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# Environmental Dimensions of Antimicrobial Resistance

## Summary for Policymakers

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# Background

Global attention to antimicrobial resistance (AMR) has been dominated by a focus on the health and agriculture sectors. However, the environment is also key to the development, transmission and spread of AMR to humans, animals and plants. In 2017 this fact was recognized by the United Nations Environment Assembly (UNEA-3), which requested a report on the environmental impacts of AMR and the causes of the development and spread of resistance in the environment, including the gaps in understanding those impacts and causes. This paper presents highlights from a full report that will be released later this year, which was prepared through a consultative process that engaged more than 50 experts and stakeholders from countries around the world, including from the Tripartite organizations the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE) and the World Health Organization (WHO).

Many human activities create pollution which promotes the emergence of AMR in the environment. AMR in the environment can cause animal or plant diseases or soil biodiversity loss that can lead to further use of antimicrobials (a negative feedback from initial use) that only increases the selective pressure further. The environmental dimensions of AMR are characterized by cyclic interrelationships, their complexities, and multiple causalities and dynamics. A systems approach, such as 'One Health', is required to better understand the environmental dimensions of AMR and inform science-based decisions and actions.

The environmental impacts of AMR, and the causes of the development and spread of resistance in the environment are complex. However, there is evidence that both biological and chemical pollutants, which enter the environment, can fundamentally influence and change what is happening in the environment, especially AMR development, transmission and spread. Human activity and increasing populations are damaging the natural microbial world – the very foundation of global ecology.

# 1 A call to **strengthen environmental action** within the 'One Health' response to AMR

The world has not taken the threat of zoonotic diseases, pandemics and their environmental dimensions seriously enough. The COVID-19 pandemic is a wake-up call to better understand and improve all areas of preparedness for and prevention of infectious diseases, including their environmental dimensions (Pachauri *et al*. 2021).

Such lack of preparedness cannot be allowed to happen again. The COVID-19 pandemic provides lessons learned, one of which is the need to prevent and tackle various health threats concurrently, especially their environmental dimensions.

Another pandemic is hiding in plain sight. Antimicrobial resistance (AMR) is already a leading threat to global health and risks adversely affecting the environmental sustainability of the planet (Murray *et al*. 2022). The consequences of the continuing development and spread of AMR could be catastrophic.

## 1.1 The effectiveness of antimicrobials is in jeopardy

For decades antimicrobials have contributed to the reduction of infectious diseases in humans, animals and plants, saving lives and increasing productivity. Their effectiveness is now in jeopardy. As microbes evolve and become resistant, antimicrobial treatments are rendered less effective. Antimicrobial compounds released into the environment, together with other factors, create a selection pressure on natural microbial communities such that those with inherited or acquired resistance have evolved and proliferated. Pollution containing minimal selective concentration of antimicrobial compounds contributes to antimicrobial resistance development in the environment.

Box 1

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

Antimicrobials are agents intended to kill or inhibit the growth of microbes. They include antibiotics, fungicides, antiviral agents and parasiticides. Disinfectants, antiseptics, other pharmaceuticals and natural products may also have antimicrobial properties.

AMR occurs when microbes such as bacteria, viruses, parasites and fungi are, or become, resistant to antimicrobial treatments to which they were previously susceptible. Antimicrobials are widely used in human and animal healthcare, and in crop and animal production.

Acquired resistance is an evolutionary response by microbes, which genetically change their DNA in such a way that they are no longer inhibited or killed by antimicrobials. AMR can be intrinsic or acquired; the latter can occur through mutations, the acquisition of DNA from different microbes, or, in the case of bacteria, horizontal gene transfer (HGT) of mobile genetic elements (MGEs) (Levy and Marshall 2004; Martínez *et al*. 2015).

Use and misuse of antimicrobials and other stressors (e.g. the presence of heavy metals and other pollutants) create favourable conditions for resistant microbes to develop (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, sewage, soil and air) (Baquero *et al*. 2019). Resistant microbes can subsequently spread and be transmitted to humans, food animals, plants and wildlife because of complex interconnections across nature (Graham *et al*. 2019). There is strong evidence that antimicrobials are increasingly failing to cure infections, the pipeline of novel antimicrobials to take their place has faltered, and AMR therefore poses a significant threat to human, animal and plant health, and food security.

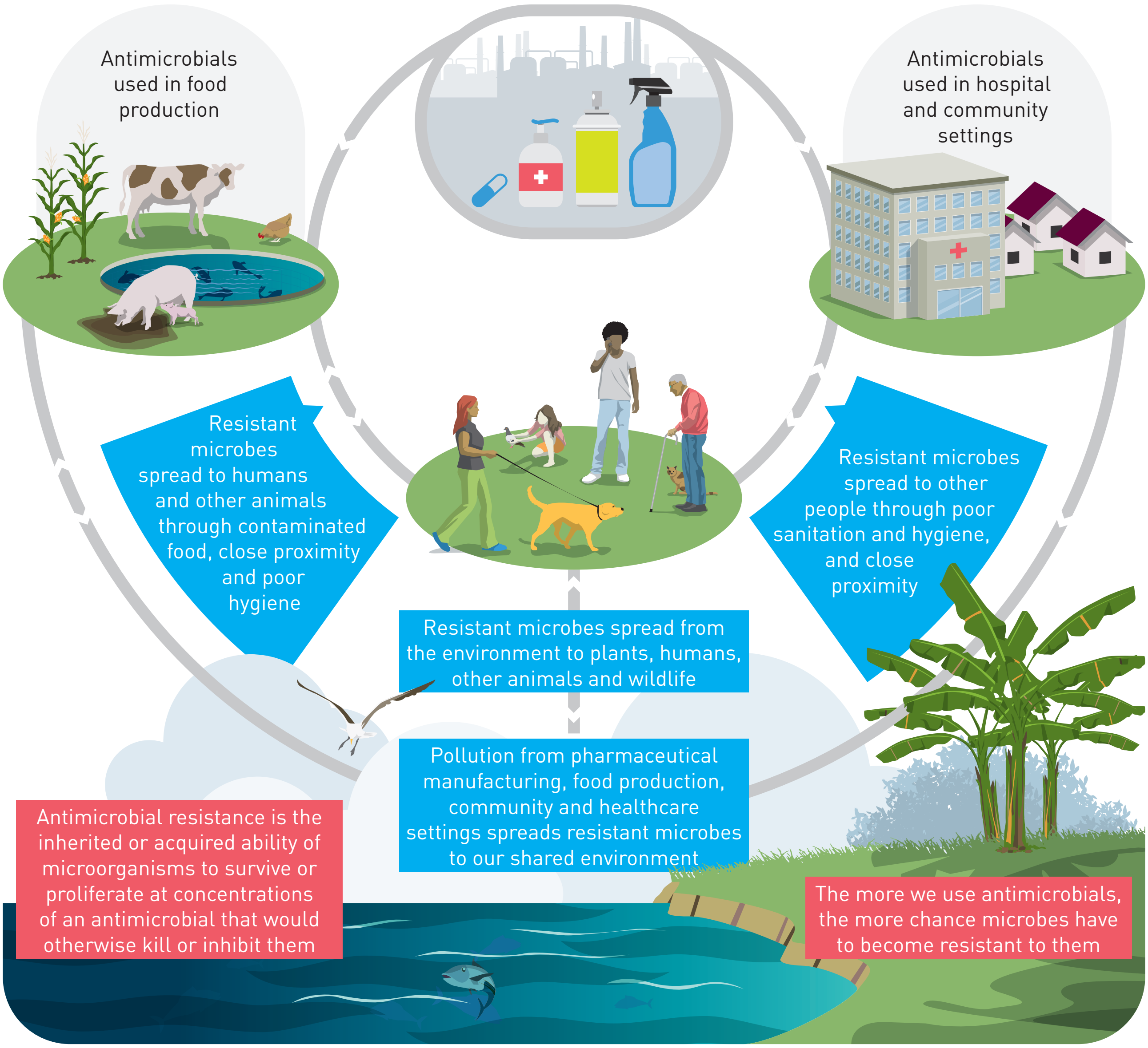


Figure 1

**How antimicrobial resistance can spread (adapted from Government of Australia 2017)**

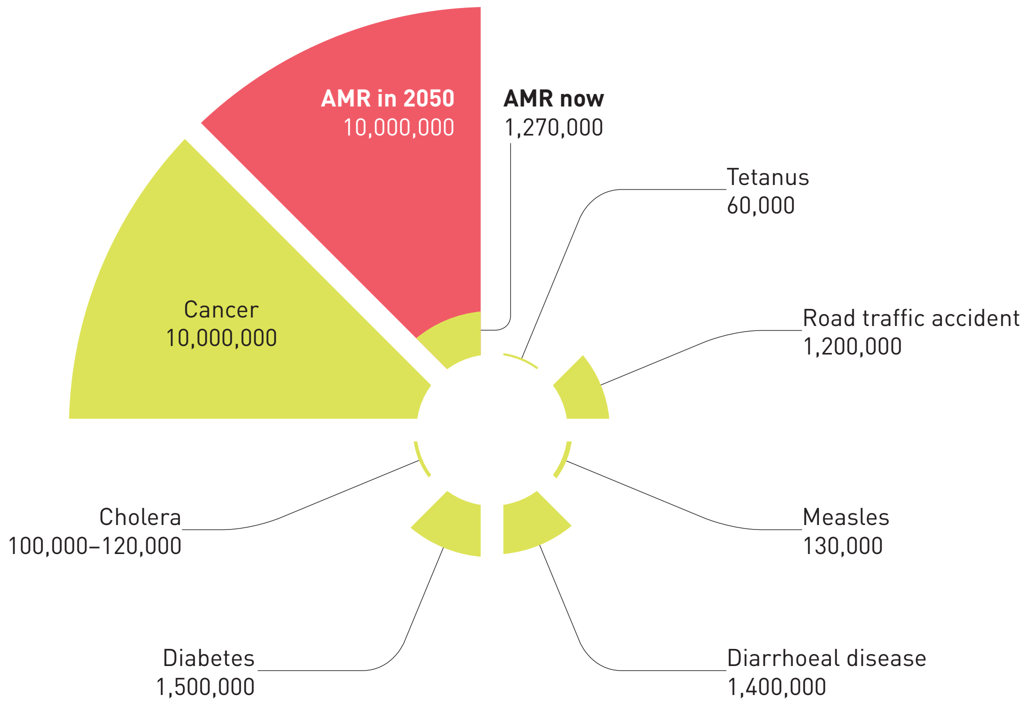


Figure 2

**Predicted mortality from AMR compared to common causes of death today (adapted from O'Neill 2016)**

In 2019, antibiotic-resistant infections were responsible for the deaths of 1.27 million people, with an overall 4.95 million deaths associated with complications from resistant bacterial infections (Murray *et al*. 2022). Immediate action is needed to tackle AMR or by 2050 it could cause up to 10 million deaths globally per year (O'Neill 2016), on par with the 2020 death toll from cancer (Ferlay *et al*. 2020). The economic impact is also likely to be significant. By 2050 it is estimated that AMR could be responsible for a loss of 3.8% of the world's annual gross domestic product (GDP); by 2030 the GDP shortfall due to AMR could be US$3.4 trillion per year, while 24 million more people could be pushed into extreme poverty (Jonas *et al*. 2017).

Given the wide prevalence of infectious diseases (Shallcross *et al*. 2015), antimicrobials play an essential role in protecting people, animals and plants (Hernando-Amado *et al*. 2019; Joint Programming Initiative on Antimicrobial Resistance 2019). Failing to address the global burden of AMR, including its environmental dimensions, could take humanity back to an era when even mild infections become deadly.

## 1.2 Joining forces to tackle AMR

Given the interconnection of human, animal, plant and ecosystems health, a 'One Health' response to AMR is essential.

> "**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."
>
> - One Health definition developed by the One Health High-Level Expert Panel (UNEP 2021a).

## 1.3 How does AMR develop, transmit and spread in the environment?

Microbes, in particular bacteria in water, soil and air can develop resistance following contact with other resistant microbes. Horizontal and vertical AMR transmission can happen in the absence of any antimicrobial compound being present. Furthermore, resistance can also develop due to selective pressures from antibiotics, fungicides, antiviral compounds, parasiticides, certain disinfectant chemicals (e.g. quaternary ammonium, triclosan and chlorine) and other co-selecting compounds (e.g. metals such as zinc and copper), which are released into the environment by human activity owing to poor sanitation, or from contaminated land and water.

Widespread environmental releases of biological AMR pollutants originate from discharges of untreated human and animal excreta into the environment as well as from antimicrobial manufacturing. This occurs when containment or barriers for these pollutants are lacking, such as toilets without confining barriers, or when wastewater is used to irrigate farmland and during fertilization of crops with untreated animal manure or human waste. Such releases transmit antimicrobial resistant microbes, and antimicrobial resistance genes (ARGs), which can enrich and promote the spread of AMR in the environment (Bengtsson-Palme, Kristiansson and Larsson 2018; Bürgmann *et al*. 2018; Karkman 2019; Berendes *et al*. 2020).

Pollution by chemicals with antimicrobial activity (e.g. pharmaceuticals, certain metals, biocides and other compounds) may enhance the mobilization of ARGs in certain microbes and/or enhance AMR in microbes in the environment (Murray *et al*. 2021).

Pollution containing antimicrobial agents (e.g. waste streams from households, hospitals, agricultural and chemical manufacturing) disrupts the microbial composition of environmental media and affects biodiversity and ecosystem services. Water, soil and air then serve as vehicles for spreading antimicrobial resistant microbes between and among people, animals and other environmental reservoirs (e.g. food production environments, including aquaculture) (EFSA Panel on Biological Hazards 2021).

# 2 Which **pollutants exacerbate AMR** in the environment and where do they come from?

Five main pollutant sources contribute to the development, transmission and spread of AMR in the environment. Sound data and further research are needed to determine the exact nature and magnitude of their relative influence on AMR, including in the environment, and in local and specific ecosystem contexts.

## 2.1 Poor sanitation, sewage and waste effluent

Hundreds of millions of cases of diarrhoea each year are treated with antibiotics, 60% of which could be prevented with safe water and sanitation in communities (O'Neill 2016). Of particular concern is open defaecation and faecal releases from uncontained sanitation facilities. Human faecal waste containing antimicrobial resistant microbes and antimicrobial residues, which cause selection pressure, alter microbial populations of environmental microbes. About 2 billion people do not have basic sanitation facilities; of these, 494 million people defaecate in the open (WHO and UNICEF 2021). Over 56% of domestic and industrial wastewater globally is released into the environment with little or no treatment (UN-Habitat and WHO 2021). However, the impact of this is not equal.

Inadequate wastewater management varies widely around the world, with regions with limited treatment showing much higher levels and diversity of AMR (Hendriksen *et al*. 2019). A lack of wastewater infrastructure was statistically more important than the level of antimicrobial usage to local AMR in healthcare (Collignon *et al*. 2018), implying environmental dimensions may dominate AMR prevalence in large parts of the world. Such sewage pollution, together with antimicrobial agents, also changes the microbial composition of environmental media and affects biodiversity and ecosystem services.

## 2.2 Effluent and waste from pharmaceutical manufacturing

Environmental releases of active pharmaceutical ingredients are a critical driver of the development and spread of AMR in some parts of the world. High prevalence of ARGs and resistant bacteria has been associated with this type of pollution (Bengtsson-Palme *et al*. 2014). Untreated pharmaceutical wastes and other stressors have been found at concentrations necessary to increase the abundance of antimicrobial resistant microbes and ARGs (Kookana *et al*. 2014). Addressing pollution from antimicrobial manufacturing has consistently been identified as a priority area of intervention.

## 2.3 Effluent and waste from healthcare facilities

As antimicrobials are frequently used in healthcare, effluent from healthcare facilities is an important source of discharges of resistant microbes, antimicrobial pollution and ARGs into the environment. Although the total amount of antimicrobials used in primary care exceeds the amount used in hospitals, it is antimicrobials used in hospitals that are classified as critically important by WHO (WHO 2019). Untreated wastewater discharges from hospitals contain significantly more resistant microbes, ARGs and antimicrobial compounds and their metabolites, particularly related to antimicrobials of last resort than treated wastewater (Quintela-Baluja *et al*. 2019). Hospital waste is produced in much smaller volumes and is often diluted within municipal wastewater treatment plants. However, hospital waste can contain up to ten times higher concentrations of ARGs and resistant microbes than wastewater from community sources (Hassoun-Kheir *et al*. 2020).

## 2.4 Use of antimicrobials and manure in crop production

Pesticides with antimicrobial properties such as antibiotics and fungicides (including metal-based plant protection products) are widely used in industrial crop production and could impact AMR in the environment.

Antibiotic residues, ARGs and antibiotic-resistant bacteria are released into the environment when manure or sewage sludge are used to fertilize or condition soil, or untreated wastewater is used for irrigation (Marti *et al*. 2013; Li *et al*. 2015). For example, about 11% of all globally irrigated cropland receives inadequately treated wastewater (Kookana *et al*. 2020).

Contamination of food crops with antimicrobial residues and antimicrobial-resistant bacteria from environmental sources during primary production has implications for public health. 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. In addition, farm workers may be exposed to hazardous amounts of antimicrobials if they do not use proper personal protective equipment.

## 2.5 Releases, effluent and waste in animal production

In intensive terrestrial and aquatic animal production systems antimicrobials are frequently used to maintain livestock health, welfare and productivity. An increase in demand for animal protein globally has led to an overreliance on antimicrobials as their uses include promotion of growth — administration of antimicrobials to animals with no diagnosed illness. A sustainable global food system would phase out antibiotic use in livestock for growth promotion, and replace unsound use of antimicrobials through best practices in the production of healthy animals.

The amount of antimicrobials excreted in an active form in faeces and urine is highly variable. It is dependent upon the class of antimicrobial, the route of administration, drug formulation, and the health status of the animal in which it is used, and many other factors (Giguère, Prescott and Dowling 2013).

Table 1

**Summary of the major pollution sources affecting AMR in the environment**

| Major sources | Type and nature of potential environmental releases |
|---|---|
| Poor sanitation, sewage and waste effluent | • Preventable use of antimicrobials due to disease burden caused by poor WASH conditions<br>• Lack of sanitation or poorly functioning sanitation or fragmented systems (e.g. open defaecation, poorly contained pit latrines, septic tanks and sewers) that contaminate water sources and spread AMR<br>• Effluent from septic tanks and wastewater treatment plants<br>• Faecal sludge and wastewater biosolids<br>• Releases from unused drugs disposed of in toilets, bins or waste dumps<br>• Leaching from open waste dumps<br>• Urban runoff |
| Effluent and waste from pharmaceutical manufacturing | • High concentrations of antimicrobials in untreated effluent<br>• Residual antimicrobials in solid wastes discharged from pharmaceutical fermentation processes<br>• Resistant microbes in effluent if biological treatment is applied |
| Effluent and waste from healthcare facilities | • Antimicrobial products and residues in hospital solid wastes<br>• Resistant microbes (including those with more abundant and diverse ARGs) and antimicrobial residues (particularly antimicrobial compounds of last resort) in hospital wastewater/effluent |
| Use of antimicrobials and manure in crop production | • Fungicides, herbicides, heavy metals and antibiotics used in the production of food, feed and raw materials<br>• Untreated manure and wastewater that may contain pharmaceutical residues, ARGs and resistant microbes intentionally applied to soil and crops<br>• Inappropriate disposal of unused antimicrobials (e.g. fungicides) |
| Releases, effluent and waste in animal production | • Manure and effluent from aquatic and terrestrial animal production that may contain pharmaceutical residues, ARGs and resistant microbes<br>• Application of antibiotics and parasiticides in aquaculture that go directly into the environment<br>• Improper disposal of unused drugs |

Antimicrobials and co-selective agents (e.g. zinc and copper) used in animal production, as well as AMR in microbes and genes, pollute the environment where AMR selection, transmission and spread occur (Topp *et al*. 2018). Especially when these antimicrobials are those of critical importance and last resort in human medicine, this fact takes on clinical significance.

## Global trends and the climate crisis are shaping the environmental dimensions of AMR

AMR challenges cannot be understood or addressed separately from the triple planetary crisis of climate change, biodiversity loss and pollution and waste, all of which are driven by unsustainable consumption and production patterns (Cavicchioli *et al*. 2019; UNEP 2021b). 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. Unless swift action is taken to reduce these increases, they will result in greater environmental releases and concentrations of AMR relevant pollutants. Other important global drivers include transnational and intercontinental transport and movements of food, goods and people, all of which may contribute to the spread of AMR (Zhu *et al*. 2017).

The climate crisis has numerous impacts on ecosystems, human health, animal health and food production. Many of these impacts affect AMR (Global Leaders Group on Antimicrobial Resistance [GLG] 2021).


Figure 3

**Type of environmental AMR pollution sources and areas for prevention and treatment action**

Higher temperatures are associated with increased antimicrobial resistant infections (MacFadden *et al*. 2018; McGough *et al*. 2020), many diseases are climate-sensitive, and changes in environmental conditions and temperature may lead to an increase in the spread of many bacterial, viral, parasitic, fungal and vector-borne diseases in humans, animals and plants, many that have increasing resistance to antimicrobials (GLG 2021).

The climate crisis also contributes to the spread of AMR in the environment. More frequent and severe weather events and rising water tables, all of which may lead to flooding, can cause wastewater and sewage to overwhelm treatment plants, allowing untreated sewage rich in antimicrobial resistant microbes to contaminate surrounding communities with human and livestock faecal material (Kravchenko *et al*. 2018). 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 use of antimicrobials.

# 3 Overview of **environmental action needed**

The burden of AMR can be reduced. Solutions exist and can be implemented through international commitment – from specific prevention and mitigation actions and the promotion of sustainable production and consumption, to establishing ambitious targets and setting out clear visions for a global road map.

Environmental stakeholders have key roles to play in addressing AMR, for example developing strong and achievable regulatory frameworks to reduce AMR relevant discharges into the environment and promote sustainable production and consumption patterns, which balance population growth. While knowledge gaps remain, sufficient information is already available for stakeholders to act and include AMR as an issue of environmental concern. Doing so will require a range of new strategies and technologies tailored to specific sectors, as well as to financial/business, climate and cultural contexts. Regulatory, economic and, in some instances, cultural barriers will need to be overcome (Hernando-Amado *et al*. 2020).

To be better prepared to meet this global threat and to mitigate the environmental risks of AMR, stakeholder action should focus on four specific areas:

## 3.1 Enhance environmental governance, planning and regulatory frameworks

Include Ministries of Environment and environmental agencies in developing and implementing all national action plans (NAPs) to tackle AMR. Consideration of environmental regulations related to antimicrobial manufacturing, water, sanitation and hygiene standards (WASH), agricultural standards, solid waste management and infrastructure should be ensured.

Specific actions could include developing legislation, codes of good practice and policy guidance to support action to reduce and minimize environmental releases of AMR relevant pollutants, as well as strengthening research and innovation frameworks, transparency and accountability systems that allow consumers to hold producers accountable for prudent antimicrobial use.

## 3.2 Identify and target priority AMR relevant pollutants

Reduce releases of chemical and biological pollutants affecting AMR in the environment and address their origins. AMR National Action Plans and AMR sensitive environmental policy and plans need to be tailored to countries' public health and environmental issues, systems and frameworks, and sociocultural and economic realities (Collignon *et al*. 2018). There should be a focus on prevention and control measures, as well as on innovation (e.g. through green and sustainable chemistry), to reduce the AMR burden by curbing releases of pollutants into urban and rural environments including from important value chains.

Wastewater treatment and management at known sources of contamination (e.g. sewage systems, livestock production, hospitals and pharmaceutical manufacturing sites) can reduce the number of antimicrobial resistant microbes and gene concentrations. Prioritising the most suitable waste treatment and management options that compliment local civil infrastructure and resources are critical to tailored solutions (Graham, Giesen and Bunce 2019). The environmental application of antimicrobials such as fungicides, antibiotics and antivirals in plant-based food production systems needs to be reduced through measures such as integrated pest management.

## 3.3 Improve reporting, surveillance and monitoring

As part of plans to mitigate discharges of antimicrobials into the environment, it is essential to measure the impact of antimicrobial pollution on biodiversity and integrate environmental monitoring data (e.g. from monitoring of surface water, solid waste and airborne particulate matter) with existing AMR surveillance and pollutants data. Risk profiles to establish how likely AMR relevant pollution is to occur may also be built into surveillance methodologies based on other monitoring systems (e.g. stewardship programmes), and approaches standardised around the world (Hassoun-Kheir *et al*. 2021).

Systems for transparent and swift collection and reporting of the production, sales, use and disposal of unused or expired antimicrobials should also be strengthened. Releases of antimicrobials, resistant microbes and their genetic material to the environment, and their impact on biodiversity need to be documented (e.g. through national Pollutant Release and Transfer Registers).
Also documented should be the safety of bioproducts (e.g. biofertilizers, bioplastics, biosolid and manure applications, and plant growth promoters) and novel agricultural practices, as well as documenting key sources of pollution that indicate an impact on AMR in the environment.

## 3.4 Prioritize financing, innovation and capacity development

Ministries of Environment need to introduce innovative and sustainable financing to address AMR. This could include the elimination of distorting subsidies in agriculture, sustainable public procurement, social and green bonds, and exploring the possibility to include AMR in initiatives such as the Taskforce on Nature-related Financial Disclosures. It is also important to encourage public and private sector collaboration, and to realign incentives in key value chains to curb unnecessary use of antimicrobials.
A clear business case needs to be made for investment, including the investment of domestic resources, in cost-saving or alternative technology approaches that reduce environmental AMR risks.

Box 2

**Knowledge Gaps**

We already know enough to act, but what key knowledge gaps remain to help better understand and address the problem?

While actionable evidence of the importance of the environmental dimensions of AMR has been mounting, some key data and knowledge gaps remain, including on interlinkages and negative feedback loops that increase AMR proliferation in the environment. This hinders systematic priority-setting and the selection of cost-effective, context-specific mitigation action. Additional data on the following topics would enhance and facilitate systematic priority setting and decision making:

- studies to assess the global burden of AMR, particularly improving fungal and viral disease reporting to align with recent antibiotic-resistant mortality estimates, including improvements to understanding infection emergence and spread from environmental sources;
- the relative importance (exact nature and magnitude) of each pollution source in causing global and regional exposure (World Economic Forum 2021), the relative impact on AMR in the environment and in local and specific ecosystem contexts;
- the type, quantity and dynamics of environmental releases of chemicals (e.g. with co-selection potential) and biological pollutants (e.g. rich in resistant microbes) that affect AMR development, transmission and spread in local environments or specific conditions;
- identification and characterization of the risk to biodiversity and ecosystems arising from anthropogenic antimicrobial resistance in the environment;
- a more comprehensive understanding of the concentrations of antimicrobials, metals, biocides and other pharmaceuticals, as well as chemical compounds (e.g. microplastics) — found in pollution in the environment — that play a role in selection, co-selection and maintenance of AMR where resistance already exists;
- the phylogeny and potential environmental origin of ARGs to aid understanding of the additional factors that can prevent or delay the emergence of new ARGs in pathogens;
- the role of the environment as affected by human activity (e.g. pollution) on the evolution (mobilization, selection, transfer, persistence etc.) of antimicrobial resistant microbes
- the technological, social, economic and behavioral interventions that will be effective to mitigate the development and spread of antibiotic resistance via the environment

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

# 4 **Concerted international environmental action** is imperative

This report demonstrates the immediate need for ambitious, collaborative action by all stakeholders, but especially Ministries of Environment, to prevent and minimize the adverse impacts of environmental pollution in exacerbating the global AMR crisis. Given all the synergies, such action will impact and create co-benefits within all 'One Health' sectors and contribute to achieving the Sustainable Development Goals (SDGs).

UNEP has placed the triple environmental crises of climate change, biodiversity loss and pollution at the heart of its work, and UNEP's Medium-Term Strategy for 2022-2025 seeks to deliver a transformational change for people and nature. The latter includes antimicrobial resistance among the topics to focus on. Therefore, UNEP remains committed to continuing working at global, regional and country levels to support the implementation of the measures to address AMR. Focus on tackling AMR will not only help deliver this change but will also contribute to the achievement of Agenda 2030 and the SDGs.

The public sector has an important role to play, not only in regulating these pollutants and their sources, but also in putting in place enabling policies and actions. Although some private sector actors have taken first steps to control the environmental dimensions of AMR, considerable additional work is required.

Further research will provide more data and evidence to better understand the complex dynamics of AMR and will lead to improved science-policy interfaces to ensure informed decision-making.

However, despite evidence being limited there is enough knowledge to act now. Human action is responsible for worsening AMR, but also has the potential to mitigate it.

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