Whitepaper | November 2022

Confronting a permacrisis

The intersection between antimicrobial resistance, climate change and biodiversity loss

BRITISH SOCIETY FOR ANTIMICROBIAL CHEMOTHERAPY

University of Exeter Medical School

Supported by BSAC with research contribution from Professor Will Gaze at the University of Exeter Medical School's European Centre for Environment and Human Health.

AVIVA INVESTORS

Abigail Herron

Global Head of ESG Strategic Partnerships, Sustainable Finance Centre for Excellence, Aviva Investors

Abigail leads Aviva Investors' work on sustainability focused strategic partnerships within the sustainable finance centre for excellence. She also fosters innovative thinking by developing approaches to frontier ESG themes. Abigail has a special interest in antibiotic resistance and biodiversity.

On maternity leave, she completed a Masters focusing on antibiotic resistance at the University of Cambridge which won the Forum pour l´Investissement Responsable (French Social Investment Forum) and Principles of Responsible Investment (UNPRI) award for best Masters thesis, 2020. She is an ambassador for the Global AMR Insights Network, an Antibiotic Action Champion and is working with the Investor Action on AMR project to raise the profile of AMR within the investment community.

Professor Will Gaze

Microbiologist, University of Exeter Medical School's European Centre for Environment and Human Health

Professor Will Gaze is a microbiologist at the University of Exeter Medical School's European Centre for Environment and Human Health with over 20 years experience researching AMR evolution, ecology and epidemiology across the One Health continuum. His contribution to this report is funded through a UK Natural Environment Research Council (NERC) Knowledge Exchange grant (NE/V019279/1) to work with government and industry on the environmental dimension of antimicrobial resistance.

British Society for Antimicrobial Chemotherapy

Michael Corley

Deputy Chief Executive, British Society for Antimicrobial Therapy (BSAC)

Michael joined BSAC in 2017 to lead on Policy and Public Affairs in 2017, before becoming Deputy Chief Executive.

BSAC is a leading influencer of responsible, sustainable antimicrobial use globally. Its internationally renowned publications are among the foremost international journals in antimicrobial research, while its commitment to scientific excellence is reflected in its varied programme of events, training and free educational resources.

BSAC knows that better education can help prevent disease, develop more effective practice and influence international policy. Working together, BSAC believes we can ensure a safer world by developing new drugs, while making sure we use the ones we already have are used responsibly and protected for future generations.

Contents

Antimicrobial resistance (AMR), climate change and biodiversity are linked in complex ways: this report discusses the intersection of these three planetary crises. It argues climate change and nature loss are contributing to conditions that allow certain pathogens to spread, while antimicrobials – an essential part of the human toolkit against disease – are becoming less effective. AMR is the result of governance failure; it has become a critical public health issue, which demands an urgent, coordinated policy response. This report intends to trigger debate about what that response could look like.

Executive summary

The warning from G7 health ministers that the antimicrobials we rely on to treat infections in humans, animals and plants will no longer be effective has enormous implications.[1]

Addressing antimicrobial resistance needs a whole-of-society approach, including focused attention from investors

Antibiotics and other antimicrobials have been a global success story, underpinning industrial agriculture and modern medicine, to the point where many pathogens are not considered particularly alarming.

Yet by overusing these important compounds, the emergence of drug-resistant microbes is increasing, where the strongest survive and multiply. If these 'superbugs' continue to spread, we will again be at risk from simple infections and routine surgeries. Life expectancy could plummet,[2] as could fatalities among the young[3] and vulnerable.

At the same time, research suggests over half of known human pathogenic diseases can be aggravated by climate change.[4] As the biosphere warms, the way in which people and pathogens interact is expected to shift, altering the vectors of disease.[5] Ultimately, a warmer world with more extreme climate events and reduced biodiversity is likely to leave populations exposed to different pathogens. Our reliance on antimicrobials as a quick fix could mean we lack effective treatments in the medical toolkit.

At present there is no international scientific body overseeing the management of antimicrobials, and attention to antimicrobial resistance (AMR) is lacking in crucial multilateral agreements such as the UN Sustainable Development Goals (SDGs), European Sustainable Finance Disclosure Regulation (SFDR), and the EU taxonomy for sustainable activities. Omitting AMR is a major failure of national and corporate governance. Like the climate and biodiversity crises, it needs better global governance mechanisms to confront it, which is what we are calling for today.

Addressing AMR needs a whole-of-society approach, including focused attention from investors. We have an important role to ensure the companies in which we invest consider antimicrobials and AMR.

Investors need to be made aware they face material risks in companies that do not appreciate how fast AMR is growing, its impacts, and that risk is accruing for those ill-prepared for tighter restrictions on antimicrobial use. The COVID-19 pandemic shows how a global public health crisis is a systemic risk from which portfolio diversification offers little or no protection. As such, diversified portfolios are at risk from AMR proliferation, even when individual company contributors in those portfolios are not themselves at material financial risk.

This is an area where spinoffs impact everyone, as we use water, deliver or access healthcare or work in global food chains, because we all need antimicrobials that work.

1. Department of Health & Social Care, 'Policy paper: G7 Health Ministers' Ministers Communique, Oxford, 4 June, 2021', GOV.UK, June 4, 2021.
2. 'Antibiotic resistance', World Health Organisation, July 31, 2020.
3. 'Global burden of antimicrobial resistance in 2019: a systematic analysis', The Lancet, Vol 399, Issue 10325, January 20, 2022.
4. Camilo Mora, et al., 'Over half of known human pathogenic diseases can be aggravated by climate change', Nature Climate Change, 12, 869-875, August 8, 2022.
5. Camilo Mora, et al., 'Over half of known human pathogenic diseases can be aggravated by climate change', Nature Climate Change, 12, 869-875, August 8, 2022.

Key policy asks

To address AMR in a warming world with reduced biodiversity, we are calling for:

1. An **international panel of scientists to address AMR**, modelled on the Intergovernmental Panel on Climate Change (IPCC). This would contribute to more rigorous reviews and monitoring and support intergenerational equity, to ensure future generations have access to effective antimicrobials. It would also meet a key priority set out by the Global Leaders Group on AMR, which acknowledges the scale and global significance of the issue.

2. A **ban on the use of antimicrobials in agricultural supply chains for prophylactic treatment and growth stimulation**, modelled on the Montreal Protocol. The Protocol – a landmark multilateral agreement designed to scale down the use of ozone-depleting chemicals to address climate forcing – acknowledged differentiated responsibilities of developed and developing countries but set structured, measurable targets.

3. Global leadership from the G7, G20 and G77 with health and finance ministers leveraging the approaches used to address COVID-19. Under the UK G7 Presidency, finance ministers committed to **strengthen antimicrobial development through 'pull' incentive mechanisms for the developers of novel antimicrobials**; we seek further progress to ensure rewards are tilted towards societal value rather than product volume.

4. Coherent **national responses**, where governments embed antimicrobial stewardship (AMS) in health, economic, trade and financial decision-making processes and within regulatory and legislative architecture.

   In the UK, we highlight the importance of integrating AMR into Sustainable Disclosure Requirements (SDR) and the UK Green Taxonomy, requiring all principal financial regulators (FCA, PRC, MPC, PRA) to explicitly incorporate AMR risks in developing countries and domestically into their activities, and the activities of those they supervise.

5. **Tighter standard setting and enforcement of water quality** related to wastewater from antibiotic use and in the production of antibiotics in watercourses and public bathing areas, taking account of AMR Industry Alliance standards. These are based on scientific evidence on safe thresholds of antimicrobials in the environment.

Together, we believe these actions could help underpin the delivery of the UN SDGs. It will promote a more rigorous, science-led approach to quantify AMR risks, and ensure an appropriate commercial response to preserve the utility of antimicrobials and drive research into the development of novel treatments, including those planned for 'last-line-of-defence'.

What is AMR?

> *“Without effective antimicrobials, the death toll could rise to ten million annually by 2050, costing the global economy a cumulative US$100 trillion”*
>
> **Lord Jim O’Neill**
> Chair, UK Review of Antimicrobial Resistance, 2016

AMR is the process by which pathogens in humans, animals or plants become difficult or impossible to treat with existing antimicrobial drugs (including antibacterials, antivirals, antifungals and antiparasitics) due to changes in the pathogens themselves.

Antimicrobials (including penicillin, streptomycin, chloramphenicol, tetracycline, and various synthetic and semi-synthetic molecules) have revolutionised medicine and boosted productivity in modern agriculture.[6]

However, their overuse and prophylactic (i.e., preventative, before the onset of infection) use in farming and healthcare, combined with failures in water treatment for the removal of antimicrobial residues and AMR bacteria, are leading to more resistant pathogens (or superbugs) in animals, humans and the environment.

Meanwhile, the development of novel treatments has been slow because there is pressure for modest pricing for treatments that might be used in high volume. Novel ‘last-line’ antimicrobials are required too: these compounds are needed in reserve in health settings, to be used rarely or, ideally, not at all. The high costs of drug development and volume-based revenue models have limited the commercial appeal.

The overall decline in the efficacy of existing antimicrobials is costing millions of lives each year. It is estimated there were 1.27 million additional deaths in 2019 directly attributable to bacterial AMR, while AMR played a role in five million deaths.[7] The toll could rise to ten million by 2050.[8] (See Figure 1 for further costs.) Without effective antimicrobials, the risks of undertaking common surgeries like hip and knee replacements or caesarean sections will escalate, and human life expectancy could fall by two decades.[9]

6. Jon Clardy, et al., ‘The natural history of antibiotics’, Current Biology, 19, R437-R441, June 9, 2009.
7. ‘Global burden of antimicrobial resistance in 2019: a systematic analysis’, The Lancet, Vol 399, Issue 10325, January 20, 2022.
8. ‘Sanitation’s role in reducing the spread of AMR’, Health Europa, February 1, 2022.
9. ‘Sanitation’s role in reducing the spread of AMR’, Health Europa, February 1, 2022.

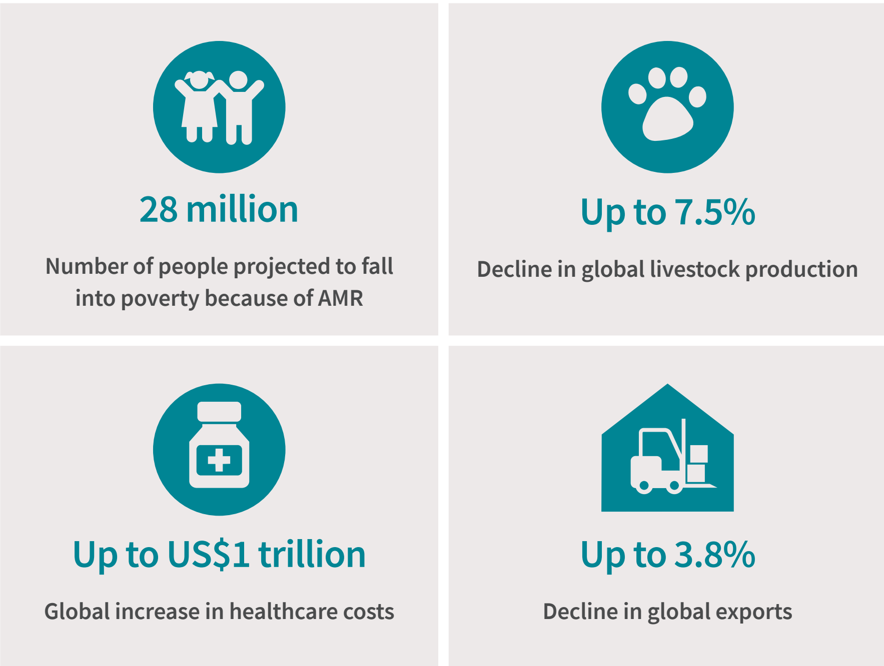
How do bacteria become drug resistant?

There are specific traits that allow bacteria to become resistant, either through mutation or the less-known process of horizontal gene transfer (HGT). Mutation is an important mechanism of acquired resistance, but HGT is arguably more significant.

Transferable resistance is conferred by pieces of DNA that encode resistance genes that can move between bacteria. Recently, successive waves of antimicrobial resistance genes have emerged from environmental reservoirs of bacteria, where they have evolved over millions or billions of years. They have transferred to human gut bacteria and other opportunistic pathogens and disseminated globally.

An even greater concern is that resistance genes are often grouped together on relatively large DNA elements, so a pathogen can acquire multidrug resistance in a single evolutionary step.

Figure 1. **Potential AMR impacts by 2050**



Source: World Bank, September 19, 2016.

How rising global temperatures impact the vectors of disease and horizontal gene transfer

> *"Over half of human pathogenic diseases could be exacerbated by higher temperatures"*

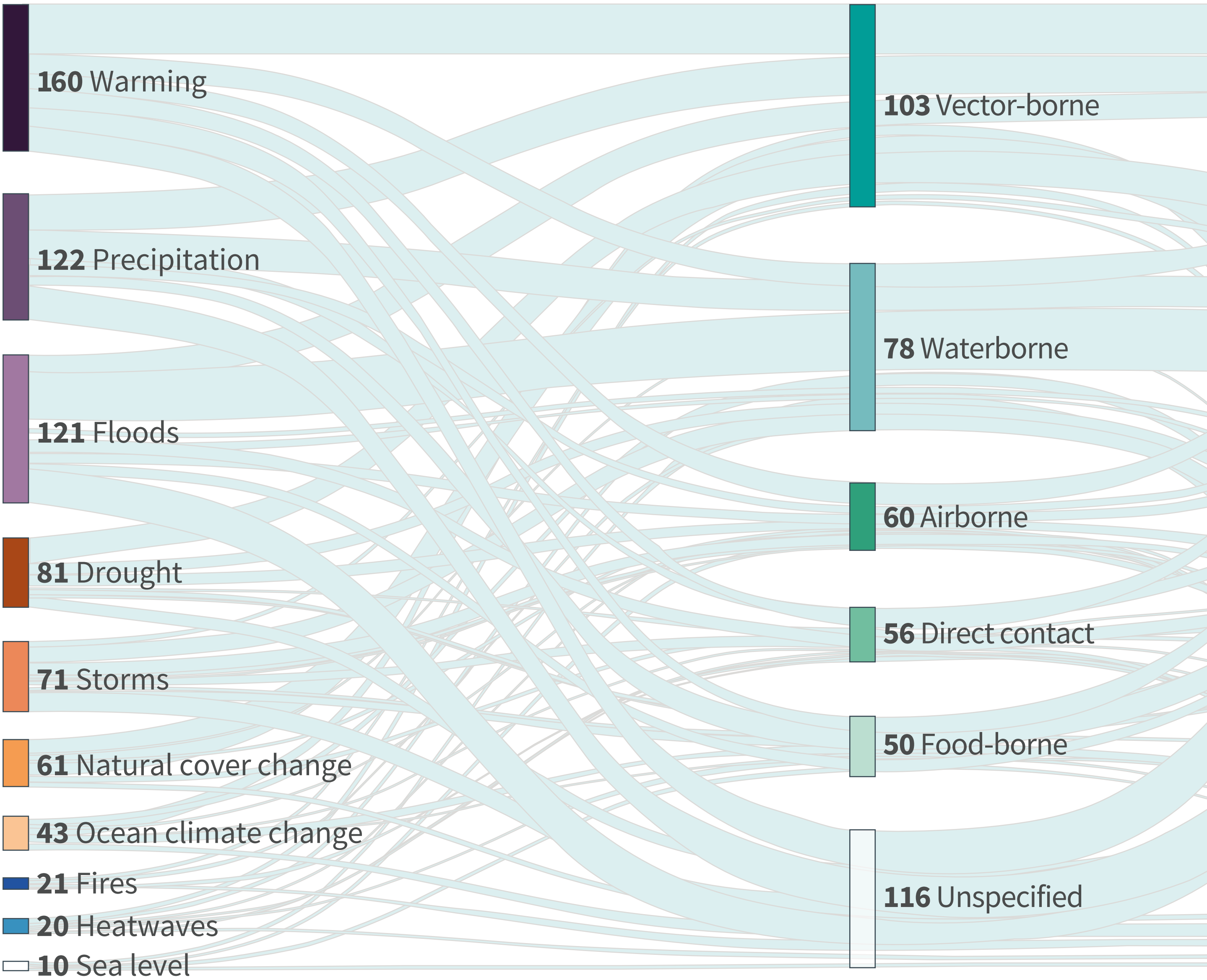
Temperature is a key variable influencing bacterial processes. Recent research suggests over half of human pathogenic diseases could be exacerbated at higher temperatures (Figure 2).[10] Horizontal gene transfer, a major mechanism for the acquisition of antibiotic resistance, is also exacerbated by heat.

A recent study of AMR in the US found a ten-degree Celsius increase caused the resistance of common pathogens like *Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus* to rise by 4.2, 2.2 and 2.7 per cent respectively.[11] Other research to note includes a study by Collignion et al. on anthropological and socioeconomic factors contributing to AMR, which identified temperature as an independent driver of increased AMR infections.[12]

Findings like this suggest the burden of AMR could prove much larger than currently anticipated as average global temperatures increase. Temperature rises are unevenly spread; certain areas already exposed to high AMR risks, such as around the equator, are likely to see higher rates of temperature increase than the global average.

10. Camilo Mora, et al., 'Over half of known human pathogenic diseases can be aggravated by climate change', Nature Climate Change, 12, 869-875, August 8, 2022.
11. Derek R. MacFadden, et al., 'Antibiotic resistance increases with local temperature', Nature Climate Change, 8, 510–514, May 21, 2018.
12. Peter Collignon, et al., 'Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis', The Lancet Planetary Health, Vol 2, Issue 9, E398-E405, September 1, 2018.

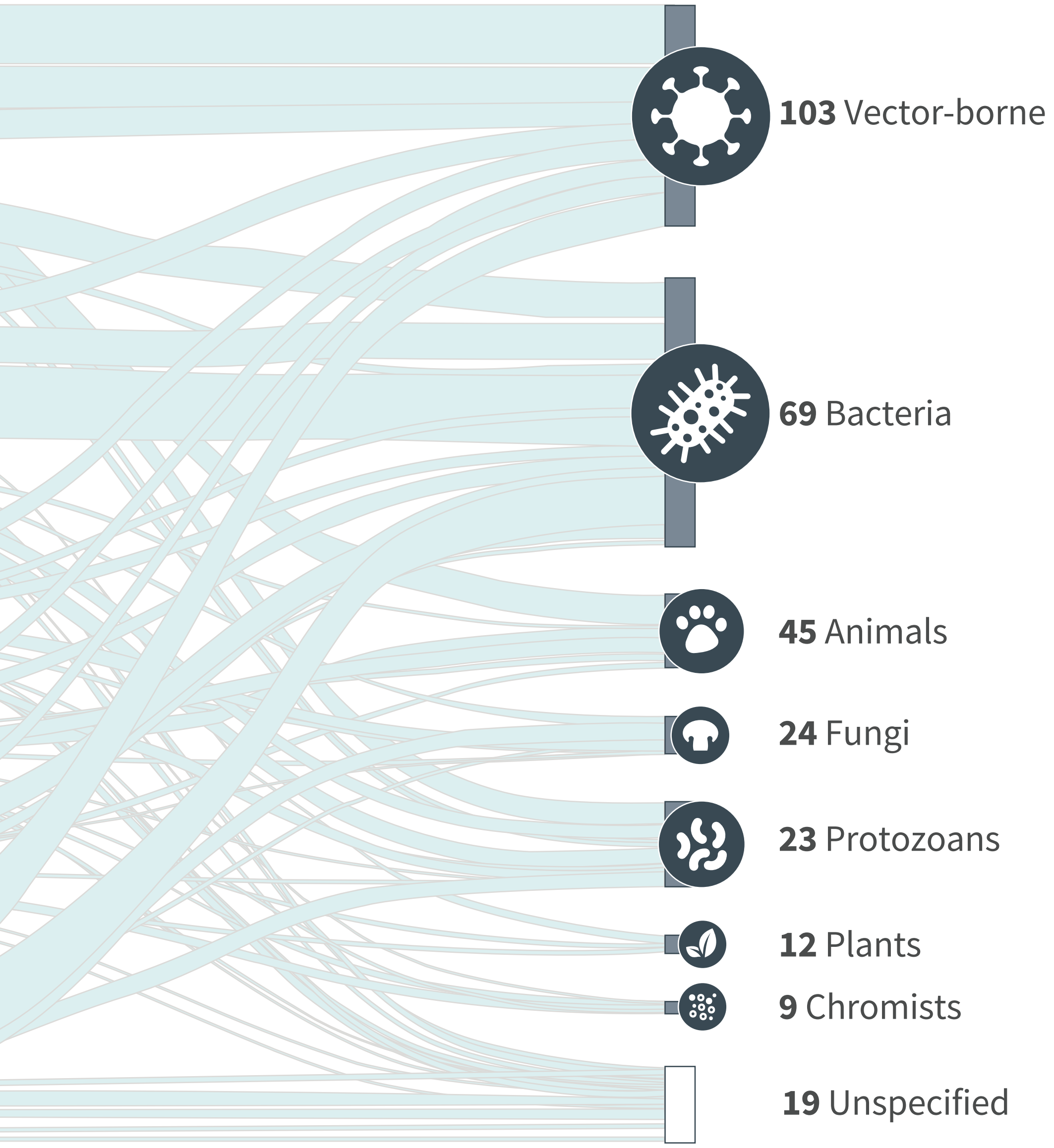
Figure 2. **Pathogenic diseases aggravated by climatic hazards**



There are many ways climatic hazards can aggravate human health. They depend on the way pathogens, allergens and people come into contact, and how peoples' resistance might be diminished, or the pathogen or allergen's prospects strengthened, by the hazard.

Source: Nature Climate Change, 2022.[13]

13. Camilo Mora, et al., 'Over half of known human pathogenic diseases can be aggravated by climate change', Nature Climate Change, 12, 869-875, August 8, 2022.



A recent study of authoritative databases[14] on pathways for known diseases showed the majority (58 per cent of infectious diseases) were aggravated by climatic hazards (captured on the right-hand side of the diagram), while 16 per cent were diminished.

14. GIDEON (Global Infectious Disease and Epidemiology Network), US CDC (Center for Disease Control and Prevention). Note: Illustration only includes positive transmission pathways. Study included plant and fungal allergens, in addition to microbes.

The pathogen/climate/biodiversity nexus

> *"If permafrost melts, dormant pathogens could be released that could be difficult to treat"*

The question then is: do we appreciate the complex ways in which changes to the climate and biosphere will impact pathogens and plant and animal health?

Some multidimensional factors to consider are set out in Figure 4. We highlight:

Climate impacts

- Storms and floods are already displacing populations and disrupting wastewater management, leading to more cases of waterborne disease. In Pakistan, for example, extreme flooding has led to a surge of skin and eye infections, diarrhoea, malaria, typhoid and dengue fever in 2022.[15]
- The UN and IPCC have flagged the issue of climate migrants[16] worldwide. The IPCC suggests they number around 20 million, but that involuntary migration is increasing.[17]
- Heatwaves and droughts contribute to the spread of pathogens as population clusters develop around food and water sources. The risk of acquiring antibiotic-resistant pathogens is exacerbated by malnutrition, crowding and poor sanitation.[18]
- If permafrost melts due to global warming, there is a risk dormant pathogens trapped in the ice could be released that could be difficult or impossible to treat[19] or new resistance mechanisms could spread. For example, a 2016 outbreak of anthrax in Siberia was reportedly associated with thawing permafrost and exposure of an infected reindeer carcass.[20]

15. Syed Raza Hassan, 'Malaria and diseases spreading fast in flood-hit Pakistan', Reuters, September 22, 2022.
16. 'UNHCR – mid-year trends 2021', UNHCR, 2021.
17. 'IPCC WGII Sixth assessment report: Technical summary', 2021.
18. Rebecca L. Brander, et al., 'Correlates of multi-drug non-susceptibility in enteric bacteria isolated from Kenyan children with acute diarrhea', PLOS Neglected Tropical Diseases,11(10), e0005974, October 2, 2017.
19. Boris A. Revich and Marina A. Podolnaya, 'Thawing of permafrost may disturb historic cattle burial grounds in East Siberia', Global Health Action, 4:1, 8482, November 21, 2011.
20. Elisa Stella, et al., 'Permafrost dynamics and the risk of anthrax transmission: a modelling study', Nature Scientific Reports, 10, 16460, October 7, 2020.

Biodiversity impacts

- Rising global temperatures are changing ecoregions and impacting species range; this is changing the way different organisms, including vectors such as ticks, fleas and mosquitos, enable pathogens to spread.[21]
- More diverse ecosystems are better buffers against disease transmission, as competition controls the population of pathogenic hosts. When biodiversity is reduced, there are greater opportunities for zoonoses, where pathogens emerge from hosts and jump from one species to another.[22] This type of cross- species disease transmission is thought to have triggered the COVID-19 pandemic; viral infection was frequently followed by bacterial infection, when immune response was supressed.
- Microbial biodiversity is affected by antimicrobials, with associated impacts on carbon and methane cycling in livestock and environmental microbiomes, potentially increasing greenhouse gas production.[23]
- The natural selection mechanism that ensures pathogens capable of 'winning' at higher temperatures might undermine the disease response in organisms which have immune systems that also use temperature – such as high fever - to combat threats.
- Nature is the inspiration for many novel drug treatments. Destroying biodiversity, for example in rainforests, limits our ability to discover and develop new ones.

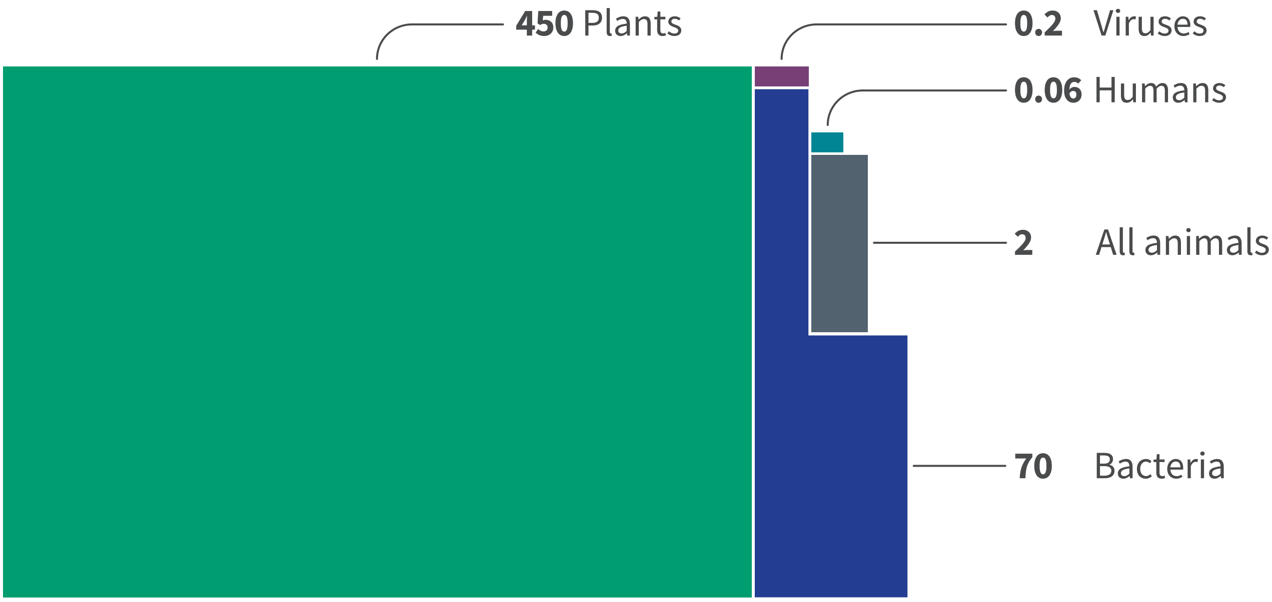
21. Camilo Mora, et al., 'Over half of known human pathogenic diseases can be aggravated by climate change', Nature Climate Change, 12, 869-875, August 8, 2022.
22. R.S. Ostfeld, 'Biodiversity loss and the rise of zoonotic pathogens', Clinical Microbiology and Infection, Vol 15, 1, 40-43, January 1, 2009.
23. E. Bollinger, et al., 'Antibiotics as a silent driver of climate change? A case study investigating methane production in freshwater sediments', Ecotoxicology and Environmental Safety, Vol 228, 113025, December 25, 2021. 'Climate change: A defining challenge for the 21st Century', Gresham College, June 14, 2018.

Antimicrobials, climate, and biodiversity: Amplification and feedbacks

> *"AMR is an emergent risk which could potentially derail the delivery of UN SDGs"*

Although plants dominate other lifeforms in terms of total mass (~450 gigatons of C (Gt C)), the diversity of micro-organisms is extraordinary (~70 GT C) (Figure 3). These communities have ecosystem and geo-planetary impacts.

Figure 3. **Micro-organisms far outweigh human life (GtC)**

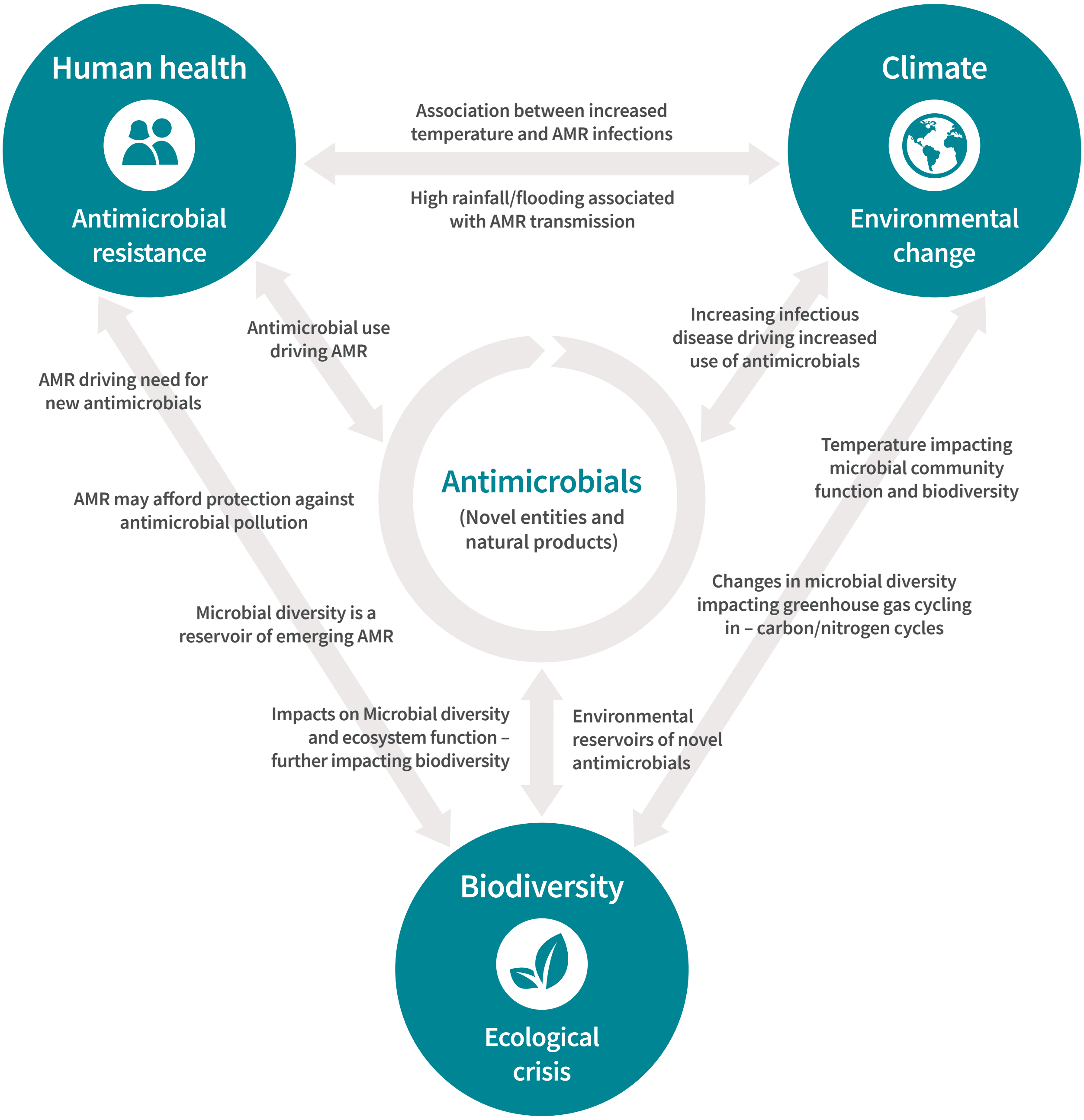


Source: World Bank, September 19, 2016.

Within the biosphere, there are numerous multidirectional relationships and feedback loops. These make outcomes difficult to anticipate, particularly as the climate is thought to be warming around ten times faster than has been experienced before.[24] Increased temperature has been identified as an independent variable associated with increased AMR infections. The complexity is amplified by biodiversity loss triggered by population growth and aggressive human intervention in multiple spheres.

24. 'Climate change: A defining challenge for the 21st Century', Gresham College, June 14, 2018.

Figure 4. **The triple crisis: Human health, climate and biodiversity**



Source: Will Gaze, [unpublished] European Centre for Environment & Human Health, University of Exeter Medical School, 2022.

Bystanders, free-riders, and the tragedy of the commons

Antimicrobial and AMR pollution is a critical environmental issue, with the potential to disrupt key environmental functions and impact human health. But as with addressing climate change and biodiversity loss, AMR suffers from bystander and free-rider issues: where the majority know what the right thing to do is but rely on others to do it. Most do nothing at all.

Unfortunately, all three global issues present perfect conditions for bystanders and free riders to thrive. Worse still, when added together, the tripartite of problems conspire to create the ultimate tragedy of the commons in ways we are only just beginning to understand.

> Capital is not being efficiently directed and asset prices are not reflecting AMR risks

There are ways to avert the highest risk outcomes (see '*Guidance for the finance community*' in Appendix), which for AMR alone could cost the global economy a staggering $100 trillion between 2015 and 2050. Better public awareness, improved surveillance and diagnostics, more rational use of antimicrobials, access to clean water and sanitation, embracing *One Health* (an approach that recognises the health of people is closely connected to the health of animals and the environment), and investments in new antimicrobials and vaccines can all play a part.[25]

Measurable progress on this financially material issue can be made in the way investment is directed, but at the moment capital is not being efficiently directed and asset prices are not reflecting AMR risks. It is a market failure, which requires regulatory intervention to correct it. Systemic change needs a wide lens: greater international cooperation, more multilateral intervention, focused changes to regulatory regimes and their oversight, as well as behavioural change from the bottom-up.

Our asks are driven by our responsibility to promote market integrity under the FRC's Stewardship Code, set out on pages 4 and 18-21. Addressing antimicrobial stewardship is an urgent priority because we consider AMR a systemic risk that threatens the functioning of global markets, with potentially catastrophic human and environmental consequences.

Figure 5. **Addressing AMR to target UN Sustainable Development Goals**

For responsible investors, AMR is an emergent but pertinent risk that could potentially derail the delivery of the UN SDGs.

Poverty (SDG1) is likely to be exacerbated by AMR due to increased costs of healthcare and chronic infections.

Ambition for ***zero hunger (SDG2)*** will be affected by increased AMR infections of livestock and poultry, with negative productivity impacts.

25. 'Antimicrobial resistance: time to repurpose the Global Fund', The Lancet, Vol 399, Issue 10322, P335, January 22, 2022.

3 GOOD HEALTH AND WELL BEING	Achieving ***good health and wellbeing (SDG3)*** is threatened by AMR, which may increase infant mortality and undermine modern medicine.
6 CLEAN WATER AND SANITATION	Delivery of ***clean water and sanitation (SDG6***) is directly impacted.
8 DECENT WORK AND ECONOMIC GROWTH	***Decent work and economic growth (SDG8)*** are affected by the financial burden of AMR infections, and the impact is expected to grow.
12 RESPONSIBLE CONSUMPTION AND PRODUCTION	Responsible production and consumption (SDG12) are affected across human food chains and in the production of pharmaceuticals.
13 CLIMATE ACTION	***Climate action (SDG 13)*** may be impacted, if disturbances to microbial life disrupt the carbon cycle.
14 LIFE BELOW WATER; 15 LIFE ON LAND	***Life below water and on land (SDG14, SDG15)*** is exposed to AMR risk.

Source: Aviva Investors, 2022.

AMR risks

> *“Cheap antimicrobials used in agriculture are contributing to resistance to antimicrobials reserved to treat highly resistant bacteria, causing life-threatening infections”*

Intensive agriculture – factory farming

Routine use of antimicrobials in intensive agriculture and aquaculture is fuelling drug resistance, proving a growing threat for human and animal health. Over 70 per cent of the world’s farms use intensive production methods to accelerate animal protein production, encompassing most (an estimated 99 per cent) US farm animals.[26]

Recent data suggests 75-90 per cent of antimicrobials are excreted from livestock unmetabolised. They leak into the environment, hence the importance of prudent use by farmers and veterinarians,[27] because natural selection ensures the most resilient bacteria live on.

The use of antimicrobials solely for infection prevention and, more importantly, growth promotion is contentious. An EU-wide ban on antimicrobials as growth promoters in animal feed came into effect on January 1, 2006,[28] part of the European Commission’s strategy to tackle overexploitation or misuse of antimicrobials. China has now introduced much stricter controls on antibiotic use[29] and the US FDA has also been campaigning to reduce consumption in food-producing animals.[30]

Nevertheless, there is a lack of comprehensive data that captures antimicrobial consumption globally. A recent projection incorporating 41 developed and emerging markets suggests consumption by poultry, cattle and pigs in food production systems could increase 11.5 per cent between 2017 and 2030.[31]

The link between antimicrobial usage and the development of AMR is well established, as highlighted by the detection of the first plasmid-mediated polymyxin resistance (AMR mechanism, MCR-1) in *Enterobacteriaceae* in animals and humans in China.[32] Links have also been established between antimicrobials used in farming like tetracycline and ampicillin,[33,34] and tigecycline and carbapenem resistance in human pathogens.

The most worrying aspect is that cheap antimicrobials, used in large volumes in agriculture, are contributing to resistance to antimicrobials currently reserved to treat highly resistant bacteria causing life-threatening infections in critical patients, such as neonatal sepsis.[35,36]

26. ‘Factory farming: assessing investment risks’, FAIRR, August 11, 2016.
27. C McKernan, et al., ‘Antimicrobial use in agriculture: critical review of the factors influencing behaviour’, JAC-Antimicrobial Resistance, Vol 3, Issue 4, November 30, 2021.
28. ‘Ban on antibiotics as growth promoters in animal feed comes into effect’, European Commission, December 22, 2005.
29. Kevin Schoenmakers, ‘How China is getting farmers to kick their antibiotics habit’, Nature, October 21, 2020.
30. ‘FDA releases annual summary report on antimicrobials sold or distributed in 2020 for us in food producing animals’, U.S. Food & Drug Administration, December 14, 2021.
31. Katie Tiseo, et al., ‘Global trends in antimicrobial use in food animals from 2017 to 2030’, Antibiotics, 9.12, 918, December 17, 2020.
32. Yi-Yin Liu, et al., ‘Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: A microbiological and molecular biological study’, The Lancet Infectious Diseases, Vol 16, Issue 2, P161–8, November 18, 2015.
33. Tao He, et al., ‘Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans’, Nature Microbiology, 4, 1450-1456, May 27, 2019.
34. Ruidong Zhai, et al., ‘Contaminated in-house environment contributes to the persistence and transmission of NDM-producing bacteria in a Chinese poultry farm’, Environment International, Vol 139, 105715, June 2020.
35. Tao He, et al., ‘Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans’, Nature Microbiology, 4, 1450-1456, May 27, 2019.
36. Ruidong Zhai, et al., ‘Contaminated in-house environment contributes to the persistence and transmission of NDM-producing bacteria in a Chinese poultry farm’, Environment International, Vol 139, 105715, June 2020.

Unsafe sanitation and inadequate treatment of effluent

Unsafe sanitation and inadequate wastewater infrastructure are among the world's largest health and environmental problems, particularly for the poorest. They are responsible for around five per cent of deaths in low-income countries.[37]

A lack of access to clean water and decent sanitation contributes to the spread of infectious diseases, including cholera, diarrhoea, dysentery, hepatitis A, typhoid, and polio. It also exacerbates malnutrition and, in particular, childhood stunting. It is estimated that improving sanitation in low-income countries would decrease the use of antimicrobials to treat diarrhoea by around 60 per cent,[38] with associated benefits in addressing AMR.

While billions of bacteria found in human faecal material are removed via wastewater treatment plants, not all are removed, and some output includes traces of resistance DNA that could be acquired by other bacteria.

In a chapter by Araújo et al. (2020) on AMR, sanitation and public health, the authors highlight the relationship between sewage and livestock manure and the role of wastewater treatment plants (WWTP).[39] They review different treatment technologies in reducing AMR from municipal and livestock wastewaters. They observe the role municipal WWTPs with tertiary treatment systems, combined with emerging technologies, including membrane separation, advanced oxidation, adsorption and disinfection, can deliver in the prevention and control of AMR spread. This contributes to the maintenance of environmental and public health and, if effective, delivers societal and environmental benefits.

> Improving sanitation in low-income countries would decrease the use of antimicrobials to treat diarrhoea, with associated benefits in addressing AMR

Biodiversity loss and cross-species transfer of opportunistic micro-organisms

Opportunistic micro-organisms and viruses that infect wild animals encounter new hosts all the time. Some make successful jumps across species; if they infect humans, these pathogens are known as zoonoses. It may be the case that a virus makes the leap, as with COVID-19, with infection closely followed by a bacterial infection. In those cases, broad spectrum antimicrobials may be prescribed, although research suggests a number of prescriptions written during the recent COVID-19 pandemic were unnecessary and could have been avoided.[40] This overuse can contribute to AMR.

Many people are not aware of the scale of troubling zoonotic infections: the World Health Organization attributes around one billion cases of disease each year to them.[41] Recent outbreaks have been traced to rats (Hanta), bats (Hendra, Ebola), birds (Bird Flu, West Nile) and pigs (Nipah). Some have alarmingly high fatality rates.

37. 'Global burden of antimicrobial resistance in 2019: a systematic analysis', The Lancet, Vol 399, Issue 10325, January 20, 2022.
38. Teja Sirec and Tomasz Benedyk, 'One Health: 10 ways to tackle antimicrobial resistance', FEMS, September 19, 2017.
39. Juliana Calabria de Araújo, et al., 'Antibiotic resistance, sanitation, and public health', Antibiotic Resistance in the Environment, The Handbook of Environmental Chemistry, vol 91, P189-216, March 25, 2020.
40. Megan M. Petteys, et al., 'Outcomes and antibiotic use in patients with coronavirus disease 2019 (COVID-19) admitted to an intensive care unit', Antimicrob Steward Health Epidemiol, 2(1)L e12, January 17, 2022.
41. 'Zoonotic disease: emerging public health threats in the Region', World Health Organization, 2022.

Evidence suggests the risk of newly emerging zoonoses is increasing. Around the world, the human population has grown by around 2.6 billion since 1990,[42] while around 420 million hectares or one billion acres of forest has been lost[43] to agriculture, industry and housing. By moving into virgin forest or sparsely populated habitats, there are more opportunities for the emergence of zoonotic infections in humans.

"Rampant deforestation, uncontrolled expansion of agriculture, intensive farming, mining and infrastructure development, as well as the exploitation of wild species, have created a 'perfect storm' for the spill over of disease," noted the 2019 Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES).[44] More monitoring and research is needed into the way in which pathogens emerge from wildlife and ecosystems that have lost finely balanced equilibria.

There is a direct analogy between zoonotic infections and AMR. Transferable resistance genes in some human bacterial pathogens are known to have originated in environmental bacteria.[45,46] The mobile pieces of DNA that carry these genes, and allow transfer between bacteria, are similar in some ways to viruses. In the same way biodiversity loss and human encroachment into natural environments drive the emergence of zoonotic pathogens, these processes are likely to enable new AMR mechanisms to emerge from microbial communities in nature and be transferred to susceptible human pathogens.

More monitoring and research is needed into the way in which pathogens emerge from wildlife

42. 'Population pyramids of the World from 1950 to 2100: World 2022', Populationpyramid.net, 2022.
43. 'The State of the World's Forests 2020', Food and Agriculture Organization of the United Nations, 2020.
44. S. Diaz, et al., 'The global Assessment report on biodiversity and ecosystem services', Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES), 2019.
45. Gerard D. Wright, 'The antibiotic resistome: the nexus of chemical and genetic diversity', Nature Reviews Microbiology, 5, 175-86, May 2007.
46. Poirel L, Kämpfer P, Nordmann P. 'Chromosome-encoded Ambler class A beta-lactamase of Kluyvera georgiana, a probable progenitor of a subgroup of CTX-M extended-spectrum beta-lactamases', Antimicrobial Agents and Chemotherapy, Vol 46, No. 12, December 1, 2002.

Addressing AMR: Progress and planning priorities

1. Considering intergenerational equity and calling for an IPCC for AMR

The timescales of cause and effect in relation to climate change and AMR raise the question of intergenerational equity and a just transition. Future generations will lose the benefits society has today from the use of antimicrobials, but will also have to face future economic, environmental and societal costs.

Predicting the future trajectory of antimicrobial usage and resistance is challenging, but global, co-ordinated action could result in antimicrobials being managed better and the development of novel treatments.

A practical solution might include establishing a global network of laboratories working to the same high standard to track and report on rates of resistance to drugs of critical importance. Without an early-warning defence network with accurate and contemporaneous surveillance data, other attempts at targeting support are likely to be compromised.

> Co-ordinated action could result in antimicrobials being managed better and the development of novel treatments

We call on the Global Leaders' Group on AMR, working with the AMR Quadripartite Joint Secretariat (QJS), to advocate for an international panel of scientists to address the AMR challenge, modelled on the Intergovernmental Panel on Climate Change (IPCC), supported by a global network of laboratories to track and report on resilience to drugs of critical importance.

2. A ban on the use of antimicrobials in agricultural supply chains for prophylactic treatment and growth stimulation, modelled on the Montreal Protocol

The Protocol – a landmark multilateral agreement designed to scale down the use of ozone-depleting chemicals to address climate forcing – acknowledged differentiated responsibilities of developed and developing countries but set structured, measurable targets.

We call on the UN General Assembly to address AMR risk with the same rigour used to confront the depletion of the ozone layer, resulting in the successful scaling down in the use of ozone-depleting substances, by agreeing measurable targets within a defined timescale.

3. Multilateral interventions to ensure better stewardship and drive commercial pull incentives for novel treatments

Staying one step ahead of superbugs requires global leadership from the G7 and G20, with support from the G77, with health and finance ministers leveraging approaches used to address COVID-19. Under the UK G7 Presidency in 2021, finance ministers made commitments to strengthen antimicrobial development through ‘pull’ incentive mechanisms.

Finance ministers have committed to taking steps to create economic conditions to catalyse innovation and bring novel antimicrobials to market, push for better stewardship of existing medicines, and ensure the antimicrobial supply chain is safe and transparent. With Germany’s leadership of the G7 this year, finance ministers reiterated their commitments, and we look to Japan to ensure they are delivered.

The UK has already begun using a world-first subscription-based model to finance access to antimicrobials like *cefiderocol* and *avibactam* for NHS patients, based on their value rather than the volume of drugs consumed, in a project involving Shionogi and Pfizer. Because of broken economics, the global pipeline of new antimicrobials is dangerously thin. We need novel antimicrobials, but the incentives needed to develop them are not in place.

> Staying one step ahead of superbugs requires global leadership from the G7 and G20

The incentivisation to drive new antimicrobial research and development contained in the US PASTEUR Act (2021) is key to addressing this present and future threat to our modern medicine system, which are underpinned by antimicrobials. The Act aims to establish market incentives via a subscription-based payment mechanism to encourage the commercialisation of novel antimicrobials to protect our ability to treat resistant infections. It is intended to strengthen the drug development pipeline, to ensure it remains dynamic.

If implemented effectively, this could be a watershed moment in addressing AMR and send a signal to other economies on the importance of changing their approach to antimicrobial consumption. It gives a glimpse of what the future might look like, where it makes as much commercial sense for companies to develop new antimicrobial treatments as it might be to pursue new cancer therapies.

We support the development of commercial ‘pull’ incentives for novel antimicrobials to reflect societal value rather than volume, and call for more dedicated focus on incentive design.

Specifically, we believe the PASTEUR Act will protect modern medicine by supporting the development of critically important new antimicrobials for bacterial and fungal infections. We commend this bipartisan piece of legislation and call for it to be supported in its passage through the legislature.

4. Tighter standard setting for watercourses and public bathing areas

Clinically important AMR bacteria can be found in UK bathing waters at levels high enough for people to be at risk of infection when they swim. It is estimated more than six million water sports sessions occur that involved the ingestion of these AMR bacteria every year.[47] Moreover, it is thought there are more than 123 million exposures to *E. coli* harbouring one or more resistance genes in England alone each year.[48]

We encourage DEFRA to consider the AMR Industry Alliance standards and fast-track production of the wastewater standards the UK committed to produce when it held the G7 Presidency and, looking ahead to India's G20 Presidency, to consider how best to encourage India to seek buy-in for G20 wastewater standards.

5. A collaborative, whole-of-society approach to embed antimicrobial stewardship in regulatory and legislative architecture

The UK government has pledged to put *One Health* at the heart of policymaking. Antimicrobial stewardship (AMS) should not just be a task for the private sector: the government must also embed AMS into core health, economic, trade and financial decision-making processes.

> Antimicrobial stewardship should not just be a task for the private sector

In the G7, the Informal Consultation Group brought together industry, heath and finance representatives to address the issue of pull incentives. This collaboration worked well, and we commend this approach to HM Treasury, DEFRA, and the Department of Health and Social Care to address AMR.

We call on Her Majesty's Treasury (HMT), the UK Department for Business, Energy and Industrial Strategy (BEIS) and their global equivalents to embed stewardship in regulatory and legislative architecture, such as the Sustainable Disclosure Requirements (SDR) and the UK Green Taxonomy, requiring all principal financial regulators (FCA, PRC, MPC, PRA) to explicitly incorporate AMR risks into their activities.

47. 'Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters', Environmental International, Vol 82, 92-100, September 2015.
48. A F C Leonard, et al., 'A coliform-targeted metagenomic method facilitating human exposure estimates to Escherichia coli-borne antibiotic resistance genes', FEMS Microbiology Ecology, Vol 94, Issue 3, February 19, 2018.

Conclusion

Failing to manage AMR is already enormously costly: millions of lives are lost every year. The health crises being played out after extreme flooding in Pakistan and in populations on the move illustrate what is at stake. But these will pale in comparison to the costs if existing antimicrobials lose their efficacy while the pathogens that carry disease thrive in a warmer, less biodiverse world. More lives lost, less growth, the destruction of asset value and impaired rates of return can all be anticipated if AMR is not addressed.

While investors have a vital role to play in highlighting risks in industrial agriculture, commercial wastewater treatment and the pharmaceutical industry, achieving systemic change needs holistic action. Risk at this scale cannot be addressed by the financial sector alone. Public awareness, better surveillance and diagnostics, a *One Health* approach and investments in new antimicrobials are all needed, within carefully focused regulatory architecture.

While the challenges are significant, governments are now much more aware of the risks and costs of failing to devote enough resources and attention to managing infectious disease after COVID-19. This could be a once-in-a-generation opportunity to reset attitudes, concentrate on more judicious use of precious resources and make real strides in addressing AMR.

Appendix

AMR resources for the finance community

Investor Action on AMR Initiative

Alongside FAIRR, the UN Principles for Responsible Investment, and the Access to Medicine Foundation, the UK's Department of Health and Social Care launched the Investor Action on AMR initiative. Aviva Investors was a founding member of this important initiative and now one of over 16 investors with combined assets of over US$11 trillion aligning with global best practices by calling on global leaders to combat antimicrobial resistance.

The Access to Medicine Foundation's AMR benchmark

The Access to Medicine Foundation is a non-profit, independent organisation based in Amsterdam. The Foundation incentivises companies and mobilises powerful allies – including investors, policymakers and global health organisations – to expand access to medicines, vaccines and other essential health products in low- and middle-income countries. Investors use the Foundation's insights and analysis to better manage risks and opportunities related to access-to-medicine and antimicrobial resistance, and inform direct engagements with investee companies.

The Access to Medicine Foundation publishes a periodic report evaluating the performance of 17 companies, including large companies engaged in research and development and generic medicine manufacturers in the anti-infectives field.[49] The AMR Benchmark reports where companies have the greatest opportunity and responsibility to limit AMR and compares performance across 20 metrics spanning four broad categories, including:

- **Research and development**, including an analysis of the projects in companies' pipelines that target priority pathogens, i.e., those that present the greatest threat to human health, including *C.difficile* and carbapenem-resistant *Enterobacteriaceae*.
- **Responsible manufacturing**, including governance of how sites manage and dispose of waste that may contain active pharmaceutical ingredients (APIs) and monitoring to ensure the level of antimicrobials in wastewater do not exceed safe limits.
- **Appropriate access**, including registering products in low- and middle- income countries, ensuring medicines are affordable through equitable pricing structures, and building capacity to help lower-income countries build up knowledge and expertise in manufacturing.

49. '2021 antimicrobial resistance benchmark 2021', Access to Medicine Foundation, November 18, 2021.

- **Stewardship**, including gathering and sharing data to track where infection rates are rising and resistance is emerging, aligning sales and marketing practices with stewardship guidelines, and supporting patients to adhere to dosing and treatment regimes.

The 2021 Benchmark provides specific actions investors can take to curb AMR, for example by considering as part of their investment decisions whether a company manufactures responsibly. The Benchmark supports the integration of these considerations into investment decisions by scoring companies and giving them a 'Report Card', detailing their performance year-on-year, and outlining opportunities for improvement. This provides an additional tool for investors to gain insight into company actions and commitments.

Business Benchmark on Farm Animal Welfare

Now in its tenth year, the Business Benchmark on Farm Animal Welfare (BBFAW) is an annual publication reporting on 150 companies across industry subsectors, including food retailers and wholesalers, restaurants and bars, and food producers, across 23 different countries.[50] This helps investors understand how investee companies are managing farm animal welfare, including in their supply chains, to compare performance, identify leaders and laggards, and examine how farm animal welfare in the global food industry is changing. This informs investor engagement around farm animal welfare.

The Benchmark uses published information to examine company performance on 37 distinct, objective criteria across four categories:

- Management commitment, which considers a company's policies on farm animal welfare, including specific issues around close confinement and long-distance live transportation. Here, best practice includes publishing the risks and opportunities farm animal welfare poses and a policy setting out core principles and their implementation.
- Governance and management, including management oversight of policy commitments and progress against objectives and targets. Here, best practice includes specifying who is responsible for farm animal welfare on a day-to-day basis and at a senior management level.
- Leadership and innovation, including investment in projects to support and advocate for farm animal welfare. Here, best practice includes participation in research and development to enhance farm animal welfare or engaging clients and customers on the topic.
- Performance reporting and impact, including reporting on performance against policies and targets as well as outcome-based measures of welfare. Here, best practice includes reporting on commonly accepted welfare issues like close confinement and routine mutilations like tail docking as well as issues affecting individual species, like feather coverage in laying hens.

50. Nicky Amos, et al., 'The business benchmark on farm animal welfare report 2021', Business Benchmark on Farm Animal Welfare, 2021.

FAIRR

Established by the Jeremy Coller Foundation, the FAIRR Initiative is a collaborative investor network that raises awareness of the environmental, social and governance (ESG) risks and opportunities in the food system.

With offices based in London, it provides cutting-edge research, best practice tools and collaborative engagement opportunities to help investors integrate these risks and opportunities into their investment decision-making and active stewardship processes. FAIRR's network counts over 350 members globally, representing over $68 trillion in combined assets.

FAIRR has produced resources to support investor engagement with the global food sector. One is the Best Practice Policy on Antibiotic Stewardship for Food Companies.[51] This is a publicly available resource developed in consultation with leading industry and issue experts. It provides guidance for food companies, including animal protein producers and purchasers, when developing their individual policies. The guidance encourages companies to phase out the use of medically important antimicrobials in their supply chains, restrict the use of any antimicrobials for prophylactic and metaphylactic use and to set time-bound targets.

Second, the Coller FAIRR Protein Producer is a benchmarking took that provides investors with a systematic assessment of the 60 largest animal protein producers on key strategic ESG issues, including antibiotic use and policies.[52] The tool enables investors to identify companies that are low, medium, or high risk according to the strength of their antimicrobials policy and disclosure.

Finally, FAIRR has developed a comprehensive list of company dialogue questions to provide investors with guidance and direction in their engagement with animal protein producers on several topics including antibiotic use. Using these questions, collaborative engagements provide opportunities for investors to start open dialogues with companies to improve their practices.

The FAIRR Initiative conducted an engagement with 20 companies in the casual dining and fast-food sector to improve antibiotic stewardship and usage. The engagement ran for three years and encouraged all 20 companies to implement policies to address AMR. FAIRR has also launched an engagement this year targeting the animal pharmaceutical industry to diversify their portfolios and provide greater disclosure on their practices and policies to address the risk of AMR throughout their value chain. Collaborative engagements enable investors to leverage their influence to induce companies to enhance and improve their policies.

51. Nicky Amos, et al., 'The business benchmark on farm animal welfare report 2021', Business Benchmark on Farm Animal Welfare, 2021.
52. Nicky Amos, et al., 'The business benchmark on farm animal welfare report 2021', Business Benchmark on Farm Animal Welfare, 2021.

The Shareholder Commons

The Shareholder Commons (TSC) addresses social and environmental issues from the perspective of shareholders who diversify their investments to optimise risk and return. In September 2022, TSC released two case studies[53] demonstrating the engagement gap between company-first ESG advocacy and portfolio-first system stewardship for investors concerned about the harmful impacts of climate change and AMR. The case studies show that shareholders must reject the conventional assumption that shareholder advocacy should be limited to actions intended to increase a company's enterprise value. This rejection will mean firmly prioritising the economy and portfolio-wide value over enterprise value at individual companies.

The studies start from the simple observation that many companies optimise cashflows by selling products and services responsible for excess greenhouse gas emissions and antimicrobial overuse and mismanagement.

Despite the enormous social costs of these practices, they are financially efficient from the perspective of these companies—even over the long term—because each receives all the margin improvement from its choices, while the costs of climate change and AMR are borne by the entire economy. But most shareholders have diversified portfolios that depend on the health of the economy for long-term performance. As a result, shareholders internalise the same costs externalised by the companies they own. The studies emphasise phasise the relationship between externalised costs and diversified portfolios means company executives, who (understandably) focus only on their own companies' performance, have an inherent conflict with the majority of their shareholders. Unlike executives, who are incentivised to increase enterprise value, diversified shareholders can benefit when a company reduces its own value to preserve the value of the economy and diversified portfolios.

The case studies conclude shareholders should address this conflict by supporting guardrails that encourage companies to compete for revenue and margin without excess externalisation of social and environmental costs. TSC is currently working with investors to implement such guardrails on climate change and AMR, among other systemic risks.

53. 'Closing the engagement gap: climate change and antimicrobial resistance', The Shareholder Commons, 2022.

Important Information

THIS IS A MARKETING COMMUNICATION

Except where stated as otherwise, the source of all information is Aviva Investors Global Services Limited (AIGSL). Unless stated otherwise any views and opinions are those of Aviva Investors. They should not be viewed as indicating any guarantee of return from an investment managed by Aviva Investors nor as advice of any nature. Information contained herein has been obtained from sources believed to be reliable, but has not been independently verified by Aviva Investors and is not guaranteed to be accurate. Past performance is not a guide to the future. The value of an investment and any income from it may go down as well as up and the investor may not get back the original amount invested. Nothing in this material, including any references to specific securities, assets classes and financial markets is intended to or should be construed as advice or recommendations of any nature. Some data shown are hypothetical or projected and may not come to pass as stated due to changes in market conditions and are not guarantees of future outcomes. This material is not a recommendation to sell or purchase any investment.

In Europe this document is issued by Aviva Investors Luxembourg S.A. Registered Office: 2 rue du Fort Bourbon, 1st Floor, 1249 Luxembourg. Supervised by Commission de Surveillance du Secteur Financier. An Aviva company. In the UK Issued by Aviva Investors Global Services Limited. Registered in England No. 1151805. Registered Office: 80 Fenchurch Street, London EC3M 4AE. Authorised and regulated by the Financial Conduct Authority. Firm Reference No. 119178. In Switzerland, this document is issued by Aviva Investors Schweiz GmbH.

In Singapore, this material is being circulated by way of an arrangement with Aviva Investors Asia Pte. Limited (AIAPL) for distribution to institutional investors only. Please note that AIAPL does not provide any independent research or analysis in the substance or preparation of this material. Recipients of this material are to contact AIAPL in respect of any matters arising from, or in connection with, this material. AIAPL, a company incorporated under the laws of Singapore with registration number 200813519W, holds a valid Capital Markets Services Licence to carry out fund management activities issued under the Securities and Futures Act (Singapore Statute Cap. 289) and Asian Exempt Financial Adviser for the purposes of the Financial Advisers Act (Singapore Statute Cap.110). Registered Office: 138 Market Street, #05-01 CapitaGreen, Singapore 048946. In Australia, this material is being circulated by way of an arrangement with Aviva Investors Pacific Pty Ltd (AIPPL) for distribution to wholesale investors only. Please note that AIPPL does not provide any independent research or analysis in the substance or preparation of this material. Recipients of this material are to contact AIPPL in respect of any matters arising from, or in connection with, this material. AIPPL, a company incorporated under the laws of Australia with Australian Business No. 87 153 200 278 and Australian Company No. 153 200 278, holds an Australian Financial Services License (AFSL 411458) issued by the Australian Securities and Investments Commission. Business Address: Level 27, 101 Collins Street, Melbourne, VIC 3000 Australia.

The name “Aviva Investors” as used in this material refers to the global organization of affiliated asset management businesses operating under the Aviva Investors name. Each Aviva investors’ affiliate is a subsidiary of Aviva plc, a publicly- traded multi-national financial services company headquartered in the United Kingdom. Aviva Investors Canada, Inc. (“AIC”) is located in Toronto and is registered with the Ontario Securities Commission (“OSC”) as a Portfolio Manager, an Exempt Market Dealer, and a Commodity Trading Manager. Aviva Investors Americas LLC is a federally registered investment advisor with the U.S. Securities and Exchange Commission. Aviva Investors Americas is also a commodity trading advisor (“CTA”) registered with the Commodity Futures Trading Commission (“CFTC”), and is a member of the National Futures Association (“NFA”). AIA’s Form ADV Part 2A, which provides background information about the firm and its business practices, is available upon written request to: Compliance Department, 225 West Wacker Drive, Suite 2250, Chicago, IL 60606.

364255 – 30/11/2024

Contact us

Aviva Investors
80 Fenchurch Street
London EC3M 4AE
+44 (0)20 7809 6000

www.avivainvestors.com