies and urban transition zones that do not have adequate WASH infrastructure such as sewerage systems, wastewater treatment, solid waste management and drinking water treatment. Fast-growing cities require adequate infrastructure to provide potable water, green spaces and waste management. However, the development of critical civil infrastructure is not keeping pace with urban growth (Nadimpalli *et al.* 2020). Even in high-income countries, wastewater treatment does not fully remove AMR and antimicrobials from effluent, stimulating interest in retrofitting existing systems and examining new technologies to further reduce discharges

to the environment. The amount of cropland in peri-urban areas irrigated by mostly untreated urban wastewater has reached about 36 million hectares globally, equivalent to the size of Germany, and is likely to increase (Thebo *et al.* 2017; FAO, WOA and WHO 2020).

The resulting environmental pressures on water, soil and air compromise ecosystem services and create city/geographically specific hotspots fostering the development, transmission and spread of AMR (Danko *et al.* 2021). In addition, urbanization is linked to land use change, habitat destruction and biodiversity loss.

Municipal solid waste landfills and open dumps can become hotspots

Municipal solid waste (MSW) landfills and open dumps provide environments for the development and transmission of AMR (Wang *et al.* 2015; Wang *et al.* 2020). This is particularly true where there are high human population densities, limited solid waste management and where leachates are not contained, such as near informal communities (Nadimpalli *et al.* 2020). Open waste dumps are also more prone to wildlife and feral animal interaction and can contribute to the spread of AMR by migratory wildlife (Ahlstrom *et al.* 2018; Tarabai *et al.* 2019; Ahlstrom *et al.* 2021; Jarma *et al.* 2021).

In many LICs and LMICs, MSW handling can be ad hoc and disposal is usually not an engineered process. MSW ends up predominantly being disposed at open dump sites (66 per cent for LMICs and 93 per cent in LICs) with minimal waste and water containment (Ferronato and Torretta 2019). Dumps are often adjacent to population centres and can be above groundwater sources. In addition, such landfills frequently receive industrial, agricultural and medical wastes, and in many countries, are picked over by scavengers and subject to open defecation. Such conditions create a confluence of widely varying pollutants, microbes and human exposures, which has the potential to promote the evolution, transmission and spread of AMR.

Landfill leachate contains elevated resistant organisms and is rich in other contaminants that stress microorganisms, which may then select for resistance. This results in potential contamination of surface and groundwater (Anand *et al.* 2021). Even from

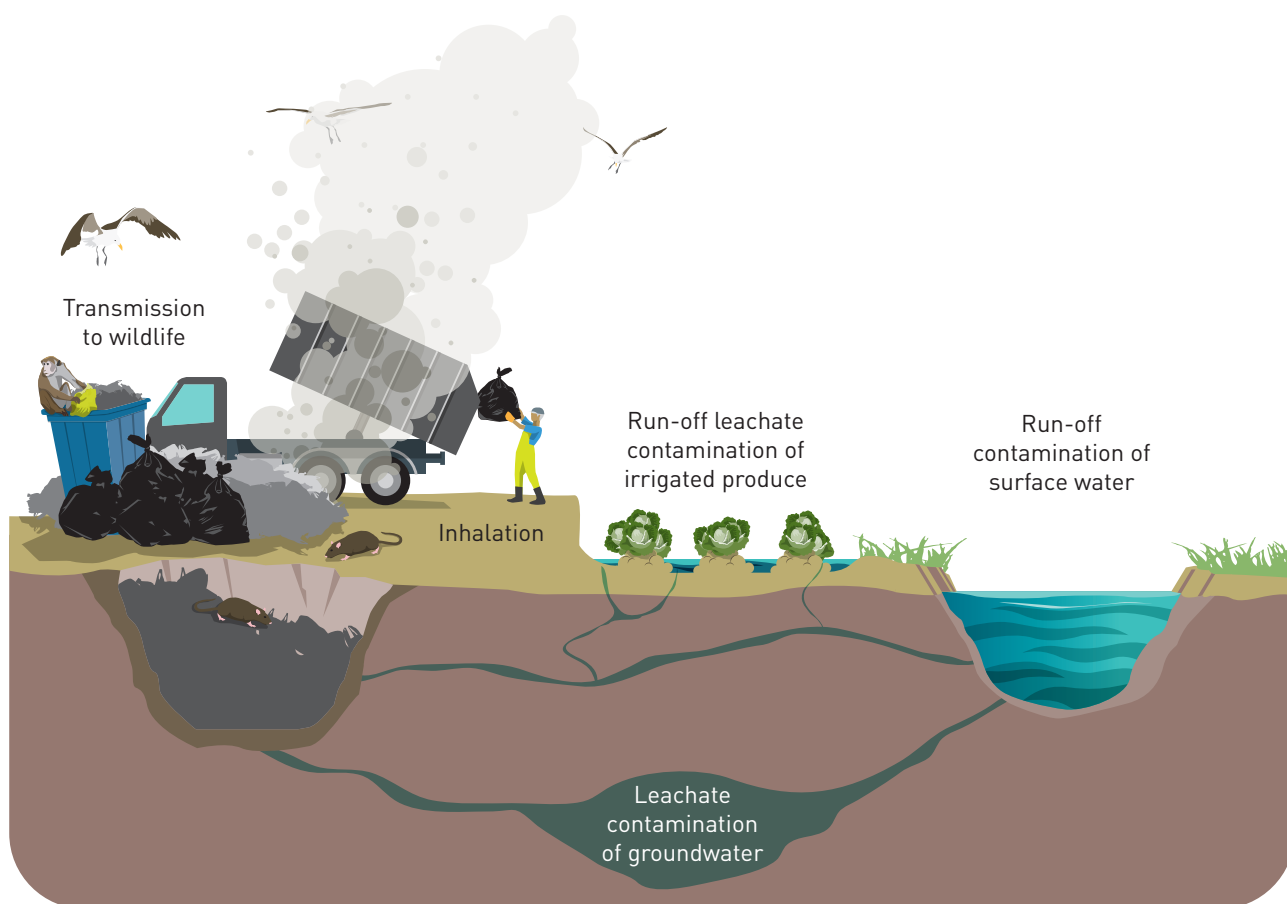


Figure 18

Potential AMR transmission pathways from landfills

well-managed landfills, leachate can carry abundant resistant microorganisms and contribute to the spread of AMR in ground and surface water. Soil and plant health also can be impaired when exposed to landfill leachates (Nwaogu *et al.* 2017; Vongdala *et al.* 2019).

Landfill leachate can also contain microplastics, which can selectively enrich certain ARGs (Shi *et al.* 2021). Some studies indicate that the accumulation of pollutants and dense bacterial communities on microplastics provide favourable conditions for higher transfer rate and evolution of ARGs (Pham, Clark and Li 2021).

Groundwater is of particular concern when used for domestic consumption or agriculture because it is typically consumed with little to no water treatment. Negative impacts on nearby ground and surface water are more severe near old or unmanaged landfills with no or inadequate liners, or limited leachate

containment and treatment (Barnes *et al.* 2004; Graham *et al.* 2011; Velpandian *et al.* 2018).

By 2050, the daily per capita MSW generation is projected to increase by 19 per cent in HICs and by over 40 per cent in LICs and LMICs (Kaza *et al.* 2018). Therefore, without greater waste minimization, improved management and better recovery strategies, the environmental and human health burden of AMR associated with MSW releases will increase substantially in the future (Anand *et al.* 2021). Improved infrastructure for solid waste handling needs to be prioritized globally. Important management measures for controlling AMR pollution can include modern sanitary landfills, as they are typically designed with a composite liner to prevent leachate leakage and often include leachate treatment. Sanitary landfills are also usually located away from dense human populations, aquifers and surface waters to reduce environmental and human health impacts.

An important dimension of reducing these risks is proper disposal and management of unused pharmaceuticals. This can be achieved through various measures such as take-back programmes that enable pharmacies, other medicinal dispensaries and veterinarian centres to properly dispose of antibiotics, anti-parasiticides, antifungal and antiviral medications, thus preventing them from entering municipal waste streams (Anwar, Iqbal and Saleem 2020). Other management options include collection of pharmaceuticals in mixed municipal solid waste that is either destined for high-temperature incineration (of at least 1000 °C) in facilities with proper ash treatment and air cleaning, or in sanitary landfills with capture and treatment of the leachate.

Effective wastewater and sludge treatment are critical to minimize AMR relevant pollution

Immediate handling, containment, processing and treatment of faecal waste defines the abundance,

type, genetic mobility and main pathway(s) by which resistant microorganisms enter the environment (Bürgmann *et al.* 2018). Well-maintained wastewater treatment plants are among the best defences against AMR spread, but retrofitting and affordable new technologies are needed to further reduce antimicrobial and AMR releases, especially low-energy technologies (Bürgmann *et al.* 2018). Of promise are technologies with improved biosolids removal. Sludge from wastewater treatment plants may be contaminated with antimicrobials, resistant microorganisms and ARGs, and the sludge needs to be adequately treated before being used, for example in agriculture.

Many primary treatment methods, such as allowing solids to settle out of liquid wastes, allow some non-flocculating microorganisms to pass untreated into the environment (Quintela-Baluja *et al.* 2019). Because of their prior exposure to antimicrobials,

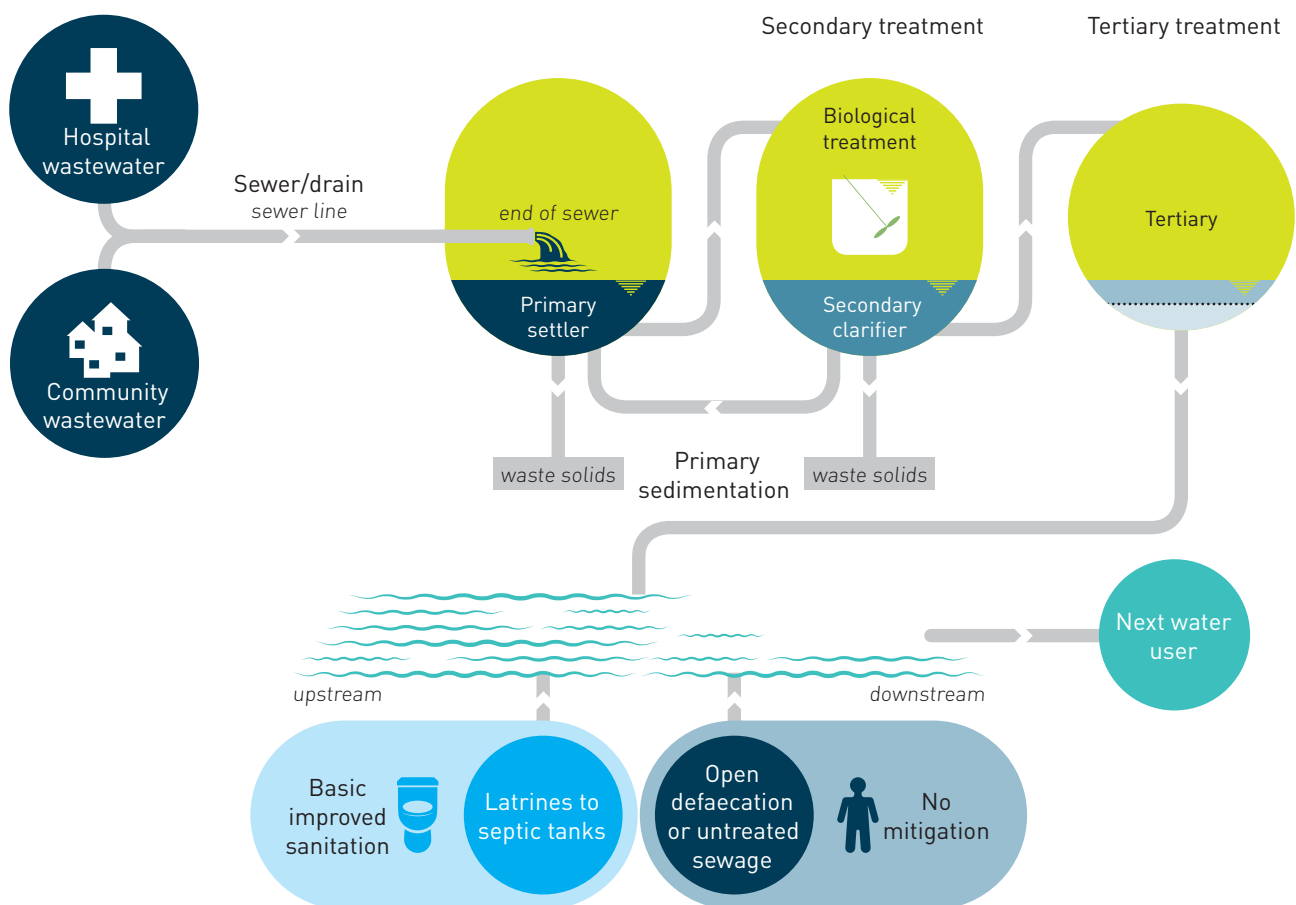


Figure 19

Wastewater and faecal sludge management solutions needed to address local contexts (adapted from Graham, Giesen and Bunce 2019, p. 3)

Box 4

Household animals, pets and companion animals

There is minimal data on the rate of antimicrobial use or overuse in household animals because few countries have included household animals and antimicrobial use in national surveillance data (Pomba *et al.* 2017). Worldwide, there are veterinary hospitals dedicated to companion animals. Especially in urban areas of lower income countries, use of antimicrobials for household animals has increased substantially (Bandyopadhyay and Samanta 2020).

In the European Union, reports of antibiotic use in household animals only covers sales of tableted veterinary antimicrobial agents for companion animals (European Medicines Agency 2020). A recent study found resistance to at least one antibiotic in 27 per cent of *E. coli* cultured from companion animals in the EU, with 13 per cent resistant to at least three antibiotic classes and with significant variation between countries and species (Joosten *et al.* 2020). Colistin resistance in *E. coli* among companion animals has been described in China, Germany, Finland, Ecuador and the Netherlands with possible transmission from companion animals to humans (Joosten *et al.* 2020).

Many antimicrobial drug classes designated by the WHO as medically important or critically important in treating humans are commonly used for household animals, including cephalosporins, fluoroquinolones, lincosamides, macrolides, penicillins and tetracyclines (WHO 2019), as well as parasiticides. In Denmark, all the fluoroquinolones and more than half of the cephalosporins used in treatment of animals are for dogs and cats (Hog *et al.* 2021). Other studies on household animals have shown elevated use of critically important antimicrobials for human medicine and prescription behaviour that is often not in line with current guidelines and that result in AMR (Hartantyo *et al.* 2018; Joosten *et al.* 2020).

Prudent use of antimicrobials in animals to prevent AMR is not only important from a public health perspective, but also for animal health and welfare. Household animals typically have close contact with humans, creating opportunities for interspecies transmission and spread of resistant bacteria (Hartantyo *et al.* 2018). It is known that humans and household animals readily exchange and share MRSA isolates from the same population and there is ample evidence that antibiotic usage in household animals is shaping the population of MRSA (Harrison *et al.* 2014). However, the risks of AMR from household animals have been considered low (van den Bunt 2020) and often deemed to be outweighed by the health benefits of animal ownership (Dall 2016).

bacterial populations present in this liquid phase of effluent may be rich in ARGs and serve as a source for seeding AMR and ARGs in sediments downstream from the sewage WWTPs effluent discharge. (Amos *et al.* 2014; Quintela-Baluja *et al.* 2021). Receiving environments, such as downstream river sediments, can accumulate resistant strains that may be capable of HGT in the environment (Quintela-Baluja *et al.* 2021). Wastewater treatment processes that effectively attenuate resistant microbes in liquid waste before release into the aquatic environment are needed.

When considering improvements in sanitation, wastewater treatment and sludge management (the storage, collection, transport, treatment and safe end use or disposal of sludge), the local context must be considered including available physical infrastructure, environment, social and economic circumstances (UNEP and International Water Management Institute [IWMI] 2020). Service needs to be appropriate both for sewer and non-sewer communities, with professionally managed and regulated service models (WHO 2018b; UNICEF and WHO 2020).

The level to which populations adopt sanitation interventions is dependent on their design, cost-effectiveness, ease of use and appropriateness for the local context. Sanitation technologies should be designed considering both the needs of men and women thus motivating use. Furthermore, accessibility, privacy and security are also key for female users who have reported suffering assault on their way

to access water points or toilet facilities (Travers, Khosla and Dhar 2011; House *et al.* 2014; UNEP and IUCN 2018, p. 25). Interventions for achieving sanitation goals involving behaviour modification and infrastructure development should consult and involve local communities, stakeholders, civil authorities and religious leaders to ensure adoption (UNEP and IWMI 2020).

Management options for addressing wastewater and solid waste



Implement safeguard measures to protect local women and men's human rights to a clean, healthy and sustainable environment, including improved access to high quality and sustainable water sources, such as in SDG 6, clean water and sanitation.



Improve gender-responsive sanitation systems to reduce environmental contamination.



Improve hygiene through behavioural interventions and increasing access to handwashing facilities.



Increase waste containment and optimize wastewater treatment and sludge management processes (function and types) to reduce antimicrobial resistant microorganisms, ARGs and pharmaceutical pollutants which may select for AMR.



Consider technologies for additional treatment of wastewaters, such as ozonation and bio-membrane technologies, or use of activated carbon to help remove selective and co-selective agents where they are above predicted no effect concentrations or minimum selective concentrations.



Implement cost-efficient and practical technologies (e.g. anaerobic digestion with thermal hydrolysis treatment) of human and animal waste sludge.



Implement measures for safe disposal of unused antimicrobials from households such as take-back programmes.



Promote locally appropriate and sustainable technologies in waste management, encouraging incremental improvement and available resources in technology decisions.



Treat companion animals with antimicrobials under the supervision of a veterinary professional.

Household animals, pets and companion animals contribute to AMR transmission to humans

Community and municipal settings also include household animals, which are not immune to the global challenge of AMR, and are potentially underrecognized carriers of it. The increase of pets in urban areas in the last decade has increased the use

of antimicrobials for these animals with consequences for the AMR carriage and environmental ecotoxicity (Domingo-Echaburu *et al.* 2021). More research about transmission of AMR from household animals is needed to quantify the scale and contextualise the impact of antimicrobial use and contamination of the environment.

4.4 Summary

- AMR requires a response based on a concerted systems approach, such as 'One Health', which recognises that the health of people, animals, plants and the environment are closely linked and interdependent.
- Three economic sectors and their value chains are key drivers of AMR development and spread in the environment: pharmaceuticals and other chemical manufacturing, agriculture and food production, and healthcare.
- Implementing policies or regulations, effective monitoring, disclosure and transparency are all needed in each supply chain to understand when and where antimicrobials are used and where AMR is likely to occur.
- Actions targeting the reduction of antimicrobial, and other co-selective chemical releases to the environment need to cover the entire chemical lifecycle - design, synthesis, production, transport, use and waste management.
- To reduce the release of antimicrobials and antimicrobial resistant microorganisms into the environment several points in the agriculture value chain need to be considered such as the use of antimicrobials, the use of reclaimed water for irrigating crops, the use of manure as a fertilizer and waste management. In healthcare delivery and community settings, antimicrobials enter the environment through disposal, as part of patient treatments and their excretion, and as disinfectants, sterilants and biocides used in clinical and community settings.
- There are five key pollution sources that impact the development, transmission and spread of AMR in the environment including: i) poor sanitation, sewage and waste effluent in municipalities; ii) effluent and waste from pharmaceutical manufacturing; iii) effluent and waste from healthcare facilities; iv) application of antimicrobials, animal manure and irrigation in crop production; v) and effluent and waste from terrestrial and aquatic animal production.
- The level of pollution or exposure from these sources are varied, and the risks for selection differ with many orders of magnitude depending on the pollution source and environment. Management approaches exist for many sources to prevent AMR spread, however additional work is required to develop incentives to utilize and design degradable antibiotics. It is important to consider research and development of new antimicrobials, as replacements and substitutes are needed as resistance develops.

Next steps to tackle AMR in the environment

There are numerous stakeholders at the national, regional and international levels to take forward actions to tackle AMR in the environment, these include, but are not limited to:

- Public authorities and organizations responsible for health, agriculture and the environment and industrial development, such as the Codex Alimentarius Commission, the Centre for Agricultural Bioscience International (CABI) and the European Commission
- Private sector entities and associations, and industry engaged in the production of antimicrobials, food crops and animals, healthcare delivery, pollution prevention and control and waste management
- Academic and research institutions and relevant networks conducting basic and applied research relevant to understanding the development, transmission and spread of AMR in the environment
- Collaboration between countries and among intergovernmental organizations such as UNEP, the Quadripartite Alliance and high-level initiatives like the AMR Global Leaders Group
- Civil society organizations involved in promoting a 'One Health' response to tackle AMR and minimizing the release of pollutants affecting AMR into the environment. They include community groups, youth, consumers' associations and professional organizations and schools for professionals including doctors, pharmacists, veterinarians and farmers
- Citizens, indigenous peoples and local women and men, the public at large and the media.

5.1 Strengthen national action

National implementation is at the heart of a successful response to AMR. While countries might have different processes for developing and managing an effective national governance mechanism for AMR, the need for a robust multisectoral coordination system has been highlighted across multiple fora as key for tackling AMR in a sustainable manner.

The Global Action Plan (GAP) on AMR, adopted in 2015, includes the goal that by 2017 all World Health Assembly Member States would have a National Action Plan on AMR (NAP) aligned with the GAP objectives (Interagency Coordinating Group [IACG]

2018a). Over 85 per cent of the world's population live in countries which have developed, or are in the process of developing, a NAP. However, very few NAPs in LICs and LMICs are based on a situational analysis and have resources to be properly implemented. Country progress, capacity and resources vary, and sometimes countries need focused support to advance the development, implementation and monitoring of NAPs on AMR and 'One Health' activities. Achieving this has been shown to be complex, especially as a 'one-size-fits-all approach' cannot be implemented.

Despite growing recognition of its role, the environmental sector and its considerations are often not well represented in national AMR-related planning and action. Although improvement is consistently seen over the past few years, more than a third of countries do not include the environment sector in developing and implementing their NAPs (WHO 2022b). A true 'One Health' approach requires inputs and governance equally from all sectors to tackle AMR in policies, legislation and practice. What is especially lacking in NAPs development is the critical role and contribution of environmental authorities, experts and practitioners. This may be due to lack of the awareness, understanding or evidence needed to inform environmental and other relevant-sector authorities.

5.1.1 Boost governance, planning and regulatory frameworks

Integrate AMR in national development planning and budgeting

This can ensure that national budgets provide funding for AMR surveillance, prevention and mitigation. As well as ensuring the approach considers gender and socio-economic dimensions, which is crucial for countries to ensure that no one is left behind. The return on investment of environment-related interventions that mitigate AMR, such as improving wastewater treatment plants or initiating WASH practices (WHO and UNICEF 2020; WHO and UNICEF 2021), is likely to create significant benefits, particularly reducing infections with resistant microorganisms in humans, animals and plants.

Incorporate environmental considerations into National Action Plans on AMR

Given the lack of environmental engagement in NAPs, issues related to waste, discharge, effluent and other sources of AMR may not be adequately considered. Data, combining 2021 and early 2022, shows that of the 166 countries analysed the majority (65 per cent) include the environmental sector in their multi-sector 'One Health' coordination and collaboration response to AMR (WHO 2022b, question 2.2.8).

However, the participation of the environmental sector does not translate into, nor is it reflected in, environmental legislation and/or regulation (43 per cent) nor in having environmental risk

assessments (16 per cent) (WHO 2022b, Questions 6.1, 6.2). Based on specific country context and situational analysis, it is important to enhance the engagement of Ministries of Environment and environmental agencies in developing and implementing environmental protections through environmental risk assessments and legislation and/ or policy setting that address AMR in the environment into NAPs. Similarly, it is important to enhance the engagement of Ministries of Health and health agencies, as well as Ministries of Agriculture, in developing and implementing National Biodiversity Strategies and Action Plans and other nationally determined contributions.

Recognise important role of environmental authorities and regulators

Environmental authorities and regulators are key players because they prevent, monitor, control and mitigate chemical and biological emission pathways driving AMR in the environment (Singer *et al.* 2016). They must become drivers of change by taking actions to prevent and reduce environmental pressures affecting AMR, and, for that, supporting gender-responsive environmental legislation is needed to address AMR drivers and impacts.

Opportunities for action include setting and monitoring effluent standards; working with production, water and wastewater engineers to promote the most suitable mitigation technologies that reduce AMR pollution; increasing inspections and improving system maintenance; and taking greater responsibility for waste management and promoting a circular economy. They can also support surveillance of AMR in wastewater as a means of providing integrated information about AMR in the communities served and address a key need for environmental monitoring, while also informing research needed to inform discharge limits. Their active participation in cross-sectoral collaboration mechanisms is essential (e.g. 'One Health'/AMR national coordination committees), including in the definition and implementation of NAPs.

Include in national biodiversity planning

National Biodiversity Strategies and Action Plans prepared under the Convention on Biological Diversity (CBD) and updated under the Post-2020 Global Biodiversity Framework (GBF) (UN CBD 2021) discuss the importance of soil biodiversity, including

considerations of AMR. The recently approved 'Kunming-Montreal Global Biodiversity Framework' (UN CBD 2022), provides an opportunity to integrate antimicrobial use and pollution, as it impacts AMR development, into considerations of biodiversity planning (Jørgensen *et al.* 2017).

Protecting ecosystems and maintaining biodiversity was explicitly recognized by the Conference of the Parties to the CBD on its fourteenth meeting (COP14), where the COP "encouraged Parties to promote dialogue among ministries and agencies responsible for the sectors of health (including domestic animal and wildlife health), environment, pollution (such as marine plastic debris), pesticides, antimicrobial resistance, agriculture, nutrition and food security, food safety, planning (including urban planning), climate change adaptation and mitigation and disaster risk reduction, to foster integrated approaches, with a view to enhancing implementation of the Strategic Plan for Biodiversity 2011-2021 and the 2030 Agenda for Sustainable Development, including by mainstreaming biodiversity and health linkages into existing and future policies, plans and strategies, as appropriate" (UN CBD 2018, p. 2-3).

The Global Biodiversity Framework goals and targets for achievement by 2030, adopted by COP15

in December 2022 that was chaired by China and hosted by Canada, include measures that relate to and may have a positive impact on ecosystem services and mitigate the environmental dimensions of AMR because they address some of the factors and drivers that exacerbate both biodiversity loss and AMR problems.

Therefore, using a planetary health lens contributes to more than protecting ecosystems and maintaining biodiversity. Keeping in mind and dealing with the effect of antimicrobials also reduces environmental AMR risks and creates incentives to reduce pollutants relevant for AMR, such as antimicrobial agents, chemicals and biocides, and human and animal faecal wastes that contain antimicrobial resistant organisms and genes.

Ensure national climate change planning considers AMR

Given the linkages between AMR and climate, it would be beneficial to consider AMR in climate change action and adaptation planning. Continuing disruption of the natural environment due to extreme weather patterns contributes to the emergence and spread of AMR while the climate crisis puts greater pressure on food production systems, which in turn, without interventions, will become more reliant on increased



Governing bodies meeting during COP14 (17 - 29 November 2018 - Sharm El-Sheikh, Egypt) © Franz Dejon



Figure 20

Elements of a system approach to address AMR at the national level

use of antimicrobials. In addition, the potential effect of antimicrobials on microbial biodiversity may affect ecosystem services.

Yet, there is currently no global initiative focused specifically on the intersection of these two crises. The linkages require more attention, including the National Action Plans on AMR and the Nationally Determined Contributions.

Encompass AMR concerns into national chemical pollution and waste management programmes

As chemicals, including pharmaceutical antimicrobials, may select or co-select for resistant microorganisms in the environment, under certain conditions, the environmentally sound production, use and disposal of such chemicals is essential. At the international level, the development of an approach on chemicals and waste management beyond 2020 (Strategic Approach to International Chemicals Management [SAICM] 2021) provides an opportunity to link AMR

with international chemicals and waste management policymaking. National chemicals and waste management programmes also provide an opportunity to integrate AMR considerations (Brack *et al.* 2022). For example, countries may consider including relevant pharmaceutical antimicrobials as pollutants into their national Pollutant Release and Transfer Registers.

Consider a systems approach for a possible national action framework

Owing to the multisectoral implications of the environmental dimensions of AMR, it is important for countries to have robust and coherent regulatory and legal frameworks for addressing AMR in environmental media (water, soil and air). Broader environmental regulations affecting point and non-point pollution sources, WASH infrastructure, standards and other aspects need to include considerations of antimicrobial pollution and AMR. A national framework for action to address AMR may be strengthened by implementing a systems approach as shown in Figure 20. These elements need not be in a linear

cycle but are components that can be addressed within policy frameworks simultaneously as they are interconnected and impact one another.

Given diverse points of interventions, the process of targeting priorities is critical to identify financial resources and to make a case for why resources should be mobilized. Priority-setting may involve

defining which social/health, economic and environmental outcomes matter the most, assessing the environmental risks contributing to these outcomes and recognizing key environmental drivers of AMR. Monitoring the changes that take place because of interventions is key to the success of any policy action.

5.2 Strengthen global action

Global governance is increasingly recognizing environmental dimensions of AMR. Calls have been made to address environmental considerations and to include them in global, regional and national governance for a 'One Health' response to AMR.

In 2015, the World Health Assembly adopted the Global Action Plan on Antimicrobial Resistance, developed by WHO in collaboration with FAO and OIE (current WOAHA). The 2016 political declaration of the United Nations High-Level Meeting on Antimicrobial Resistance (UNGA 2016) emphasized the need for a coordinated approach that engages the human, animal, plant and environmental health sectors. In accordance with the 'leave no one behind' principle, the declaration further recognized the fewer options available in protecting the most vulnerable groups specifically: women giving birth, newborns, patients with certain chronic diseases and those undergoing chemotherapy or surgery. The declaration requested that the UN Secretary-General establish an ad hoc Interagency Coordination Group on AMR (IACG) to provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance.

In its 2019 report, the IACG made several recommendations concerning global governance (IACG 2019). These included the creation of a Global Leaders Group (GLG) on AMR, the convening of an Independent Panel on Evidence for Action against Antimicrobial Resistance in a 'One Health' Context, and the establishment of a constituency-based multi-stakeholder partnership platform to develop a shared global vision, narrative and targets for the 'One Health' response.

The GLG on AMR was established in November 2020 to accelerate political action (GLG on AMR 2021b). It includes participation at the Head of State level and plays a key role in advocating a better understanding of environmental pathways that contribute to the development and transmission of AMR (Tripartite Joint Secretariat on Antimicrobial Resistance 2021). In November 2022, the Antimicrobial Resistance Multi-Stakeholder Partnership Platform was established to galvanize and guide a collective response and foster collaboration in tackling common threats to human, animal, plant and ecosystems health.

At its 76th session, in March 2022, the United Nations General Assembly adopted a resolution (A/RES/76/257) on the need to elevate pandemic prevention, preparedness and response to the highest levels of political leadership (UNGA 2022b). In Section 17 of the resolution, the UNGA agreed to hold a high-level meeting on AMR in 2024. The President of the UNGA will therefore appoint two co-facilitators who will present options and modalities for the meeting, including potential deliverables in collaboration with FAO, UNEP, WHO and WOAHA and with the support of the GLG. This meeting is a critical opportunity to review progress on and update the political declaration from the 2016 High-Level Meeting on AMR.

The Third Global High-Level Ministerial Conference on Antimicrobial Resistance, hosted in Muscat, Oman, 24-25 November 2022, and its subsequent Muscat Manifesto, pave the way for bold political commitments at the forthcoming UN General Assembly High-Level Meeting on AMR in 2024



H.E. Mia Amor Mottley, Prime Minister of Barbados, Chair of the AMR Global Leaders Group. AMR Global Leaders Group (GLG) side event at the United Nations General Assembly 77th Session. © Malta

(Global High-level Ministerial Conference on Antimicrobial Resistance 2022).

Other examples include the Call to Action on AMR 2021 (UN 2021b), which has 113 Member State signatories and 40 supporting organizations and policymaking bodies including the Group of Seven (G7), the Group of Twenty (G20) and Caribbean Community Secretariat (CARICOM) that have acknowledged the need for and support to action with respect to various environmental dimensions of AMR (Caribbean Community Secretariat 2021; G20 2021; G7 2021b). In line with UNEA resolution 4/17 adopted by Member States, on 'Promoting gender equality and the human rights and empowerment of women and girls in environmental governance', which states that it is expected that environmental governance fora aim for gender parity through the equitable inclusion of women in both participation and leadership roles (UNEA 2019).

To advance international co-operation on 'One Health' matters, leaders of those organizations working in the multilateral system on human, animal, plant and environmental health (i.e. FAO, UNEP, WHO and WOA) signed an agreement to strengthen their co-operation and fully integrate environmental considerations into 'One Health' efforts, including those related to AMR. In 2021, the four organizations developed a joint strategic framework for collaboration on AMR and a common work plan over the next years. The Quadripartite

organizations consolidated their Joint Secretariat and prepared the 'One Health Joint Plan of Action', with AMR as one of the six action tracks.

Besides the mentioned AMR global governance structures, the Quadripartite established the 'One Health High Level Expert Panel' to encourage further coordination and collaboration, including full integration of environmental and ecosystem considerations in 'One Health' (UNEP 2020; FAO 2021b).

Prior to those, in 2019, the AMR Multi-Partner Trust Fund was created with the overall goal of reducing levels of AMR and slowing development of resistance. The Fund largely focuses on supporting implementation of NAPs on AMR. In mid-2021, UNEP became a co-signatory of the Fund, an important step forward for enhancing the understanding of the critical environmental dimensions of AMR and the AMR associated biological and chemical pollutants that can impact human, animal, plant and ecosystems health.

Significant momentum has thus developed at the international level to address AMR and its environmental dimensions. This includes an increased engagement of UNEP in strengthening the global 'One Health' approach, in collaboration particularly with the Quadripartite Alliance.

5.3 Improve reporting, surveillance and monitoring systems

The environmental dimensions of AMR present opportunities to complement traditional clinical surveillance systems, especially in LICs and LMICs. Surveillance of resistant microorganisms, and ARGs in wastewater is far less costly than testing individuals and is thus attractive in resource constrained settings.

Environmental monitoring is an essential component of 'One Health' integrated surveillance for AMR and can complement traditional public health surveillance systems. Environmental surveillance accompanied by gender impact assessments further helps isolate gender-differentiated impacts and outcomes of antimicrobial use and resistant infections, as these are crucial towards public health responses (WHO 2007). In addition, environmental surveillance captures transmission routes such as water, soil, air, plants and wildlife. It can track spatial and temporal patterns of resistance in the environment, survey risk factors that can contribute to emergence and amplification of ARGs from environmental microorganisms, facilitate assessments of AMR-related environmental exposure

in humans and animals and also track actual use (e.g. through testing wastewater).

Examining the content of wastewater influent (i.e. wastewater prior to treatment) provides an indication of the community burden of AMR, as well as what could be discharged to the environment. There is growing momentum for wastewater surveillance, particularly considering ongoing investments in wastewater monitoring for COVID-19 and poliovirus, and for AMR in sewage around the world (Daughton 2020; Pruden *et al.* 2021). Surveillance of resistant microorganisms, and ARGs in wastewater is far less costly than testing individuals and is thus attractive in resource constrained settings, such as LICs and LMICs. The experience with wastewater surveillance of COVID-19 prevalence (i.e. detecting SARS-CoV-2) attests to the utility of the approach (Sims and Kasprzyk-Hordern 2020). At the urban community level, some studies are already available using genomic methods (Liguori 2022; Munk *et al.* 2022).

Wastewater treatment plants may be important sampling sites as part of environmental surveillance plans
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There also exists the need for implementation of broader environmental surveillance across the 'One Health' spectrum, which would help to better identify relative sources and contributions of antimicrobial pollution and AMR in the environment. Monitoring of surface waters provides an integrated measure of both point and non-point AMR inputs to the environment (Keely *et al.* 2022). Monitoring wildlife would also be of value given that they can serve as local and global vectors of transmission. This would enable better understanding of the AMR dynamics within the environment and quantify the contribution of the environment to the burden of AMR relative to the human and animal sectors.

E. coli is a common target, indicator bacteria in AMR studies because it is found across 'One Health', and allows harmonization of data collection, including from human, livestock, wildlife, and anthropogenically impacted environment, enabling comparison across sectors (Lagerstrom *et al.* 2021).

An integrated environmental AMR monitoring infrastructure is needed to complement AMR surveillance in human, animals and plants. There are many options available for monitoring AMR in the environment. Target environments can be tested for antimicrobial compounds as well as qualitative or quantitative measures of AMR. Currently, there are no international standards for what constitutes a good microbiological indicator of AMR from environmental samples. Microorganisms that hold significant public health importance, such as extended spectrum beta-lactamase (ESBL) producing bacteria, are of special interest (WHO 2021c). Low-cost and accessible methods are needed to support monitoring of AMR in resource-limited settings in LICs and LMICs, where environmental impacts may be greatest (IACG 2018b; Huijbers, Flach and Larsson 2019).

To address the need for a unified 'One Health' monitoring target, the WHO launched an integrated global surveillance protocol targeting ESBL-producing *E. coli*, which enables comparison across 'One Health' sectors. This 'Tricycle' protocol is intended to be simple and cost-effective, and therefore accessible by LICs and LMICs. The standardized methodology produces comparable data that can be followed up over time and establish a baseline for national integrated multisectoral 'One Health' surveillance system for AMR.

The protocol detects ESBL *E. coli* in three key sectors: humans (including health facilities and communities), food systems and the environment. Comprehensive and combined data analysis can describe trends in evolution of AMR at national, regional and global levels (WHO 2021c).

Monitoring targets based on DNA-sequencing are also of value because they provide integrated information across the thousands of microbes in a given environment, whereas culture can only detect one organism at a time. To this end, the US EPA has implemented quantitative polymerase chain reaction for sensitive detection of specific ARGs of interest (Keely *et al.* 2022) and efforts are underway for unified and harmonized protocols (Keenum *et al.* 2022; Milobedzka *et al.* 2022). Shotgun metagenomic sequencing is an emerging technology that can broadly survey ARGs in the sample of interest in a non-targeted fashion (Ruppé *et al.* 2019; Gupta, Tiwari and Cytryn 2020). Whole-genome sequencing of cultured isolates can also provide valuable information to support source-tracking. DNA-sequencing based methods are more costly at present but could be strategically applied at a global level at key surveillance points (Pruden *et al.* 2021).

Regardless of the method selected, surveillance and monitoring plans should describe epidemiological and laboratory methods to detect antimicrobial resistant microorganisms and/or ARGs. In addition, a system should include assessing risks for emergence and transmission of resistant microorganisms. Surveillance data gathered will help to inform effective policy interventions for combating AMR. Context specific considerations and specific monitoring goals may inform the laboratory methods most appropriate. Low-cost and accessible methods are needed to support monitoring of AMR in resource-limited settings in LICs and LMICs where environmental impacts may be greatest (IACG 2018b; Huijbers, Flach and Larsson 2019).

Infrastructure for sewage monitoring of disease has been rapidly expanded globally because of the COVID-19 pandemic and previously has been shown to be particularly successful for detection of communities with polio (Asghar *et al.* 2014; Sims and Kasprzyk-Hordern 2020). Surveillance and monitoring infrastructure can be built upon to advance

Box 5

Environmental surveillance methodologies

Methods for environmental surveillance can either be culture-dependent or culture-independent (i.e. phenotypic or genotypic). Culture-dependent methods may include growing target bacteria in agar plates or nutrient broth, and then adding specific antimicrobials to test for resistance and the use of selective or non-selective media. Susceptibility testing is then undertaken for selected isolates. Culture-independent methods include the use of quantitative polymerase chain reaction (qPCR) and metagenomic approaches, where sequencing of environmentally sourced microbiological DNA (e.g. whole genome sequencing) is done using next-generation sequencing methods (Klümper *et al.* 2022; Munk *et al.* 2022). Whole genome sequencing can be applied to cultured isolates for source tracking of resistant strains and their ARGs and MGEs.

Surveillance can take a comprehensive approach or minimum strategy approach. The former uses all the above-mentioned techniques such as culture, metagenomics, antimicrobial residues and physiochemical samples, but still addresses questions that can be informed with surveillance using appropriate methods (Liguori 2022). It also determines optimal sampling strategies, considers multiple transmission routes, links environmental surveillance to existing monitoring systems and is adaptable to regional, national and subnational conditions for global comparisons.

A minimum strategy approach includes sampling hotspots such as sewage, wastewater effluent, water, sediment, soil and wildlife, testing for clinically important microorganisms for human and animal populations and using spatial and temporal metadata such as temperature, pH and other water chemistry variables (Klümper *et al.* 2022). Over time, as local capacity increases and analytical costs decrease, integrated surveillance can be developed to include culture-independent methodologies that allow full understanding of resistome evolution and transmission dynamics within and between 'One Health' sectors.

global, coordinated and/or integrated monitoring of antimicrobials, antimicrobial resistant microorganisms and ARGs. This can help to better understand the causes of the AMR crisis and inform and assess corresponding mitigation measures (Aarestrup and Woolhouse 2020; Pruden *et al.* 2021; WHO 2021c).

Priority actions to improve reporting, surveillance and monitoring systems

- Strengthen systems for transparent and swift collection and reporting of production, sales, use and disposal of unused or expired pharmaceuticals such as antimicrobials
- Monitor and document releases of antimicrobials, resistant microorganisms and their genetic material to the environment (e.g. through national Pollutant Release and Transfer Registers)
- Develop and harmonize local surveillance networks that connect to national and regional systems to collect and compare data on AMR prevalence in the environment, to assess environmental and biodiversity antimicrobial pollution risks and to assess effectiveness of action
- Develop and integrate environmental monitoring data (e.g. from wastewater, surface water, solid waste and airborne particulate matter, crops and aquaculture) with existing or proposed sex- and age-disaggregated AMR surveillance data
- Strengthen surveillance for pandemic preparedness and response as related to AMR exposure, emissions, circulation in human populations and the identification of emerging AMR threats

5.4 Future data, information and knowledge needs

Despite increased actionable evidence of the importance of the environmental dimensions of AMR, some key data and knowledge gaps remain. This hinders systematic priority-setting and the selection of cost-effective, context-specific management action. Additional research and further work is needed to:

Improve surveillance and transparency in data collection

- Develop and integrate surveillance approaches, including transparency in data collection for AMR, AMU and antimicrobial residues across all 'One Health' sectors
- Understand the challenges to systematic collection, analysis, interpretation and reporting of data on AMR for risk assessment and intervention impact assessments in LICs and LMICs settings
- Optimize strategies and resources, to include minimum standards such that adequate laboratory and human resource capacity can be established to maintain quality integrated surveillance at scale
- Increase the transparency of relevant chemical and pharmaceutical production, sales, use and disposal, as well as data on environmental releases
- Gather accurate data on the socioeconomic risks of AMR, to include data disaggregated by sex and age, and determine how it can be most cost-effectively collected and analysed in low resource settings

Address the global burden of AMR through a 'One Health' lens

- Better incorporate the 'One Health' approach, examining the interface of human, animal, plant and environmental health into all responses to AMR
- Assess the global burden of AMR, particularly improving fungal and viral disease reporting to align with recent antibiotic-resistant mortality estimates, including gender- and age-differentiated impacts of AMR

- Improve understanding of fungal infection emergence and spread from environmental sources
- Determine how antimicrobial use in livestock affects ecosystem services
- Among 'One Health' professionals, improve understanding of infection prevention and control practices that can reduce AMR transmission
- Address what specific gender-differentiated human health risks are associated with exposure to antimicrobial residues, their mixtures, interaction through various exposure routes, such as drinking water and food consumption
- Determine the cost of inaction related to environmental and societal burden

Expound the role of the environment in the emergence and development of AMR

- Clarify the role of the environment as affected by human activity (e.g. pollution) on the evolution (mobilization, selection, transfer, persistence etc.) of AMR
- Understand the relative importance (exact nature and magnitude) of each pollution source in causing global and regional exposure and the contribution to AMR in the environment and in local and specific ecosystem contexts
- Characterize the type, quantity and dynamics of chemicals (e.g. with co-selection potential) to the environment that might differentially affect AMR development, transmission and spread under LIC, MIC or HIC conditions
- Better measure the concentrations of antimicrobials, metals, biocides and other pharmaceuticals, as well as chemical compounds (e.g. microplastics) – found in pollution in the environment – that can play a role in selection, co-selection and maintenance of AMR where resistance already exists

- Develop and enforce standards to reduce antimicrobial discharges/emissions that prevent AMR emergence in the environment
- Identify and validate indicator microorganisms and diagnostic assays with gene targets for AMR in the environment.
- Measure the impact of antimicrobial, heavy metal and co-selecting biocide pollution on biodiversity, including microbial diversity and biofilms in soil and water ecosystems and in other environmental niches.
- Document the use of bioproducts (e.g. biofertilizers, biosolid and manure applications and plant growth promoters) and novel agricultural practices do not select for AMR or serve as sources of pollution that propagate AMR in the environment (e.g. microplastics).
- Include behavioural sciences that study the challenges and barriers related to reduction of AMR, such as stewardship in different sociocultural contexts

Prevent and mitigate AMR

- Preserve the effectiveness of antimicrobials by prioritizing and optimizing use according to medical and veterinary professional stewardship programmes and recommendations
- Identify which antimicrobial resistant microbes and antimicrobial resistance genes are to be most urgently addressed in prevention and mitigation strategies
- Elucidate how phylogeny and the environmental and other origins of ARGs impact the emergence of new ARGs in pathogens to prevent or delay their emergence
- Identify cost-effective technological, social, economic and behavioural interventions that will be effective to prevent and mitigate the development and spread of AMR and the occurrence of antimicrobial residues in the environment
- Develop easily degradable antimicrobials, compounds that trigger antimicrobial degradation and adsorbents that remove antimicrobials from the human gut or in water

Collectively, as this information becomes available it can be used to prioritise interventions to prevent and mitigate AMR development and spread in the environment.

5.5 Prioritize financing, innovation and capacity development to support environmental action

Inaction to prevent and address AMR results in many preventable deaths and stands to cause even greater loss of life, economic wellbeing and environmental degradation. If left unchecked, the World Bank projected that, under a high-impact scenario, AMR could result in an annual GDP shortfall of US\$3.4 trillion by 2030 and push 24 million more people into extreme poverty by 2030 (World Bank 2017).

Furthermore, according to the World Bank, interventions to address AMR are among the most cost-effective investments. Investing in a US\$9 billion package to address AMR each year would result

in “substantial economic payoffs” for low-income countries, while over 80 per cent of the returns on implementing AMR containment would go to high-income and upper middle-income countries (World Bank 2017). An Organisation for Economic Co-operation and Development (OECD) modelling indicates that a public health package, costing just US\$2 per person, comprising measures to improve environmental hygiene and to implement antimicrobial stewardship, media campaigns and rapid diagnostics, would save 47,000 deaths per year in the OECD countries and the European Union, pay for itself in just one year and end up saving US\$4.8 billion per year in OECD countries (OECD 2018).

AMR's disproportionate impact on LICs and LMICs relates to health, poverty, sanitation and hygiene, pollution, vulnerability, food safety and security, and makes it a development issue that stands to inhibit the attainment of the SDGs (Hone, Macinko and Millet 2018; World Bank 2019). Improving social and environmental conditions and tackling AMR has a positive impact that contributes to the achievement of different SDGs. This intersectoral nature and the co-benefits of AMR would need to be better reflected in the total official support for sustainable development for bilateral development agencies, development financing organizations, philanthropic organizations and private sector resource mobilization and monitoring.

Sustainable funding, including the allocation of sufficient domestic resources, is therefore needed to tackle AMR. Financing will need to be mobilized to effectively address the pandemic level threat of antimicrobial resistant infections and their global spread. Capacity development work and support to the implementation of NAPs that is taking place through the AMR Multi-Partner Trust Fund is a step in the right direction but needs to be scaled-up.

There are options to redirect investments. For example, 87 per cent of US\$540 billion annual support to agricultural producers is either price distorting or harmful to nature and health (FAO, UNDP and UNEP 2021). This repurposing represents a significant opportunity to help transform primary health care system, food systems, support climate action, tackle AMR and contribute to achieve the SDGs.

In addition, new and innovative financial incentives and schemes are needed to support technology innovation (e.g. green and social bonds, and the combination of gender and green bonds). The adoption of integrated approaches is also crucial. For example, gender and green bonds adopt a multi-pronged approach that addresses all three dimensions of sustainable development simultaneously, (Carbon Care Asia 2020; UN 2021a). Furthermore, resources to bring solutions to scale will be needed to support more country-level programmes that address AMR from a 'One Health' perspective.

5.6 A call to action

Limiting the emergence and spread of resistant pathogens is critical to preserving the world's ability to treat diseases in humans, animals and plants, reduce food safety and security risks, protect the environment and maintain progress towards the SDGs (WHO *et al.* 2021). The global response to AMR rests on collaboration between sectors that have traditionally fallen within separate policy spheres.

The environment has received limited attention in tackling AMR, but evidence shows that the environment plays a key role in the development, transmission and spread of AMR. Now, while its contribution and significance are determined, further and more coordinated action, with a focus on prevention, needs to be taken to limit the role of the environment in mediating, driving and causing AMR.

This report has shown that the environmental dimensions of AMR are multifaceted, requiring action at local, national, regional and global levels and with a broad array of stakeholders. Country implementation is particularly at the heart of a successful response to AMR, as it is in countries that the work of addressing the many challenges of AMR ultimately takes place. What is needed is a robust legal and regulatory framework that prevents the risk of AMR addressing the drivers and factors with an impact on environmental dimensions of AMR. This includes regulating the use of antimicrobials on farms, including aquaculture; limiting the discharge of effluent from pharmaceutical and other chemical industries, and hospital waste; improving integrated water management; promoting water, sanitation and hygiene; and waste management.

While countries might have different processes for developing and managing an effective national governance mechanism for AMR, the need for a robust multisectoral coordination system has been highlighted across multiple fora as key for tackling AMR in a sustainable manner. Thus, countries need to integrate such environmental considerations into AMR National Action Plans, and AMR into environmental-related plans such as national chemical pollution and waste management programmes, national biodiversity and climate change planning.

Another priority area for urgent action remains to ensure continued political engagement and support in countries, including national budget allocations and scaling up technical capacity across all sectors to accelerate the implementation of the NAP on AMR. Countries need to explore innovative financial incentives and schemes, and to make the investment case to guarantee sustainable funding.

Environmental monitoring and surveillance and further research prioritization are also pivotal to provide more data and evidence and better understand the complex dynamics of AMR. This will lead to improved science-policy interfaces to ensure informed decision-making and prioritise interventions. Therefore, strengthening national, regional and global surveillance systems through improved data management, private sector engagement, implementation of data-driven practices and reporting is critical.

Further engagement and commitment are needed from industry actors from the three economic sectors and their value chains that are key drivers of AMR development and spread in the environment i.e. pharmaceuticals and other chemicals, agriculture

and food, and healthcare. This commitment should include further steps to ensure more transparency and corporate responsibility regarding their contribution to the risk of AMR.

Globally, there is a need to establish international standards for what are good microbiological indicators of AMR from environmental samples, which can be used to guide risk reduction decisions and create effective incentives to follow such guidance.

National and global AMR-related planning and action, and the critical role and contribution of environmental authorities, experts and practitioners need to be strengthened. Strategies and plans need to utilise the 'One Health' approach while addressing financial/business, climate and cultural contexts. Regulatory, economic and in some instances cultural barriers will need to be overcome. Gender equality and rights-based approaches need to be adopted in order to make progress towards environmental sustainability. These issues need to be addressed and given prominence in deliberations on the topic.

The Quadripartite organizations need to continue leveraging their respective organizations' resources and strengths to jointly support countries in scaling up national responses to AMR through a 'One Health' approach.

Solutions exist, and many of them have been captured in this report. They range from specific management actions to promoting sustainable production and consumption. A clear vision, ambitious targets and road maps supported by political prioritization of a 'One Health' response to AMR and international enabling action are needed to leverage the momentum.



5.7 Summary

- The need for a robust multisectoral coordination system by all stakeholders, especially environment ministries and agencies, has been highlighted across multiple fora as key for tackling AMR in a sustainable manner.
- Strengthening national actions require boosting governance, planning and regulatory frameworks, through integrating AMR in national development planning and budgeting, and into environmental-related plans and processes. Likewise, incorporating environmental considerations into NAPs on AMR, and considering a systems approach for a possible national action framework.
- Priority actions required to improve reporting, surveillance and monitoring systems include developing and integrating environmental monitoring systems, strengthening systems for transparent and swift collection and reporting, monitoring and documenting releases of antimicrobials, resistant microorganisms and their genetic material to the environment, and strengthening surveillance for pandemic preparedness.
- Additional research and further work are needed such as clarifying the role of the environment as affected by human activity (e.g. pollution) on the evolution of AMR, understanding the relative importance of each pollution source, developing and enforcing standards to reduce antimicrobial discharges/emissions, and identifying cost-effective technological, social, economic and behavioural interventions.
- Prioritizing financing, including domestic resources, innovation and capacity development to support environmental action are crucial elements for strengthening the environmental action to tackle AMR.

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United Nations Avenue, Gigiri
P O Box 30552, 00100 Nairobi, Kenya
Tel +254 720 200200
unep-info@un.org
www.unep.org