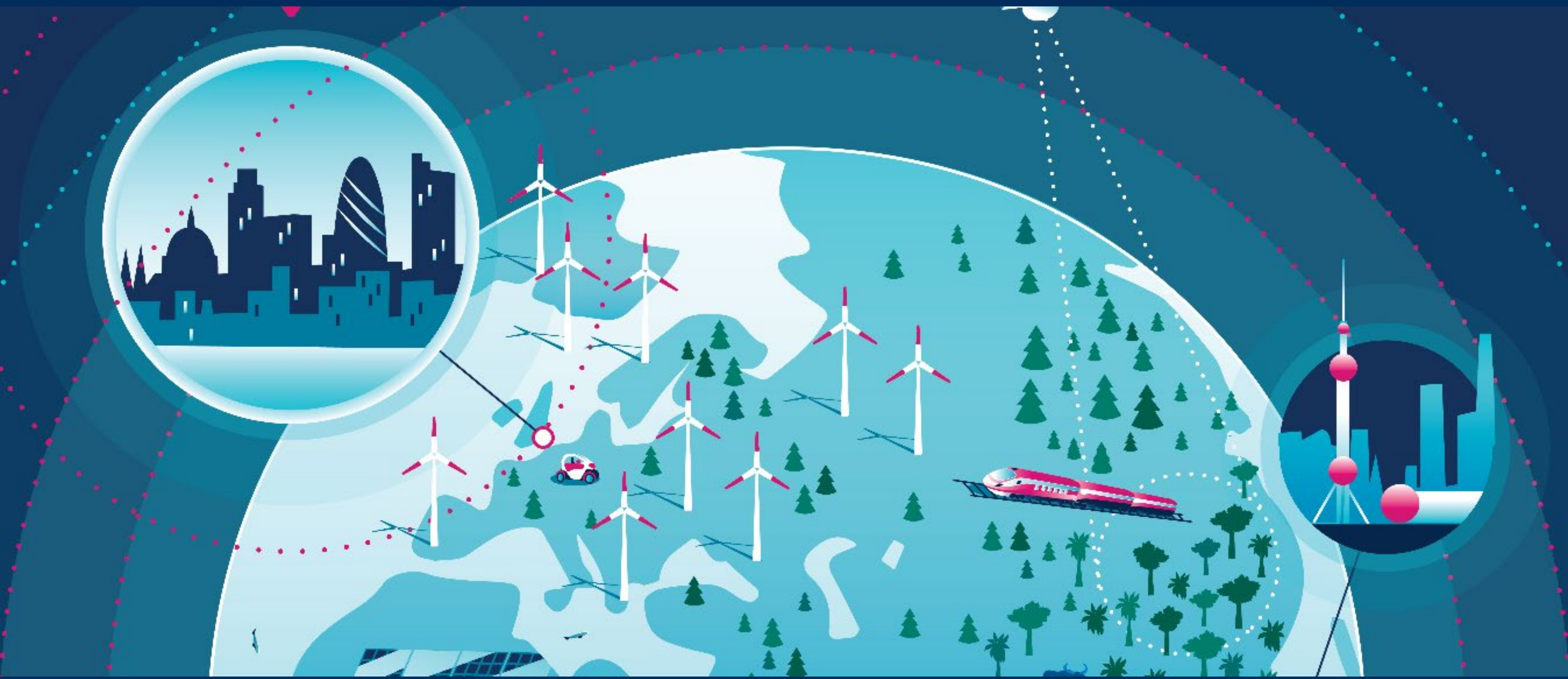
The costs and risks of AMR water pollution



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Executive Summary

Antimicrobial resistance (AMR) from water pollution is a major global health challenge. Antimicrobial drugs play an essential role in healthcare systems around the world – since their discovery, many infectious diseases that were once leading causes of death can now be treated straightforwardly. But they are losing their effectiveness due to the development of AMR, with between 2.4 and 10 million additional deaths per year by 2050 expected as a result. Water pollution and management strategies can have a pivotal effect on the rapidity of AMR development and the outcomes this leads to, but the relative importance of various impact channels and management options remains poorly understood. This paper aims to provide a basis for more effective action to address AMR in water by providing an accessible overview of how AMR causes risks and an assessment of the importance and distribution of this risk across the world.

AMR risk is a product of pollutant discharges and socioeconomic vulnerability. *Discharges* into waterbodies result from human consumption of antimicrobial drugs in healthcare systems and the community, animal consumption in agriculture, and the manufacture of antimicrobial drugs. *Vulnerability* then reflects the rate at which AMR propagates, the rate at which humans are exposed to it and the effect this has on their health. Key vulnerability factors are environmental, for example the temperature and quality of receiving water bodies, and societal, notably population density and the efficacy of water sanitation and hygiene (WASH) in mediating human contact with polluted water. The availability of 'last resort' antimicrobials, a product of research and investment by the pharmaceutical industry, can determine the resulting clinical outcomes.

Risk is expected to become increasingly concentrated in the Global South over the next ten years, but it will always remain a global phenomenon (Table 1). This reflects a number of trends:

- **Sustained growth in human and agricultural use of antibiotics will drive increased discharge globally**. Clinical use of antibiotics is projected to grow 28% by 2030, while rates of agricultural use are expected to increase 50% from 2013 to 2030. This will entail significant growth in manufacturing, which is expected to remain concentrated in India and China.

- **Variable progress in increasing WASH means many countries will remain highly vulnerable, particularly in Sub-Saharan Africa**.

- **Broader economic and environmental trends are expected to exacerbate risk**. Migration towards urban areas and increasing water stress, both of which are expected to be most rapid in the Global South, serve to raise risks. Global trade and mobility will continue to transmit infections across borders, ensuring that risk remains a global phenomenon.

- **The development of novel antimicrobial drugs to provide last resort care remains slow,** being regarded as unprofitable by manufacturers.

Table 1 Growth and changes in risk by 2030

	Hospital & community use		Agricultural use		Sanitation services	
Country	DDD/1m	2030 growth	Tonnes/100ht	2030 growth	Access gap	2030 gap
Bangladesh	4.1		2.20		52%	
Brazil	6.8		2.73		12%	
China	3.1		14.80		15%	
Ethiopia			1.21		93%	
India	5.0		1.47		40%	
United States	10.3		2.34		0%	

Note: For hospital and agricultural use, red cells indicate growth of greater than 10% and green cells indicate growth of less than -10%. For sanitation services, red cells indicate a gap in access of greater than 10% and green cells indicate a gap in access of less than 5%.
Source: Vivid Economics

If these trends are left unchecked, the impacts will be severe and unaffordable in many countries. Analysis for this study projects the effect of AMR pollution in water on the duration and quality of life up to 2050 to be equivalent to 25% of the total global burden of malaria and tropical diseases and more than the combined annual burden of conflict and terrorism, maternal disorders and natural disasters. Standard approaches to monetising these impacts value them at $340-680 billion per year. The costs to healthcare systems in managing the disease burden associated with AMR in water, which are concentrated in some of the world's poorest countries, will in many cases be unaffordable: in Somalia, for example, they will amount to 2% of the country's GDP.

High risk countries face much graver downside scenarios, in which waterborne AMR causes epidemics that overwhelm healthcare and economic systems. An illustrative case study shows how an epidemic of resistant cholera could affect Bangladesh. Based on data from real events, an adverse outbreak could plausibly cause 700,000 infections and 140,000 directly attributable deaths, swamp the capacity of the country's healthcare system, devastate a fishing sector that supports 18 million jobs, and cause major societal disturbances, with pressure for mass migration away from cities and severe risks to food security.

The effective management of risks entails action to address discharges and vulnerability, along with efforts to improve risk understanding. The scale and interconnectedness of AMR water contamination calls for a comprehensive, multi-sectoral response, including 'upstream' and 'downstream' interventions as well as enhanced data collection and research.

- Upstream interventions include regulatory and incentive measures to promote prudent use of antimicrobials and encourage responsible manufacturing practices. Options to curtail clinical overuse of antimicrobials are low, and in some cases zero cost, with an ambitious global programme costing only $4-9 billion per year, while evidence from Denmark suggests that reductions in agricultural use of the order of 10-25% can be achieved without a loss in competitiveness. Green procurement, which can incentivise responsible manufacturing along international supply chains, has been pioneered by Swedish health authorities and could be adopted internationally. Public-private partnerships, such as the US's CARB-X and the EU's New Drugs for Bad Bugs initiatives, can incentivise the development of novel antimicrobials, leveraging the research capacity of the pharmaceutical industry.

- Downstream interventions, while costly, are required to attain development goals. Improved access to WASH is critical to reducing vulnerability to AMR – and in any case is a global development priority, enshrined in SDG 6. While the costs of meeting global targets are substantial, estimated at $13-$47 billion annually, the benefits are large and pervasive, ranging from reduced AMR risk to improved nutrition, and higher rates of school attendance.

- Improved data can improve understanding and monitoring of risk. The case for interventions to reduce AMR risk is already clear, but further data would allow enhanced monitoring of risk and attribution to its sources, the latter potentially creating liabilities for irresponsible users and manufacturers. Further data can support scientific research into poorly understood aspects of AMR risk, such as 'cocktail' effects as AMR mixes with other pollutants and the effect of AMR on the natural environment.

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Table 2 List of abbreviations used in this report

Abbreviation	Description
AMR	Antimicrobial resistance
ARG	Antimicrobial resistant gene
COVID-19	Coronavirus disease 2019
DALY	Disability Adjusted Life Year
DRM	Disaster risk management
GDP	Gross Domestic Product
GIS	Geographic Information Systems
HGT	Horizontal gene transfer
LMIC	Low- and medium-income country(ies)
NAP	National action plans (for antimicrobial resistance)
OECD	Organisation for Economic Co-operation and Development
SDG	Sustainable Development Goal(s)
UV	Ultraviolet
WASH	Water, sanitation, and hygiene
WHO	World Health Organisation

Source: Vivid Economics

1 Introduction

1.1 Context and objective

There is widespread recognition that anti-microbial resistance (AMR) is a material and increasing risk to global healthcare systems. Since their discovery, antimicrobials have steadily been losing their effectiveness through the development of AMR. Globally, resistant diseases are projected to kill 2.4 to 10 million people per year by 2050[1][2]. In countries where wastewater treatment and sanitation services are not universal, water is one of the primary vectors for the spread of resistant diseases.

However, there remains a lack of accessible evidence on the nature and magnitude of risks that stem from AMR in water and how these risks can be managed. Investors and policy makers face a lack of clarity on the relative importance of water pollution in spreading AMR and how this can cause economic and societal impacts across regions and sectors. This lack of clarity is a fundamental impediment to effective action to manage risks.

The contribution of this report is to provide a consolidated account of the risks associated with AMR in water that can form the basis for public and private action. This report sets out:

- **Global assessment of drivers of AMR risk in water**, highlighting key sectors and geographies. These are projected forward to 2050 and consolidated in a global risk index.
- **Global economic assessment of 'normal year' impacts** of AMR water pollution, in order to make AMR comparable with other water pollutants.
- **Local economic assessment of 'adverse year' impacts,** highlighting the much greater severity of impacts in an adverse, but plausible, case where AMR causes an epidemic that overwhelms local healthcare capacity.
- **Assessment of management options,** their costs and models for public and private sector implementation.

1.2 Structure of report

The rest of the report is structured as follows:

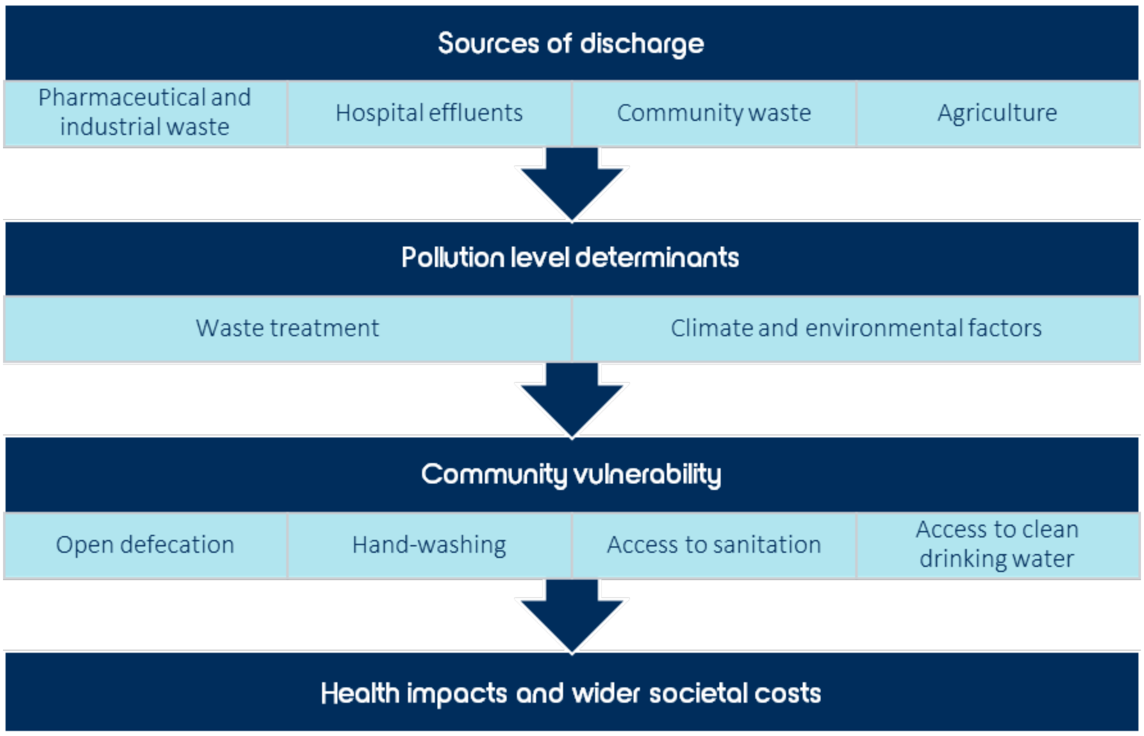
- Chapter 2 outlines key risk factors for AMR water pollution impacts and assesses these globally;
- Chapter 3 details findings from economic analysis of the global impacts of AMR water pollution to 2050;
- Chapter 4 reviews the costs and benefits of taking action to tackle the global challenges of AMR water pollution and concludes with ways forward.

[1] World Bank, "Drug-Resistant Infections: A Threat to Our Economic Future."
[2] OECD, *Stemming the Superbug Tide*.

2 Global risk assessment

The risk from water-borne AMR is the product of a variety of sources of pollution discharge and numerous vulnerability factors. This section disentangles this causal chain following the structure depicted in Figure 1, summarising current scientific understanding of the critical factors that determine AMR risk, and reviewing the global distribution, trends and drivers of these risk factors. It concludes by presenting a global risk index that consolidates diverse sources of data on AMR risk for all countries in the world, thus setting the scene for the assessment of impacts in the next section.

Figure 1 Conceptual link between sources of discharge and risk to communities



Note: Discharge includes microbes, antimicrobials, chemicals, and heavy metals which promote the development of resistant genes

Source: Vivid Economics

Box 1 Introduction to antimicrobial resistance

In this report, AMR water pollution encompasses resistant microbes, pathogens, genetic elements, or drivers of resistance which enter or develop in environmental waters.

Microbes are tiny organisms that include bacteria, fungi, and viruses. While most are not harmful, some microbes are pathogens that can have detrimental effects on human health.

Modern medicine relies on antimicrobial drugs, including antibiotics, antivirals, and antimalarials to control various conditions. Antimicrobials work either by killing microbes or preventing them from multiplying. By allowing effective treatment of common infections, antimicrobials have – where they are available – facilitated sweeping advances in health and wellbeing. Before the advent of antimicrobials, the leading causes of death were infectious diseases and the average life expectancy at birth was less than 50 years old[3]. Diseases which formerly were leading causes of death are now easily treated with antimicrobials. For example, scarlet fever was a leading cause of childhood death in the 19th and early 20th centuries, with case fatality rates as high as 20 to 30%. Prior to the development of antibitoics, there were as many 350 cases and 18 deaths per 100,000 people in England and Wales per year. Since the 1940s, the mortality rate of scarlet fever has dropped to nearly zero in the UK. Even in a recent outbreak where cases reached nearly 50 per 100,000 people, no deaths were recorded.[4]

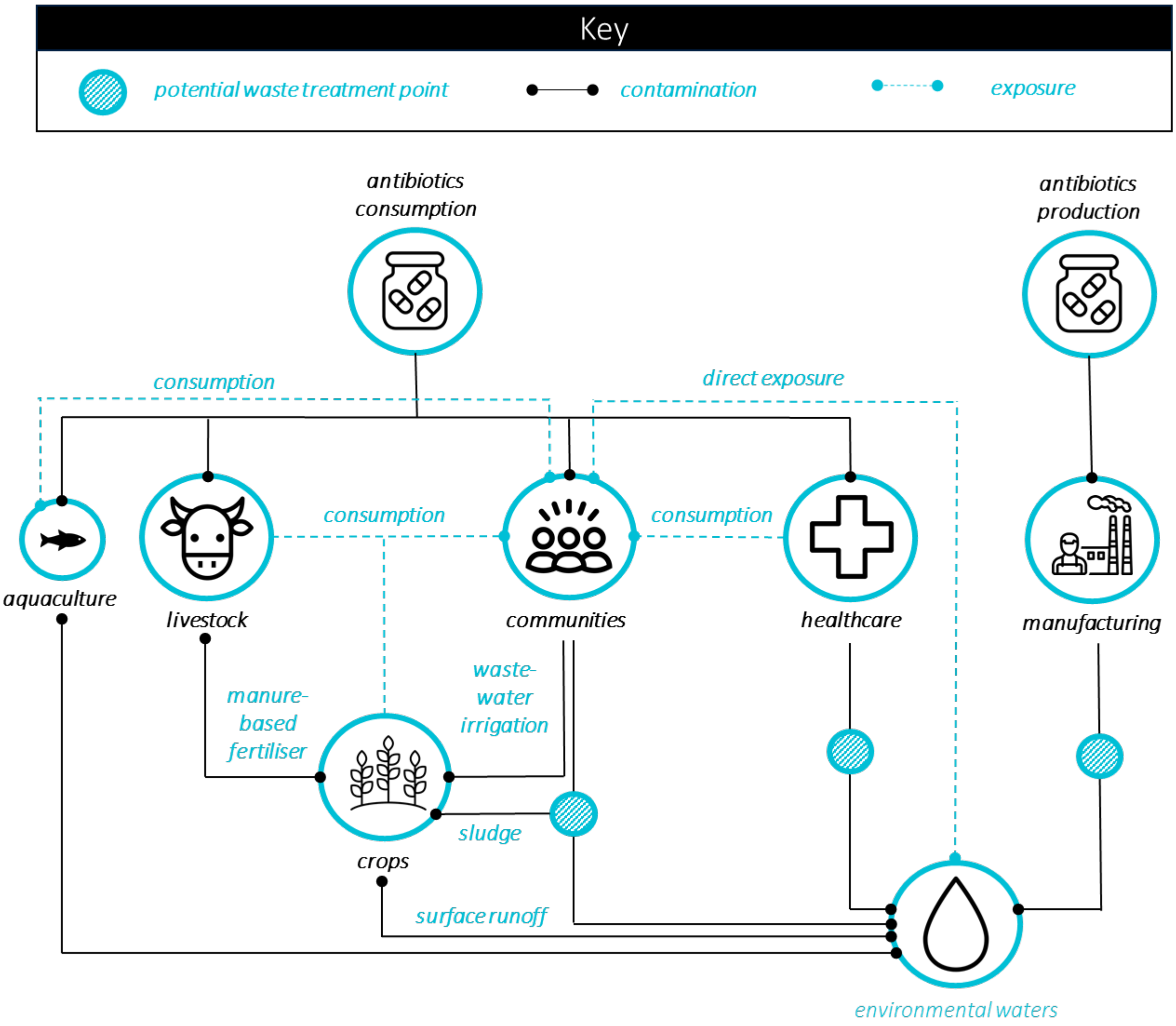
AMR causes these critical drugs to become ineffective. Antimicrobials lose their effectiveness as a result of a process of natural selection, where microbes develop genetic mutations that allow them to withstand antimicrobial therapies. As antimicrobials stop working, new drugs can be developed to take their place. However, few new drugs have been produced in the last 30 years[5].

2.1 Sources of discharge

Hospital and community wastes, agricultural runoff, and by-products from pharmaceutical manufacturing are the main sources of AMR contamination in aquatic environments. Figure 2 highlights how these sources of discharge and a series of many interconnected feedbacks give rise to human exposure to AMR. A widespread lack of monitoring means the relative importance of each channel in causing exposure is poorly understood at the global level – and in any case the relative importance of the channels will vary between regions.

[3] WA., "The Treasure Called Antibiotics."
[4] Lamagni et al., "Resurgence of Scarlet Fever in England, 2014–16: A Population-Based Surveillance Study."
[5] The UK R&D Centre for Antimicrobial Resistance, "This Is a Global Problem with Resistance Spreading Ever More Quickly."

Figure 2 There are feedbacks between AMR water contamination and sources of human and animal exposure



Note: Adapted from the Swiss Federal Institute of Aquatic Science and Technology[6]
Source: Vivid Economics

2.1.1 Hospital and community wastes

AMR pollution in contaminated faecal matter enter waterways through community or hospital wastewater. This is caused initially by the consumption of antibiotics, as between 30% and 90% of oral antibiotic doses are excreted as active substances[7][8]. Where wastewater treatment fails to prevent this entering waterbodies, close contact with polluted waters can then result in a cycle of consumption and excretion. While rates of resistant bacteria in faecal matter vary widely in community wastes, rates are particularly high in hospital effluents [9][10]. However, the relative importance of hospital and community waste streams in the development and spread of AMR is poorly understood.

[6] Burgmann, "Antibiotic Resistance as an Emerging Environmental Contaminant."
[7] OECD, "Pharmaceutical Residues in Freshwater."
[8] OECD.
[9] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[10] Wellcome Trust.

Discharges through community and hospital waste are expected to grow in line with consumption of antibiotics, which is expected to increase by 28% by 2030. Antibiotic consumption remains highest in developed countries where access to medicines is more widespread. Growth, however, is fastest in lower and middle income countries (LMICs), where use is increasing in healthcare systems. In part this reflects progress in increasing the coverage of basic healthcare services for those who would otherwise lack access to them. But in many cases it reflects weaknesses of healthcare systems, where clinicians can lack sound diagnostic capabilities or face incentives to over-prescribe – or a lack of control over antibiotic distribution, particularly where antibiotics are widely available over the counter or through unlicensed outlets[11][12][13]. Limited data monitoring in LMICs may understate current levels of usage in many countries: for instance, a survey of residents in a Kenyan community found that 90% of respondents recalled using antibiotics in the past year, significantly more than official data would suggest[14].

2.1.2 Food production

Practices in agriculture and aquaculture contribute to AMR pollution in water through four key pathways, as illustrated in Figure 2. These are:

- **Use of antimicrobials in livestock**: antimicrobials are used to prevent infection and enhance feed conversion and growth in livestock.[15][16] Livestock that have been treated with antibiotics excrete 90% of the dose as a live substance, which can enter water bodies through surface run-off.[17]

- **Use of antimicrobials in crops:** antimicrobials are used to treat and prevent infection in crops, which leads to water contamination through surface runoffs.

- **Use of wastewater and sludge**: community wastewaters that may contain AMR are commonly used to irrigate fields, with at least 10% of the global population consuming food irrigated by wastewater [18][19]; sludge, a by-product of community wastewater treatment that can contain AMR, is often applied to fields as a fertiliser.

- **Use of antimicrobials in aquaculture:** antimicrobials also play an important role in aquaculture, which now supplies more than half of all seafood [20][21]. This is particularly likely to give rise to AMR pollution in freshwater-based aquaculture systems, where bacteria are more widespread.

Livestock treatment comprises the bulk of antimicrobial use by volume. China, the United States and Brazil consume the most antimicrobials for agriculture. In the United States, 70% of antibiotics sold are consumed by livestock. China consumes disproportionately more than the rest of the world. In 2013, Chinese agriculture consumed more than eight times the volume in the US and more than twelve times the volume in Brazil. Even accounting for the size of the sector, Chinese agriculture consumes antibiotics at higher intensities: by hectare, China consumed more than seven times the amount of antibiotics used in US agriculture[22].

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[11] Denyer Willis and Chandler, "Quick Fix for Care, Productivity, Hygiene and Inequality: Reframing the Entrenched Problem of Antibiotic Overuse."
[12] Denyer Willis and Chandler.
[13] CDDEP, "The State of the World's Antibiotics 2015."
[14] Omulo et al., "Evidence of Superficial Knowledge Regarding Antibiotics and Their Use: Results of Two Cross-Sectional Surveys in an Urban Informal Settlement in Kenya."
[15] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[16] Zhu et al., "Diverse and Abundant Antibiotic Resistance Genes in Chinese Swine Farms."
[17] CDDEP, "The State of the World's Antibiotics 2015."
[18] World Health Organization, "Sanitation: Key Facts."
[19] World Health Organization.
[20] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[21] Wellcome Trust.
[22] Van Boeckel et al., "Reducing Antimicrobial Use in Food Animals."

Antibiotic consumption by livestock is expected to increase with the demand for animal protein, particularly in LMICs. Use of antibiotics in animal agriculture is projected to grow by about 50% globally by 2030 relative to 2013 levels[23] due to population growth and changes in dietary preferences.

2.1.3 Pharmaceutical manufacturing

Pharmaceutical manufacturing processes can release effluents directly into local waterways, resulting in localised 'hotspots' of high levels of AMR pollution[24][25]. China and India manufacture between 80 and 90% of the world's antibiotics, supplying very large domestic markets as well as around 70% of global exports[26]. The scale of effluent release from these facilities is not understood clearly given lack of systematic monitoring or reporting, but detailed investigations of supply chain management have revealed evidence of dumping, while localised hotspots of AMR in rivers near manufacturing sites are well documented[27][28].

Recent trends suggest that pharmaceutical manufacturing will increasingly be concentrated in China and India. Brazil, Spain and Italy are also significant players in the global market but have seen declines in market shares[29]. Between 2008 and 2012 Chinese production increased at 11% annually and India, which relies to a larger extent on exports, saw sales to the US grow at a rate of 44% annually[30].

2.1.4 Wastewater treatment

Wastewater treatment practices mediate how much antimicrobial discharge or other drivers of resistance reach aquatic systems. Wastewater treatment encompasses a wide range of technologies, from basic sanitation, such as pit latrines or septic tanks, to advanced tertiary wastewater treatment facilities where wastewater is processed to be fit for reuse. Modern waste treatment processes are designed to remove conventional pollutants such as nutrients, organic matter and pathogens, as opposed to AMR[31], so while all available technologies reduce AMR contamination, none eliminates it[32][33]. Advanced wastewater treatment facilities can produce AMR-contaminated sludge as a by-product, which without advanced treatment, for example using biochar technologies, can spread AMR in the environment through application to land[34][35].

Pollution levels are driven by wastewater treatment availability. The water pollution risk map in Figure 3 shows a composite rating across agricultural and community antibiotic consumption, pharmaceutical manufacturing levels and wastewater treatment availability. China and India have both high levels of discharge and low levels of treatment have the highest pollution risk. Highly developed countries including the EU and the US have higher levels of antibiotic consumption, but pollution risk is mediated by high quality and widespread use of wastewater treatment technologies. Conversely, some countries in Africa and Russia are at higher risk of pollution despite lower levels of antibiotic consumption or production, due to limited wastewater treatment.

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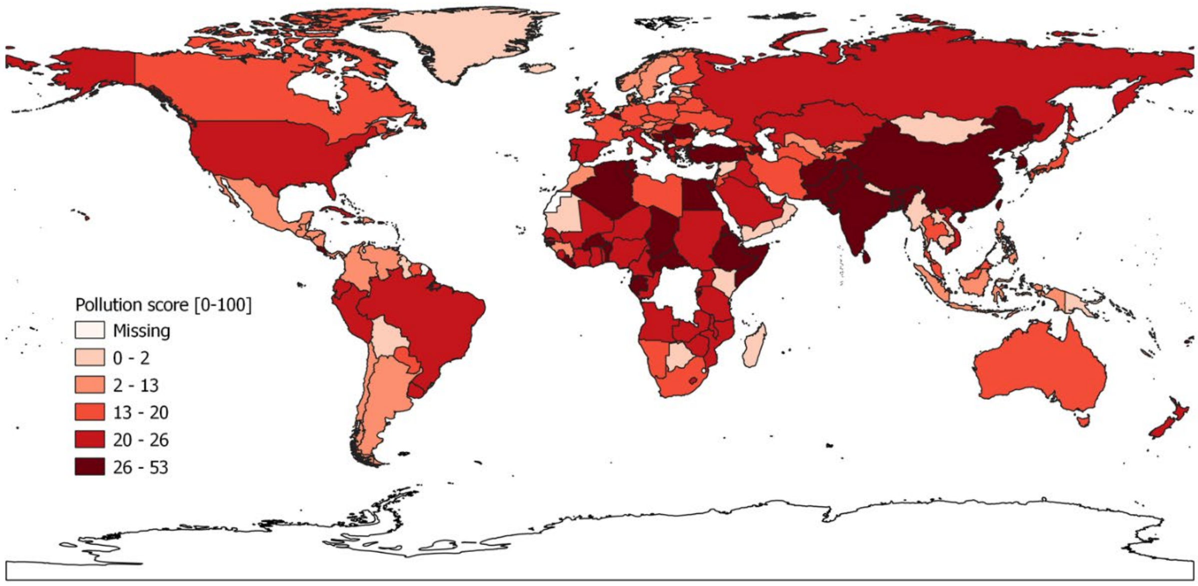
[23] Van Boeckel et al.
[24] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[25] Wellcome Trust.
[26] Changing Markets, "Superbugs in the Supply Chain: How Pollution from Antibiotics Factories in India and China Is Fuelling the Global Rise of Drug-Resistant Infections."
[27] AMR Industry Alliance, "2020 Progress Report."
[28] AMR Industry Alliance.
[29] Van Arnum, "A Shifting Landscape for the Global API Market," 2013.
[30] Van Arnum, "A Shifting Landscape for the Global API Market," 2013.
[31] WHO, "Environmental Aspects of Good Manufacturing Practices: Points To Consider for Manufacturers and Inspectors in the Prevention of Antimicrobial Resistance."
[32] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[33] Wellcome Trust.
[34] Zhu et al., "Soil Biota, Antimicrobial Resistance and Planetary Health"; FAO/WHO, "Joint FAO/WHO Expert Meeting in Collaboration with OIE on Foodborne Antimicrobial Resistance: Role of the Environment, Crops, and Biocides."
[35] Zhu et al., "Soil Biota, Antimicrobial Resistance and Planetary Health"; FAO/WHO, "Joint FAO/WHO Expert Meeting in Collaboration with OIE on Foodborne Antimicrobial Resistance: Role of the Environment, Crops, and Biocides."

Figure 3 Pollution is determined by clinical use, agricultural use, manufacturing, and mediated by whether wastewater treatment systems are in place [2020]



Note: The pollution score combines a country's average ratings across sources of discharge and connection to wastewater treatment.

Source: Vivid Economics

2.2 Vulnerability to AMR

Vulnerability factors determine the risk associated with a given level of AMR discharge. These include features of the aquatic environment into which AMR is discharged, as well as socioeconomic factors that affect the ways in which populations interact with AMR and the impact this has on them.

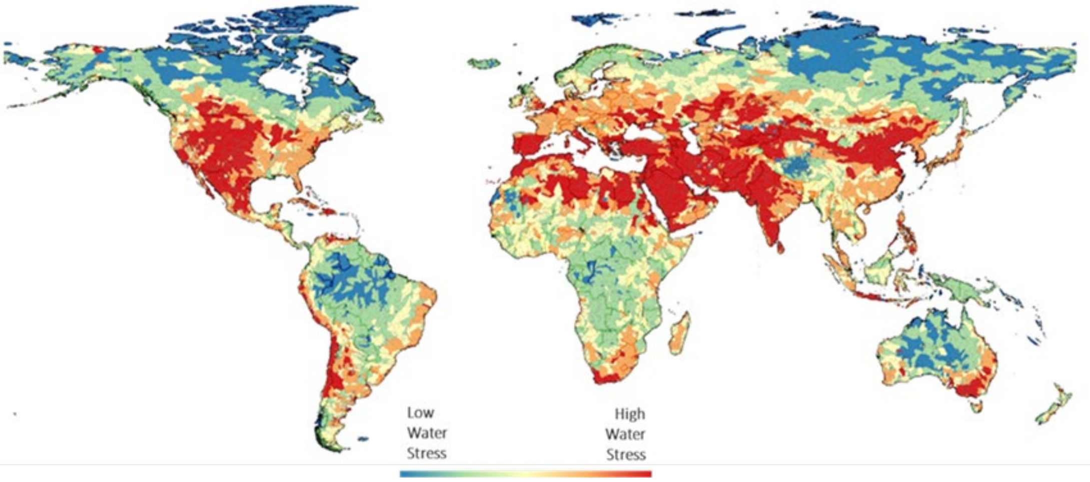
2.2.1 Environmental factors

The volume, temperature and quality of water into which AMR is discharged can all affect the spread of AMR in the receiving water. Warmer, more concentrated water bodies that contain additional pollutants are thought to be more amenable environments for AMR to develop, though the scientific processes that govern this are complicated and depend on other contextual factors[36].

Economic and climatic trends are expected to increase environmental vulnerability factors. Demand for water is set to expand by 40-50% in the food system, 50-70% in industry and municipal supply, and 85% in the energy system by 2050[37] while water availability is expected to become more volatile and water temperatures increase as climate change takes hold. The same economic trends behind increased water demand also give rise to pressures on water quality, with increased flows of wastewater. As Figure 4 below highlights, future water stress is expected to be most acute in India, northern China, the western United States, the Middle East and Central Asia.

[36] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[37] Maweni and Bisbey, *A Financial Recovery Plan for Vietnam Electricity*.

Figure 4 Projected global baseline water stress in 2040 reaches extreme levels across much of the world



Source: Vivid Economics, based on WRI Aquaduct Database

2.2.2 Socioeconomic factors

Socioeconomic factors determine the impact on humans of the presence of AMR in water bodies. They include the following:

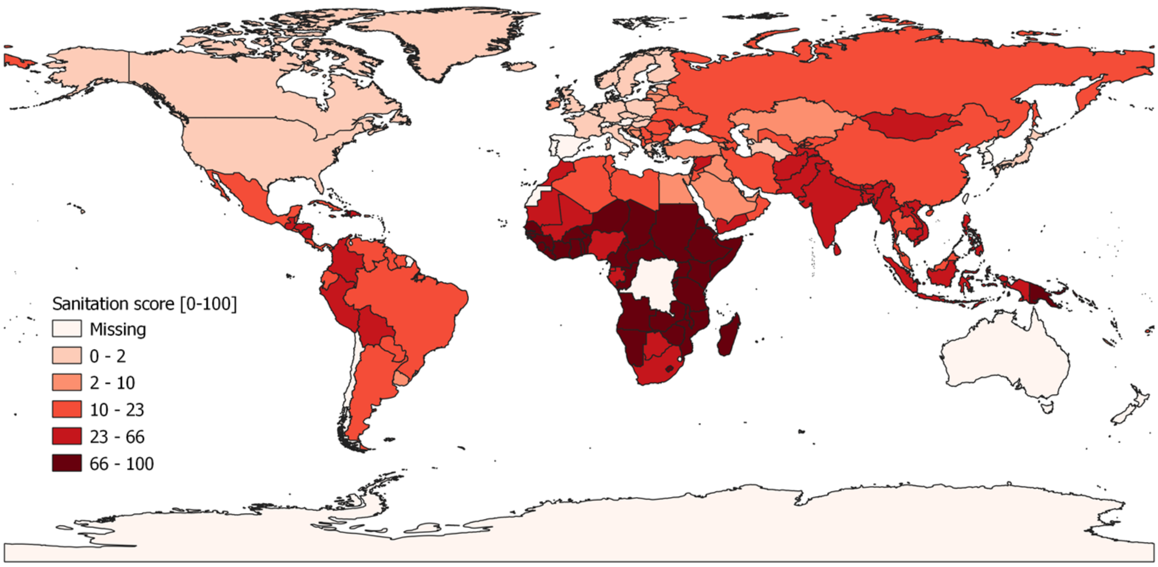
- **Water, sanitation, and hygiene (WASH) access**: Limited WASH access can greatly exacerbate the feedback loop between antibiotic consumption, excretion, contact and further consumption. Open defecation or the use of pit latrines means AMR can enter water bodies that are used by households for drinking and washing, by farmers for irrigation, or that communities come into regular contact with, for example through children playing. Where communities do not have access to handwashing facilities or are not educated in their use, this contact with AMR is much more likely to lead to its consumption[38][39].
- **Density and formality of settlements:** In dense settlements, local feedbacks between consumption and further exposure are intensified and spread around a larger population. The impacts of this can be particularly adverse in informal settlements, where access to basic services is most limited.
- **Trade and mobility.** People and animals serve as reservoirs for AMR, which means that outbreaks of resistant disease in one part of the world can transmit globally. Travel, trade, and even wildlife migratory patterns contribute to this spread[40][41].
- **Performance of the healthcare system.** At a local level, access to healthcare facilities generally improves the health outcomes associated with resistant and non-resistant infections. However, hygiene practices in hospitals can affect whether infections that emerge in one locality spread more widely[42].
- **Availability of novel antimicrobial drugs**. As explained in Box 1, the healthcare system develops and manages the use of novel antimicrobial drugs, which can be used to treat resistant infections that emerge.

[38] Allegranzi et al., "Burden of Endemic Health-Care-Associated Infection in Developing Countries: Systematic Review and Meta-Analysis."
[39] Graham, Giesen, and Bunce, "Strategic Approach for Prioritising Local and Regional Sanitation Interventions for Reducing Global Antibiotic Resistance."
[40] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."
[41] Wellcome Trust.
[42] Wellcome Trust.

While significant, albeit patchy, progress is expected on improving access to basic services, demographic pressures will tend increase vulnerability, particularly in the global South. According to the World Health Organisation (WHO), 2 billion people do not have access to basic sanitation services[43]. While this is expected to improve – 50 countries where open defecation is currently practised are expected to eliminate it by 2030 – progress is contingent on sustained investment and is not expected to be comprehensive, with significant populations in 66 countries projected to lack access to toilet facilities. Many of the countries that face the greatest challenges in WASH and healthcare delivery are also likely to experience very rapid, often informal urbanisation[44][45], raising their vulnerability.

Global risks will increase without an acceleration in the development of new drugs. So-called 'superbugs,' or multidrug resistant pathogens, are already causing significant mortalities globally: in the United States, two million infections per year fail to respond to first-line treatments[46]. A recent lack of development of new drugs to treat novel resistant infections means this risk is increasing[47].

Figure 5 Overall WASH gaps are starkest in Sub Saharan Africa, but remain in South Asia and South America as well [2020]



Note: The sanitation score is based on the worst-performing sanitation indicator to account for the fact that a sanitation system is only is strong as its weakest component. The indicators included in this metric are access to hand-washing, prevalence of open defecation, access to basic sanitation, and access to clean water.

Source: Vivid Economics

2.3 Overall risk of AMR incidence

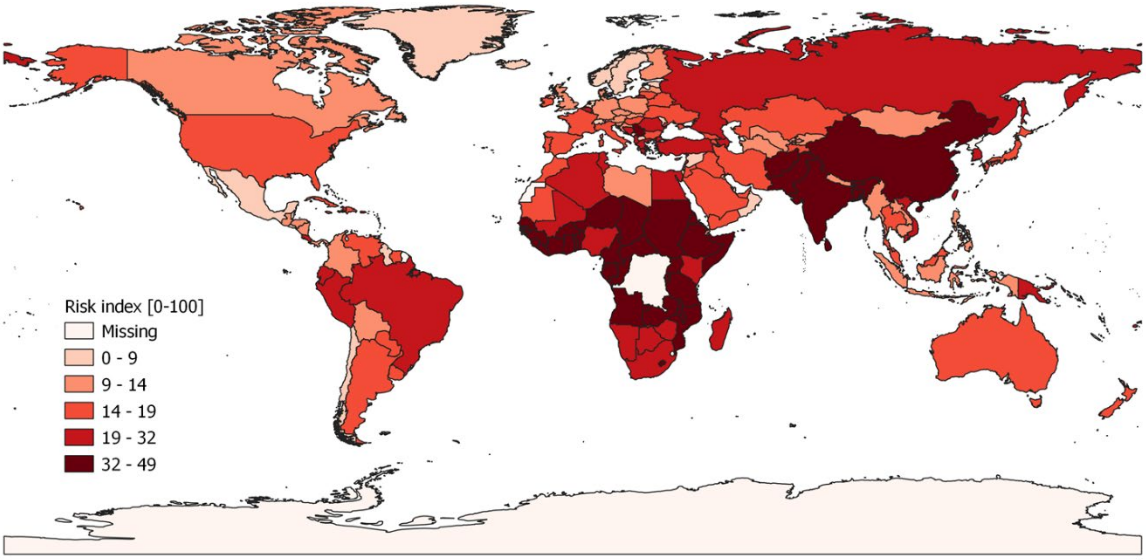
2.3.1 Current risk

Risk due to waterborne AMR is concentrated in the global South. The risk index displayed in Figure 5 capture some, though not all, of the factors that determine discharge and vulnerability laid out in Sections 2.1 and

[43] WHO, "Drinking-Water."
[44] Jones, Cummings, and Nixon, "Services in the City: Governance and Political Economy in Urban Service Delivery."
[45] Jones, Cummings, and Nixon.
[46] US CDC, "Antibiotic Resistance Threats in the United States."
[47] The UK R&D Centre for Antimicrobial Resistance, "This Is a Global Problem with Resistance Spreading Ever More Quickly."

2.2.[48] India and China stand out as high-risk for particularly high pollution levels, given rates of manufacturing and agricultural and clinical use in these countries. Nearly all of Sub-Saharan Africa is in the highest or second highest quintile of risk, driven largely by lack of access to WASH and sanitation.

Figure 6 The risk index highlights where effluent loads are high and lack of wastewater treatment and sanitation put communities at risk [2020]



Note: The risk index, as constructed, is intended to highlight regional variation within the same year, not necessarily to compare levels of risk between years.

Source: Vivid Economics

Risk factors are expected to become increasingly consolidated in the Global South over the next ten years. While discharges are projected to increase overall, existing trends predict widening disparities in risk between countries that improve access to WASH and those that do not.

- **Sustained growth in human and agricultural use of antibiotics will drive increased discharges, particularly in manufacturing hubs**. Clinical use of antibiotics is projected to grow 28% by 2030, while rates of agricultural use are expected to increase 50% from 2013 to 2030. This will entail significant growth in manufacturing, which is expected to remain concentrated in India and China. The effect of this on discharges into waterbodies will be highly sensitive to waste management practices, over which there remains a lack of data – particularly for manufacturers.

- **Variable progress in increasing WASH means many countries will remain highly vulnerable**. Based on current trends, many countries in the Global South will remain vulnerable to spread of AMR through gaps in access to toilets, hand washing, sanitation, and clean drinking water. Sixty-six countries are not on track to eliminate open defecation by 2030. In many vulnerable regions, current levels of WASH investment are unlikely to moderate the growing risk of AMR disease outcomes driven by increasing antibiotic consumption.

- **Broader economic and environmental trends are expected to exacerbate risk**. Migration towards urban areas and increasing water stress, both of which are expected to be most rapid in LMICs, serve to raise risks. Global trade and mobility will continue to transmit infections across borders, ensuring that risk remains a global phenomenon.

[48] An Annex explains the way in which the risk index is computed.

- **Without investment in new antimicrobials, diseases will become gradually more difficult, costly and, in some cases, impossible to treat.** AMR pollution is contributing to a steady erosion of capacity to treat infections among both humans and animals.

3 The costs of inaction

This section considers the implications for individuals, businesses, healthcare systems and the broader economy if the trends examined in Section 2 continue unchecked. Section 3.1 estimates global costs to economic and healthcare systems that are expected on an ongoing basis, before Section 3.2 considers the potential downside to this, exploring the potential impact of a much more severe localised event.

3.1 Ongoing costs of resistant disease development

This section presents an analysis of the expected costs of AMR pollution in water, as expected in a normal year on an ongoing basis. It differs from other analyses by estimating *only* the impacts that can be attributed to AMR pollution in water, as opposed to those from AMR in land and clinical settings[49][50]. Given the interconnectedness of the relevant discharge and exposure pathways and a paucity of data to disentangle these (see Section 2), this attribution involves some unavoidable approximations. The Annex presents more details of the methodology followed.

3.1.1 Human health impacts

Human health impacts of AMR pollution in water can break down into three categories.

- **Impact of increased disease burdens in on the duration and quality of life of those who suffer infection.** This can be measured in Disability Adjusted Life Years (DALYs)[51]. Analysis for this study suggests AMR in water leads to 15 million DALYs per year, equivalent to 25% of the total global burden of malaria and tropical diseases and *more than* annual burden of conflict and terrorism, maternal disorders and natural disasters. Applying rates of monetisation for DALYs used in cost effectiveness analyses[52][53], this translates to economic impacts of $340 to $680 billion per year.

- **Costs to healthcare systems.** AMR in water costs $1-5 billion per year in additional healthcare expenditure and is expected to increase as resistance develops further and populations grow. The costs associated with ill health from AMR diseases include short-term expenditure on treating the disease as well as those to manage the long-term implications of being ill. Short-term costs include more expensive second- or third-line drugs, specialised equipment, longer hospital stays, isolation procedures for infected patients, and the costs associated with rehabilitation[54][55].

- **Costs to the wider economy due to reduced labour supply.** Disease burdens result in time lost from work and long-term productivity losses [56]. Globally, AMR water pollution leads to 3.5 million additional sick days per year in 2020, at a cost of $300m per year. Losses are concentrated in agriculture, which has a large share of employment in countries most at risk and places a greater reliance on labour inputs to production.

These costs are concentrated in the Global South and in some countries are unaffordable. The regional concentration of costs reflects significantly greater vulnerability to AMR diseases from water in the Global

[49] O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations."
[50] OECD, *Stemming the Superbug Tide*.
[51] WHO, "Metrics: Disability-Adjusted Life Year (DALY)."
[52] NICE, "How NICE Measures Value for Money in Relation to Public Health Interventions."
[53] Cameron, Ubels, and Norström, "On What Basis Are Medical Cost-Effectiveness Thresholds Set? Clashing Opinions and an Absence of Data: A Systematic Review."
[54]Prestinaci, Pezzotti, and Pantosti, "Antimicrobial Resistance: A Global Multifaceted Phenomenon."
[55] Krupnick and Cropper, "Primer on Costs of Action / Inaction and Communication to Policymakers."
[56] Krupnick and Cropper.

South (see Section 2).[57] Countries in sub-Saharan Africa, where the burden of AMR disease is the highest, also have the least resources for public health, which in some cases will mean the impacts are unmanageable. [58][59] For example, in Somalia, the estimated additional burden of treating resistant diseases from water pollution is equivalent to more than 2% of the country's GDP, while in Niger citizens already bear nearly 50% of the costs of healthcare expenditure out of pocket, so the increased burden of $37 million per year is unlikely to be met by the public healthcare system. If, as seems plausible, these costs are simply left unmet, projected adverse health outcomes, which include 500,000 deaths per year attributed to water, are likely to be significant underestimates.

3.1.2 Animal health

Loss of antimicrobial efficacy causes increased rates of infection and mortality in agriculture and aquaculture, raising production costs. In industrialised agricultural production systems, antimicrobials play an important role in controlling infection. For example, a proposed ban on a certain antibiotic, which can serve as a proxy for loss of the ability to treat with such antibiotics, is estimated to could cost US pig producers more than $700 million over ten years, or $4.50 per animal[60][61] .

AMR water pollution could cost the agricultural sector up to $6 billion per year. Resistance to traditional treatments could increase animal agriculture mortality rates by 1 percentage point, equivalent to a loss of $13 billion in livestock value ($3 billion of which is attributed to water pollution) and $3 billion in aquaculture value.[62]

3.2 The costs of an AMR driven epidemic

The possibility that AMR water pollution leads to an epidemic means there are severe downside risks to the impacts described in Section 3.1. To illustrate the magnitude of these risks, this section examines the consequences of an epidemic of resistant cholera in Bangladesh.

Cholera is a waterborne disease that is currently treated with antibiotics, in which resistance has already been observed. Cholera spreads primarily through contaminated drinking water and causes up to 143,000 deaths annually[63], with more than 300 cholera epidemic events observed between 2011 and 2017.[64] Resistant strains of cholera have already been observed in Africa and Asia: the conditions are therefore in place for a much more severe epidemic where antibiotic treatments are unavailable.[65]

Bangladesh is a potential hotspot for a waterborne AMR epidemic due to lack of sanitation infrastructure, dense urban areas, and large refugee population. Only 35% of the population has access to hand-washing facilities at home and 48% have access to basic sanitations services. Endemic cholera already causes 100,000 cases in Bangladesh each year. [66] According to in-country experts, the entire population of Bangladesh is at risk of cholera infection.[67] Bangladesh is also home to at least 740,000 Rohingya refugees living in refugee camps that are particularly vulnerable to epidemics.[68]

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[57] Based on a composite review of expert opinions consulted in this study, the analysis assumes 10% attribution to water in countries with universal access to water and sanitation services due to transmission through international travel, and 60% attribution to water in countries with the lowest access to water and sanitation services. Full details of assumptions made in the analysis can be found in the Appendix.
[58] World Health Organization Global Health Expenditure database, "Domestic General Government Health Expenditure (% of Current Health Expenditure) - Low Income."
[59] World Health Organization Global Health Expenditure database.
[60] FAIRR, "Superbugs and Super Risks: The Investment Case for Action."
[61] Hayes and Jensen, "Lessons from the Danish Ban on Feed-Grade Antibiotics."
[62] A composite of experts in AMR and the agricultural sector consulted on this project indicated that lack of available antimicrobial treatments could increase agricultural mortality rates by 1 percentage point compared to current levels of animal mortality rates.
[63] Ali et al., "The Global Burden of Cholera."
[64] Wellcome, "Why We Need a Globally Coordinated Approach to Preparing for Epidemics."
[65] Sack et al., "Antimicrobial Resistance in Shigellosis, Cholera and Campylobacteriosis."
[66] Islam, Clemens, and Qadri, "Cholera Control and Prevention in Bangladesh: An Evaluation of the Situation and Solutions."
[67] Ali et al., "The Global Burden of Cholera."
[68] UNHCR, "Rohingya Emergency."

A resistant strain of cholera could lead to around 700,000 cases and 140,000 deaths from infection in Bangladesh. An adverse but treatable outbreak of cholera might infect around 350,000 and kill 5,000 people in Bangladesh. However, a resistant strain could double case loads, as untreated infections are prolonged and the cycle of secondary infections – propagated through a lack of WASH – is extended[69][70]. Moreover, resistance can very significantly raise fatality rates: while a 1.5% rate of mortality is normal, fatality rates observed for resistant strains in Africa have been as high as 22%.[71] A doubling of average annual cases and a case fatality rate of 20% -- 700,000 cases and 140,000 deaths – is therefore a plausible outcome for a resistant cholera epidemic.[72]

The costs to the healthcare system would in all likelihood be overwhelming, with grave knock-on impacts on broader public health outcomes. An epidemic infecting up to 700,000 people with 140,000 requiring advanced care would lead to significant public health costs in any country. However, the Bangladeshi healthcare system has one of the lowest capacities in the region, with just 130,000 hospital beds[73] and 100,000 healthcare workers[74] to serve a population of 163 million – and it is likely that this capacity would be swamped by the load and complexity of cases resulting from the epidemic. As the COVID-19 pandemic has witnessed, placing the healthcare system under such stress would be expected to increase mortality and morbidity from other causes very materially.

The costs to the economy would be severe, with key sectors at risk of total shutdown. Simply doubling the costs of an adverse but treatable epidemic, in line with its extended duration, would lead to costs to the economy of $4 billion[75]. As cholera can spread via contaminated seafood, fruit and vegetables[76], it is probable that a severe, antibiotic-resistant outbreak would lead to export embargoes. This was the case for an epidemic in Peru in 1991, where losses from agricultural export embargoes and reduced tourism alone amounted to 2% of GDP. In Bangladesh, agriculture and aquaculture are major sources of employment and exports, with 18 million jobs and $640 million of export earnings from fishing alone. [77][78] Major interruptions to these sectors would have considerable impacts on other parts of the economy.

Health and economic impacts on this scale would have a destabilising effect on Bangladeshi society. One potential aspect of this could be a loss of food security, with fish supplying 60% of total animal protein consumed in the country. [79] Another could be in migratory pressures, as seen during the 2008-9 Zimbabwe cholera epidemic, when an estimated 38,000 Zimbabweans fled into South Africa.[80] With many of the 17 million residents of Dhaka without access to sewerage likely to leave the city, migration may take place on a larger scale.

The potential culpability of the pharmaceutical industry in Bangladesh could destroy the sector's reputation. Allopathic pharmaceutical manufacturing in Bangladesh accounts for 2% of the country's GDP, with antibiotics contributing a significant share.[81] Were responsibility to be attributable to antibiotic manufacturing, the Bangladeshi sector's reputation would be irretrievably compromised, with likely effects on the wider sector and global supply chains.

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[69] Nelson et al., "Antibiotics for Both Moderate and Severe Cholera."
[70] WHO, "Use of Antibiotics for Cholera."
[71] Sack et al., "Antimicrobial Resistance in Shigellosis, Cholera and Campylobacteriosis."
[72] Sack et al.
[73] WHO, "Hospital Beds (per 1,000 People) Bangladesh."
[74] Al Faisal, "Pharmaceutical Industry of Bangladesh The Multi-Billion Dollar Industry."
[75] Oxford Economics, "Economic Impact of a Cholera Epidemic on Mozambique and Bangladesh."
[76] World Health Organization, "Frequently Asked Questions and Information for Travellers."
[77] Wardad, "Agri Exports Fetch Ever Highest $909 Million."
[78] Seafood Trade Intelligence Portal, "Bangladesh."
[79] Seafood Trade Intelligence Portal.
[80] Edelstein, Heymann, and Koser, "Health Crises and Migration."
[81] Al Faisal, "Pharmaceutical Industry of Bangladesh The Multi-Billion Dollar Industry."

4 Opportunities for action

This section outlines opportunities for the public and private sectors to better manage the impacts and risks described in Section 3, highlighting case studies that exemplify successful risk management. Sections 4.1 and 4.2 respectively review opportunities for 'upstream' and 'downstream' interventions, Section 4.3 considers the role of enhanced data collection and disclosure, before Section 4.4 considers possible areas of fruitful research.

The scale and interconnectedness of AMR water contamination calls for a comprehensive, multi-sectoral response. While interventions are categorised into separate groupings, an effective response involves interventions across all areas, which will vary locally according to the relative importance of contamination sources, the cost and feasibility of policies, and the scale and relevance of potential co-benefits.[82] This is recognised in the WHO's 'One Health' Global Action Plan for AMR, whose objectives are summarised in Table 3.[83]

Table 3 'One Health' objectives encompass all mitigation types

WHO Global Action Plan Objectives	Mitigation type
1. to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;	Upstream
2. to strengthen the knowledge and evidence base through surveillance and research;	Data and research
3. to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;	Downstream
4. to optimise the use of medicines in human and animal health;	Upstream
5. to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions	Upstream

Source: Vivid Economics and WHO (2015)

Action to date to address AMR water pollution has largely been relegated to the public sector due to multiple incentive structures which have limited significant private sector action (Box 2). The public sector and insurance sectors can play a large role in creating the incentives for businesses to mitigate these risks and facilitate coordinated public and private action.

Box 2 Barriers to effective public and private action on AMR water pollution

- **What gets measured gets managed –** AMR water pollution develops into disease outcomes in a more complex way than traditionally monitored water pollutants. This makes it more challenging to develop regulatory standards and to monitor the impact of mitigation strategies.
- **Diffuse polluters, diffuse impacts** – Multiple industries contribute to the development of resistance through water, making it challenging to identify key pollution sources[84]. This could potentially be rectified through the development of a mass balance model to more accurately

[82] Wellcome Trust (2018)
[83] WHO, "Global Action Plan on Antimicrobial Resistance."
[84] OECD, "Diffuse Pollution Degraded Waters."

predict the relationship between pollution and resistant outcomes, though the nature of resistance development limits the practicality of doing so. Additionally, the impacts of steady resistance development are currently borne primarily by the healthcare sector and individuals, limiting private sector incentives for action.

- **Limited economic incentives for action** – The price of antibiotics is very low, limiting incentives for investment in sustainable production practices. The low price also limits incentives for investing in developing new antibiotics, which can take 10-15 years and more than $1 billion[85].
- **Perception that AMR water pollution is a developing country issue** – Because AMR exposure through water is limited in countries with high quality sanitation infrastructure, there is a perception that the issue of AMR water pollution is relegated to developing countries. However, as COVID-19 has demonstrated, pathogens do not respect borders and increasing international travel and trade mean that resistance development in any part of the world can create a global threat.
- **'Competes' with existing environmental and health risks** – AMR water pollution may struggle to gain traction on the public agenda against other known risks of diseases and environmental contaminants, particularly when the costs of these risks are more visible or easily measured.

4.1 Upstream responses

Upstream policy responses encompass measures to promote prudent use of antimicrobials and encourage responsible manufacturing practices. This involves applying regulatory or incentive measures to both reduce antimicrobial use and ensure that wastes and effluents are properly treated.

Managing use by humans is low cost and can improve clinical outcomes independently of any reduction in AMR. In a clinical setting, regulatory measures to combat overuse include delayed prescribing, limiting over-the-counter availability, reducing the distribution of counterfeit drugs, policies to reduce incentives to overprescribe, education campaigns, hospital-based hand hygiene and disinfection programmes, wider use of rapid diagnostic testing, screening and isolation of patients in hospital, and expanded uptake of vaccination. [86] Many of these interventions offer strong value for money even where the benefits of AMR reduction are disregarded; a package of AMR-specific policies (including, for example, expanded diagnostics, vaccination, and awareness campaigns) costs as little as $4-9 billion per year globally. [87][88]

Reducing use in agriculture and aquaculture can require a recasting of regulatory standards and incentives. Private economic interests can be a barrier to reducing use but farmers also have a significant stake in reducing AMR – and there is evidence that policies restricting the use of medically important and growth-promoting antibiotics in veterinary practice are gaining traction in Europe and North America. [89][90] Box 3 highlights the example of the Danish pig farming sector, where a mix of stricter regulatory monitoring and enforcement, changes to veterinarians' incentives, and farmer education has led to a steep reduction.

Green procurement practices can incentivise more responsible pharmaceutical manufacturing. [91] Sustainable procurement can incentivise manufacturers to adopt environmental standards, notably through waste treatment. Such incentives may extend along across international supply chains that lie outside governments' direct regulatory purview. The government of Sweden recently embedded sustainable public

[85] Wellcome, "Why Is It so Hard to Develop New Antibiotics?"
[86] AMR Industry Alliance, "2020 Progress Report."
[87] World Bank, "Drug-Resistant Infections: A Threat to Our Economic Future."; O'Neill, "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations."
[88] The time profile of these investments may not be smooth over time; some may incur large upfront costs and then drop off over time.
[89] FAIRR, "Superbugs and Super Risks: The Investment Case for Action."
[90] European Commission, "Ban on Antibiotics as Growth Promoters in Animal Feed Enters into Effect."
[91] Wellcome Trust, "Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges."

procurement into their AMR strategy by setting procurement requirements on animal welfare, responsible use of antibiotics and reduced environmental impact of antibiotics[92].

Public-private partnerships can stimulate innovation in new antimicrobials. Investment in new antimicrobials can be unprofitable, given high development costs and often low market value. Public-private partnerships can support innovation where there may be barriers to early-stage investment. For example, CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator) [93] provides support specifically to drugs in the preclinical phase, where private sector investment would be prohibitively risky. In the European Union, the New Drugs for Bad Bugs programme[94] is a similar public-private partnership that aims to support the development of new treatments to replace increasingly ineffective antimicrobials.

Box 3 Animal Agriculture intervention – Danish Pig Farming

Cross-sector collaboration between regulators, farmers and vets in the Danish pig farming industry has resulted in a reduction in agricultural antimicrobial use.

A shift to intensive farming practices in Denmark increased antibiotic use for growth promotion and for treating animals in increasingly unhygienic living conditions. Overuse practices resulted in increased rates of resistance amongst the livestock which raised costs for farmers, increased AMR exposure for workers and increased potential water pollution through surface runoff. Collaboration between the Ministry of Environment and Food, private veterinary practitioners and swine producers led to a management programme that included:

- **Improved monitoring and surveillance of AMR –** Creation of publicly available comprehensive database of antimicrobial use and resistance in both animals and humans.
- **Altered economic incentives and regulations for antibiotic prescription** – Veterinary advisory service contracts reduced economic incentives for excessive prescription of antibiotics and promoted a holistic approach to livestock health.
- **Education on the impact of AMR for businesses** – The Yellow Card initiative targets farms with the highest antimicrobial consumption, promoting prudent usage and educating farmers and vets on the impacts of AMR to health and business.

These interventions have resulted in reduced antimicrobial consumption and water pollution from the agricultural industry, as well as increased consumer awareness of AMR issues. The Yellow Card Initiative alone resulted in a 10% reduction in antimicrobial use by 2013, with wider benefits observed for animal welfare.[95]

4.2 Downstream responses

Addressing AMR in water through water and sanitation services sits within a larger portfolio of investments needed to support healthcare systems and economies in developing countries.

[92] Government Offices of Sweden, "Swedish Strategy to Combat Antibiotic Resistance."
[93] CARB-X, "About CARB-X."
[94] Innovative Medicines Initiative, "ND4BB."
[95] FAO/Denmark Ministry of Enviornment and Food = Danish Veterinary and Food Administration, "Tackling Antimicrobial Use and Resistance in Pig Production Lessons Learned in Denmark."

WASH interventions can reduce the human health impacts of both AMR and non-AMR infections at relatively low cost.[96] In most localities, the most basic WASH interventions are the most cost-effective in reducing the spread of AMR[97]. Extending basic WASH services to the unserved would cost between $13.8 and $46.7 billion annually from 2015 to 2030.[98] This can be achieved with current levels of development financing if funds are well-directed. The benefits beyond AMR risk reduction associated with full WASH coverage include reduced spread of infectious disease, diarrhoea, and other neglected tropical diseases, and is associated with reduced incidence and severity of malnutrition, improved safety, and higher rates of school attendance[99].

A range of technologies already exist to reduce water contamination, from reducing sewage dumping to UV sanitation technologies. Further improvements can be made through the treatment and disposal of sludge that results from wastewater treatment and often ends up as fertiliser for crops. The government of India has implemented its Swachh Bharat Mission and invested heavily in Faecal Sludge Management, a management option which collects and removes sewage from pit latrines and septic tanks, rather than relying on aging sewerage infrastructure. With continued investment, India is on track for a 57% increase in access to sanitation services.

There are many examples of public and private sector partnerships and innovation across waste management, sanitation, and hygiene. Solidarités International and Borda developed OCTOPUS, a collaborative tool for disseminating guidance, decision support, and peer-to-peer exchange in the safe management of faecal sludge. The tool is designed to sit within emergency sanitation management but could facilitate learnings for non-emergency practitioners. Development was based on interviews with stakeholders and is being tested in Cox's Bazar in Bangladesh.

4.3 Monitoring and reporting

Expanding surveillance and monitoring of antimicrobial consumption and rates of resistance underpin effective and coordinated AMR action.

Better data is needed to monitor use in clinical practice and in agriculture, to trace antibiotic supply chains and to monitor AMR in the environment. Investments in AMR surveillance can sit within a larger programme of public health and environmental surveillance policies, improving policy outcomes and epidemic preparedness. The EU and China have taken the lead on regulating antimicrobials, with bans on antibiotics as growth promoters in agriculture, as well as the beginnings of monitoring and evaluation frameworks. Similar measures are being introduced in the United States.[100] Box 4 provides an overview of Singapore's National Action Plan to combat AMR, which includes a combination of upstream and downstream interventions as well as investment in surveillance and data collection.

There are opportunities for innovation in monitoring waterborne AMR, utilising recent advances in community-based infectious disease monitoring and GIS-based application development. Resistance Map[101] and WHO's GLASS programme[102] are currently on the forefront of AMR monitoring, but neither tracks waterborne pollution nor uses novel methods in the tracking of outbreaks. Innovative solutions have been developed for other infectious diseases, notably HealthMap[103], which pulls information from news aggregators and social media to circumvent delays in official reporting and provide up-to-date surveillance data to users.

[96] WHO, FAO, and OIE, *Technical Brief on Water, Sanitation, Hygiene and Wastewater Management to Prevent Infections and Reduce the Spread of Antimicrobial Resistance*; Graham, Giesen, and Bunce, "Strategic Approach for Prioritising Local and Regional Sanitation Interventions for Reducing Global Antibiotic Resistance."
[97] Graham, Giesen, and Bunce, "Strategic Approach for Prioritising Local and Regional Sanitation Interventions for Reducing Global Antibiotic Resistance."
[98] Hutton and Varughese, "The Costs of Meeting the 2030 Sustainable Development Goal Targets on Drinking Water, Sanitation, and Hygiene."
[99] World Health Organization, "Sanitation."
[100] FAIRR, "Superbugs and Super Risks: The Investment Case for Action."
[101] CDDEP, "ResistanceMap."
[102] WHO, "Global Antimicrobial Resistance Surveillance System (GLASS)."
[103] Boston Children's Hospital, "HealthMap."

Box 4 National Action Plan - Singapore

The Singapore National Action Plan (NAP) on AMR maps out key areas for understanding and controlling AMR, as well as mitigating its impact on Singapore's economy. As an international travel hub and food importer, Singapore is vulnerable to AMR developed internationally.

The NAP aims to unify and formalise the existing response of Singapore households, food producers, hospitals, manufacturers, and the environment sector. Singapore has taken a 'One Health' multi-stakeholder coordination approach to design their plan to reduce AMR through:

- **Education & Optimisation of Antimicrobial use -** 'Good Aquaculture Practices for Fish Farming' focusses on educating farmers on best practices to reduce infections, therefore reducing the need for treatment.
- **Surveillance, Risk Assessment & Research** - Regular surveys are undertaken to monitor the diversity of environmental gene reservoirs in water, providing a baseline for monitoring the trend and dynamics of gene reservoirs in the environment.
- **Prevention & Control of Infection** - The National Environment Agency's environmental hygiene programme aims to maintain hygiene standards for cooling towers, swimming pools, water features or fountains and recreational waters, to safeguard public health and prevent waterborne diseases.[104]

Surveillance and monitoring elevate the risk of AMR as an insurance liability. Insurance companies risk their reputations by association with polluting industries, particularly when the pollutant is growing in public consciousness. As the evidence on the human health impacts of water pollutants improves, and surveillance and monitoring make it more possible to link specific businesses to resistance development or outbreaks, these liability risks could become significant business risks. The insurance industry can reduce the risk of business exposure and create incentives for more sustainable practices through[105]:

- Integrating environmental, social and governance risks into insurance underwriting[106];
- Including AMR water pollution risks in risk assessment models;
- Developing new insurance products to cover AMR water pollution risk;
- Investing in companies which commit to reducing risk through sustainable business practices, such as the AMR Industry Alliance.

4.4 Gaps in knowledge

Despite depth and breadth of scholarship in this area, the implications of AMR on society are still not well understood. Lack of monitoring and resulting lack of data inhibit a complete scientific understanding AMR in the environment, and the magnitude and relative importance of transmission channels are not well understood. This includes how AMR spreads and develops in the environment, such as the possibility of 'cocktail effects' through mixing of pollutants, as well as the effects of environmental AMR on ecological function.[107] While addressing these uncertainties can support better policymaking, they are not barriers to

[104] Singapore AVA/MOH/NEA/PUB, "National Strategic Action Plan on Antimicrobial Resistance."
[105] UNEP's Principles for Sustainable Insurance Initiative, *Unwrapping the Risks of Plastic Pollution to the Insurance Industry*.
[106] UNEP Principle for Sustainable Insurance Initiative, "Underwriting Environmental, Social and Governance Risks in Non-Life Insurance Business."
[107] European Commission, "European Union Strategic Approach to Pharmaceuticals in the Environment."

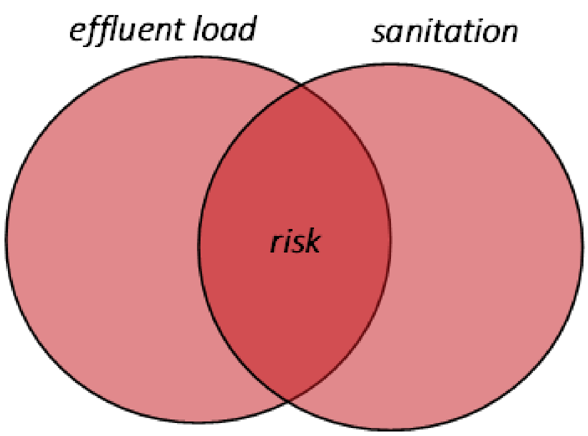
effective action being taken now, given the scale of risk identified in this report and others and the range of no-regret policy options available.

5 Appendix

5.1 Global risk index methodology

The construction of the composite score is based on a layering of contributing exposure and vulnerability factors. The approach combines measurements of antibiotic production and use with levels of access to sanitation. Antibiotic usage stands as a proxy for actual effluent loads, which are not routinely monitored or reported. We conceptualise two layers: one representing the amount of AMR present in environmental waters and one representing the degree to which communities are directly exposed to untreated (and potentially contaminated) water supplies. The layering approach is illustrated in Figure 7. The risk index is distinct from a resistance index, as has been developed elsewhere. The risk index constructed here is not based on measured rates of resistance, but on a layering of factors that contribute to the development of resistance in water.

Figure 7 The risk layering approach identifies geographies that are exposed to through high effluent loads and lack of sanitation



Note: Click here to enter note
Source: Vivid Economics

Section 2 of this report presents a composite risk indicator that is intended to identify countries at highest risk of AMR water pollution. A composite indicator is constructed by combining individual indicators into a single index based on a model. The OECD Handbook notes that as they can be easily misused, they should be seen as a means of initiating discussion or stimulating public interest[108]. The methodology employed in the construction of the risk index follows that laid out in the OECD Handbook, which is illustrated in Figure 8. In addition to following methodological steps recommended by the Handbook, the analysis also uses documentation. At each stage of the analysis, metadata, as well as notes on assumptions and limitations are collected.

[108] OECD, "Handbook on Constructing Composite Indicators: Methodology and User Guide."

Figure 8 Construction of a novel composite indicator follows the OECD framework[109]

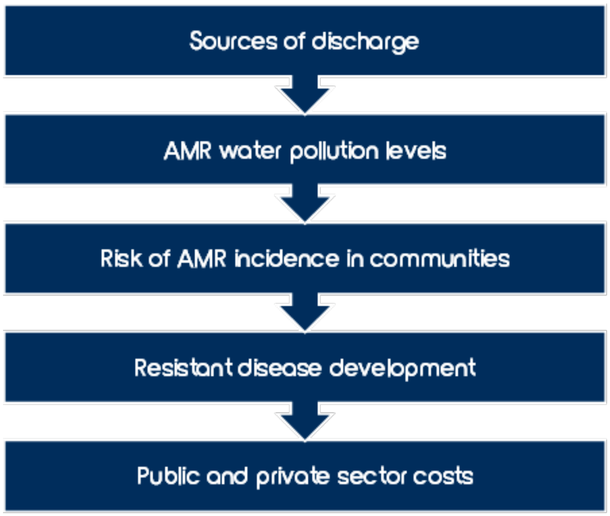
Note: Click here to enter note
Source: Vivid Economics

We have also taken steps to communicate the risk index responsibly and transparently. Composite indicators are intended to consolidate multiple trends into a single figure, which is useful for stimulating discussion and engagement with a wider audience, but steps should be taken to ensure scores are not misleading. For example, this analysis calculates risk indices in 2020 and 2030, but as scores are normalised within a given year, we avoid reporting 2030 indices to avoid comparisons between years.

5.1.1 Theoretical framework

The development of an underlying logical structuring is key for development of a robust indicator in ensuring the approach is guided by solid reasoning. The theoretical framework used here follows closely from the theory of change, particularly the first three boxes. The risk layering approach is based on this understanding of how discharge results in risk of AMR incidence.

Figure 9 The methodology follows the theory of change



Note: Click here to enter note
Source: Vivid Economics

5.1.2 Data selection

As AMR is an emerging pollutant and therefore not included in most regulatory frameworks, monitoring systems are not designed to gather data on resistant genetic elements. Therefore, this risk index is based on factors that contribute to *risk* of resistance, rather than resistance itself. In some cases, the analysis relies on

[109] OECD.

proxy data. For example, export data from the UN Comtrade database is used in place of comprehensive pharmaceutical manufacturing data, which is unavailable.

Table 4 Data coverage

Indicator	Country coverage	Historical data or projection?	Source
Hospital and community consumption	75 (mostly European)	Yes	CDDEP, Resistance Map
Agricultural use	Based on veterinary sales in 27 countries but extrapolating to nearly full coverage	Yes	Boeckel et al. (2017)
Manufacturing	180	Yes	UN Comtrade
Wastewater treatment*	95	Yes	UN
Hand-washing facilities at home*	96	Yes	WHO
Open defecation*	194	Yes	WHO
Basic sanitation*	194	Yes	WHO
Clean drinking water*	194	Yes	WHO
Resistance index	41 (mostly European)	No	CDDEP

Note: *Percentage of the population
For indicators where data is missing, values are imputed using region-income group averages.
Source: Vivid Economics

5.1.3 Normalisation

As each indicator is on a different scale, normalisation is key to aggregate disparate measures into a single indicator. This analysis followed a min-max weighting. The most appropriate normalisation procedure depends the statistical characteristics of the data and the aim for the final indicator. A min-max normalisation satisfies objectives for this modelling task as it:

- is more robust than a simple ranking and
- normalises indicators to have an identical range [0,1].

While this approach is highly sensitive to outliers, it was determined to be appropriate for this set of indicators. The formula is given below:

$$(value - min)/(max - min)$$

5.1.4 Weighting & aggregation

The risk index assigns equal weight to the three indicators that feed into the composite index. Equal weighting is not only the most-used approach in the literature, it is also the most fit-for-purpose in this analysis. The indicators that are included, and weighted equally are:

- Effluent intensity
- Wastewater treatment
- Sanitation score

5.1.5 Visualisation & results checks

The first layer of validation is a visual sense check to ensure the distribution of global risk is in line with assessment findings from the review of literature. Figure 5 presents the risk index, which is in line with expectations from the literature review. To validate results further, the index was compared against the Center for Disease Dynamics, Economics & Policy's Drug Resistance Index, which is a composite measure that combines the ability of antibiotics to treat infections with the extent of their use in clinical practice. It does not therefore capture environmental spread, but there is a high degree of correlation between the indices ($p < 0.05$).

5.2 Economic modelling methodology

Unlike other water pollutants which can affect the quality of water used in industrial processes, the impact of AMR water pollution depends on how it manifests in disease outcomes for both humans and animals. Accordingly, the costs of AMR water pollution are grounded in estimates of these outcomes over time. The cost modelling is undertaken in five stages, to develop estimates at the country and country-sector level:

The approach to estimating the cost of human health impacts is based on key outcomes of AMR diseases. Unlike other water pollutants which can affect the quality of water used in industrial processes, the impact of AMR water pollution depends on how it manifests in disease outcomes for both humans and animals. Accordingly, the costs of AMR water pollution are grounded in estimates of these outcomes over time. A methodology annex in the appendix provides further details on the approach employed, data sources used and assumptions made to estimate the costs of inaction.

Figure 10 The business-as-usual cost modelling is conducted in five stages

Note: Click here to enter note
Source: Vivid Economics

- **Key AMR disease outcome indicators:** For human impacts, the analysis draws on the OECD report "Stemming the Superbug Tide" which provides an average annual estimate of healthcare expenditure, hospital days, DALYs and deaths associated with AMR diseases on an average annual basis between 2015 and 2050.
- **Extrapolate to all countries –** Use linear regressions to project fitted values of key outcomes from OECD data, using the AMR water risk indicator
- **Attribution to water –** Attribution to water is proxied by sanitation scores, with attribution ranging from 10% to 60% (assumptions a composite of expert opinions)

- **Downscaling –** Downscale labour force impacts to economic sector using EORA GVA data for 7 aggregated sectors and ILOSTAT labour force data
- **Cost modelling –** Estimate the costs of absenteeism, healthcare expenditure, individual costs

5.2.1 Key AMR disease outcomes

We focus on the number of hospital days, healthcare expenditure, DALYs lost and mortality rate associated with AMR as indicators for the key disease outcomes across the economy. Using OECD data from a study on AMR these key indicators form the backbone of our analysis.

- **The costs associated with lost labour productivity are estimated using data on the number of hospital days related to AMR.** These days are scaled up to number of lost working days using assumptions based on an NHS study.
- **The public costs are estimated using data on hospital expenditure related to AMR.**
- **The costs to individuals are estimated using both mortality rates associated with AMR and Disability-Adjusted Life Years (DALYs) lost.** There exists much debate on the monetized value of a DALY so we present both an upper and lower bound, based on a study of the literature, in our cost analysis.
- **The costs to agriculture are estimated using an assumption for the increase in livestock and aquaculture mortality rates.** This assumption are based on the findings from expert interviews. Here we assume mortality increases uniformly across all species of animal due to lack of species-specific data and expert opinion that production systems should not be ranked by AMR risk.

The OECD data provides coverage for 33 countries, requiring extrapolation to facilitate global coverage.

5.2.2 Extrapolation to all countries

Our AMR water risk indicator forms the base of the extrapolation process for projecting resistance data and the key outcome variables to all countries. The lack of coverage of the CDDEP resistance index data meant that we could not use measured resistance within a country to extrapolate the OECD raw data. Using data and key indicators on both national exposure and vulnerability we created a normalized water risk indicator to provide a comparable measure of the risk of AMR.

The normalized risk indicator allowed the creation of a hypothetical resistance index. Regressing the CDDEP resistance index on our risk indicator showed the risk indicator provided a strong predictor of measured AMR within a country, showing high significance and model fit. This facilitated the creation of a hypothetical resistance index to provide a comparative measure of the incidence of AMR in nations where this data is lacking.

Using the hypothetical resistance index we were able to extrapolate the OECD disease outcome data to provide global coverage. This used the comparative measure of AMR incidence to make inference on the relative magnitude of disease outcome between different nations, basing the projections on the 33 countries we had data for. Here we noted highly significant results for DALYs and mortality rates however the model fit was weaker for hospital days and healthcare expenditure. This is likely due to the variation in budget constraints for healthcare expenditure, which we account for with a second extrapolation scaled by healthcare expenditure per capita.

5.2.3 Attribution to water

It is challenging to disentangle the attribution of AMR disease outcomes between water and other vectors and sources of exposure, as they are often inter-related. For example, soil can be an ecosystem for resistance development and human and animal exposure. Soil contamination can also directly contaminate water sources through runoff.

The attribution in the analysis is based on sanitation, which represents exposure to contaminated water through lack of sanitation infrastructure or clean water. Using multiple WHO sanitation indicators, we use the worst sanitation score out of four as indicative of the 'lowest common denominator.' Attribution assumptions are based on a composite of opinions garnered through expert interviews.

- **For countries with a perfect sanitation score, we attribute 10% of the costs of AMR disease outcomes to water.** This represents the cost burden as a result of AMR development through water in countries with poor sanitation, which can spread to other countries through international travel.

- **For countries with the lowest sanitation scores, we attribute 60% of the costs of AMR disease outcomes to water.** In countries with low sanitation, there is high exposure through water and open defecation; these countries often also have unregulated prescribing practices leading to higher clinical exposure.

5.2.4 Downscaling to the sector

To estimate the costs to economic sectors by country, we disaggregate sick days attributable to AMR water pollution by 6 economic sectors (Agriculture, Mining, Manufacturing, Construction, Transport & Business, and Public & Human Services) using employment rates by country. We assume that the likelihood of acquiring an AMR infection via water pollution is equal across sectors; this may be an underestimate of the burden on the agricultural sector since agricultural workers can be more exposed to contaminated runoff.

- We use ILOSTAT data to estimate labour force participation rates, to attribute the share of AMR disease outcomes experienced by the labour force

- We use EORA input-output tables to estimate employment in each sector, to attribute the share of AMR disease outcomes experienced in each sector

$$\begin{aligned} &\textit{Hospital days by sector} \\ &\qquad = \textit{Hospital days by country} \times \textit{Labour force participation rate} \\ &\qquad \times \textit{Share of labour force employed in sector} \end{aligned}$$

5.2.5 Economic modelling

The economic modelling focuses on four main sources of costs imposed by AMR: Labour costs, Public health costs, Individual costs & Agricultural costs.

Labour costs

Increased absenteeism associated with disease incidence reduces the productivity of the labour force. The incidence of infections by resistant diseases can result an increase in absenteeism as workers are unfit to work whilst ill. This reduction in days worked results in a fall in output as the productivity of the labour force is reduced.

Method of calculation:

$$\boldsymbol{Cost = Days\ absent\ from\ work\ \times Hourly\ value\ added \times Average\ hours\ worked\ per\ day}$$

This calculation is built upon a number of assumptions. Box 5 details the main assumptions underlying this calculation.

Box 5 Labour cost assumptions

- Days absent from work are calculated as a function of projected hospital days. Each hospital day is estimated to be equivalent to four sick days.
- Working and non-working individuals are equally likely to acquire an infection. Sick days are attributed based on labour participation rate.
- Hourly value added of labour is equal to the marginal productivity of labour. This means lost working days are equivalent to lost marginal productivity.
- When labour is unused so is capital. Here the sum of these gives us the marginal productivity of labour.
- Average hours worked per day are calculated from average hours per week. For countries where data is lacking we assume hours are equal to the global average.

Public health costs

AMR infections are expensive and require a higher level of expenditure on care. The increased length of infection and lack of response to treatment by traditional medications increases the difficulty in diagnosis and treatment for healthcare providers. This increases expenditure on care.

The calculation involves two methods of scaled and non-scaled calculations. Box 6 describes the main assumptions underlying these calculations.

- The non-scaled calculations use the OECD's estimates of AMR-related healthcare expenditure per 100,000 people, combined with our extrapolated projections, to provide national level expenditure estimates.
- The scaled calculation scales the OECD's estimates down using current healthcare expenditure per capita data before estimating national level expenditure.

Box 6 Public health cost assumptions

- The unscaled calculation estimates the additional healthcare expenditure that would result from AMR in the case where developing nations, not included in the OECD data, were to spend in a similar pattern to OECD countries. This is a more accurate estimate of the cost of 'full treatment'.
- The scaled calculations take into account the amount spent on healthcare by developing countries, recognising that some nations will not provide 'full treatment' and so will incur lower healthcare costs.

Individual costs

AMR infections pose costs to individuals by reducing the length of life and the quality of life. Infections and illness can result in mortality in severe cases. For those who survive they may be left in a state of 'disability' where the quality of their life is reduced.

The calculation is based on the increase in Disability Adjusted Life Years (DALYs) and mortality rates related to AMR from the OECD's data. In order to monetise this cost we use a range of monetary values for DALYs and a 'best practice' Value of a Statistical Life (VSL). The assumptions made here are outlined in Box 7.

Box 7 Individual cost assumptions

- The value of a DALY and VSL do not change between countries. Calculation methods can often present a range of values depending on the country studied but we use one universal figure for each.
- The value of a DALY is equivalent to the value of a Quality Adjusted Life Year (QALY). This is done since QALYs and DALYs are effectively equivalent measures and there is a lack of literature which monetises DALYs.
- We present results for a range of DALY values with a lower bound estimate of £20,000 from NICE to an upper bound of $50,000 from the OECD.
- We use a universal VSL of $2.94 million from the Australian OBPR.

Agriculture costs

The costs of AMR on livestock and aquaculture can include higher mortality rates and higher costs of treating animals for diseases. The death of livestock and aquaculture results in a loss in income for the agricultural sector. Furthermore, the failure of first line treatments due to AMR increases the cost to the agricultural sector as it is expensive to provide further treatments, which may also be ineffective.

Method of calculation:

$$\begin{aligned} Cost = {} & Value\ of\ livestock\ \times Proportion\ that\ die\ due\ to\ AMR \\ & + Value\ of\ aquaculture\ \times\ Proportion\ that\ die\ due\ to\ AMR \end{aligned}$$

This calculation is built upon a number of assumptions. Box 8 details the main assumptions underlying this calculation. This fails to capture the additional costs related to non-antibiotic treatments, meaning the true cost to the sector is likely to be even higher than estimated.

Box 8 Agricultural cost assumptions

- The cost scenario assumes a 1 percentage point reduction in animal survival rates. This is based on an expert opinion on the costs of resistance based on mortality rates of no-antibiotics-ever agricultural production in chickens (increase in mortality rate from 6-7%)
- Attribution to water is 25% for livestock that are exposed to contaminated water though manure use and runoff. Attribution to water is 100% for aquaculture.

Table 5 Data sources

Indicators	Source
Agricultural use of antibiotics	Article in Science
Antibiotic import and export	UN Comtrade

Aquaculture value by country	FAO
Average annual burden of AMR in DALYs (2015-2050)	OECD
Average annual deaths due to AMR (2015-2050)	OECD
Average annual healthcare expenditure related to AMR (2015-2050)	OECD
Average annual hospital days due to AMR (2015-2050)	OECD
Average hours worked per week	ILOSTAT
Drinking water services	WHO
Drug resistance index	CDDEP
GDP growth rates	World Bank
Hand washing facilities by country	WHO
Healthcare spend per capita	World Bank
Hospital and community antibiotic use	CDDEP
Livestock value by country	FAO
Open defecation practices by country	WHO
Output by sector, GVA by sector, Employment by sector, Payments to Labour and Payments to Capital by sector	Eora Global Supply Chain Database
Population employment rate	ILOSTAT
Population forecasts by country (2030)	Ourworldindata

Note: Click here to enter note
Source: Vivid Economics

5.2.6 Epidemic scenario assumptions

Table 6 Epidemic scenario assumptions

Assumption	Value	Source
Population of Bangladesh	163,046,161	World Bank
Population of Dhaka	21,005,860	World Population Review
Proportion of population of Dhaka without sewerage	82%	Water Management in Dhaka[110]
Typical Bangladesh epidemic scenario incidence rate	0.214%	Economic impact of a cholera epidemic on Mozambique and Bangladesh[111]
Multiplier of extended duration of epidemic due to resistance	2	Assumption due to evidence that antibiotics can reduce the length of symptoms for cholera by half, reducing the volume and length of time of community spread

[110] Haq, "Water Management in Dhaka."
[111] Oxford Economics, "Economic Impact of a Cholera Epidemic on Mozambique and Bangladesh."

Typical cholera case fatality rate	1.5%	Economic impact of a cholera epidemic on Mozambique and Bangladesh[112]
Resistant cholera potential case fatality rate (% of cases of cholera requiring antibiotic treatment)	20%	WHO[113]
Hospital beds per 10,000 in Bangladesh	8	World Bank
Healthcare workers per 10,000 in Bangladesh	6	The Pharmaceutical Industry of Bangladesh[114]
Average household size Bangladesh	4.675	HIES
Average household cost of treatment	$30.40	Cost of illness for cholera in a high risk urban area in Bangladesh[115]
Total length of epidemic	1.5 years (2 x 9 months)	Economic impact of a cholera epidemic on Mozambique and Bangladesh[116]

Note: Click here to enter note
Source: Vivid Economics

[112] Oxford Economics.
[113] WHO, "Cholera."
[114] Al Faisal, "Pharmaceutical Industry of Bangladesh The Multi-Billion Dollar Industry."
[115] Sarker et al., "Cost of Illness for Cholera in a High Risk Urban Area in Bangladesh: An Analysis from Household Perspective."
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Company profile

Vivid Economics is a leading strategic economics consultancy with global reach. We strive to create lasting value for our clients, both in government and the private sector, and for society at large.

We are a premier consultant in the policy-commerce interface and resource- and environment-intensive sectors, where we advise on the most critical and complex policy and commercial questions facing clients around the world. The success we bring to our clients reflects a strong partnership culture, solid foundation of skills and analytical assets, and close cooperation with a large network of contacts across key organisations.

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