ANTIMICROBIAL RESISTANCE

The Silent Pandemic

Citi GPS: Global Perspectives & Solutions

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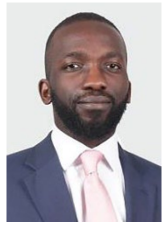

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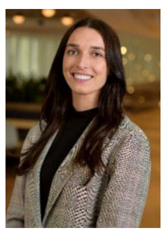

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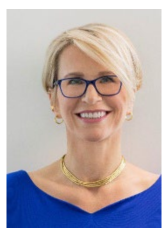

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ANTIMICROBIAL RESISTANCE

The Silent Pandemic

Kathleen Boyle, CFA
Managing Editor, Citi GPS

In the Citi GPS *Disruptive Innovation* series, we have highlighted amazing new advancements in healthcare over the years — from immunotherapy, and CRISPR-based gene editing to virtual care and blood tests for cancer. One healthcare area notably absent from the innovation series is antibiotics. In the U.S., 251.1 million antibiotic prescriptions were written in 2019, making it the second most prescribed drug category behind cholesterol reducers. But half of the antibiotics commonly used today were discovered in the 1950s, and the last antibiotic class successfully introduced as treatment was discovered in 1987.

Why is this an issue? Because bacteria are increasingly becoming resistant to today's antibiotics. In 2019, 4.95 million deaths were associated with bacterial drug resistance, with 1.27 million deaths directly attributed to it. If the issue of antimicrobial resistance (AMR) is not addressed, it could lead to 10 million deaths by 2050.

The drivers of AMR include overuse and misuse of antibiotics in humans and animals, poor hygiene and sanitation, and a lack of research and innovation to develop novel antimicrobials. At the same time, climate change is exacerbating many health challenges. Rising temperatures have increased the frequency and intensity of outbreaks of some diseases, as well as their geographical scope. Extreme weather can also increase the burden of infectious disease. Flooding leads to increased agricultural run-off as well as sewage contamination, which both increase the risk of disease spread. And as extreme weather increases, populations become displaced as homes become uninhabitable and access to potable water is threatened.

The report that follows looks at interventions that could avert the worst outcomes, and although AMR is a significant problem, many solutions are within reach. However, these solutions require the collaboration of a broad range of stakeholders, including the public and private sectors as well as civil society.

The first step in addressing AMR is reducing the burden of infectious disease. This can be done through improving sanitation and developing vaccines to prevent infections in both humans and animals. The second is reducing the use of antimicrobials in humans and animals by raising awareness on AMR, reducing unnecessary antimicrobials in food production, and developing rapid diagnostics. Facilitating innovation with investment in early-stage research and drug discovery will help in the quest for new novel antimicrobials. Finally, implementing steps to curtail the spread of resistance, such as strengthening global surveillance of drug resistance and improving treatment of wastewater with attention to antimicrobials.

Most importantly, the report calls for tackling AMR with the same effort as climate change. We view AMR, climate change, and biodiversity loss as closely related; this aligns with a "One Health" approach, which recognizes that animal, human, and environmental health should be considered holistically.

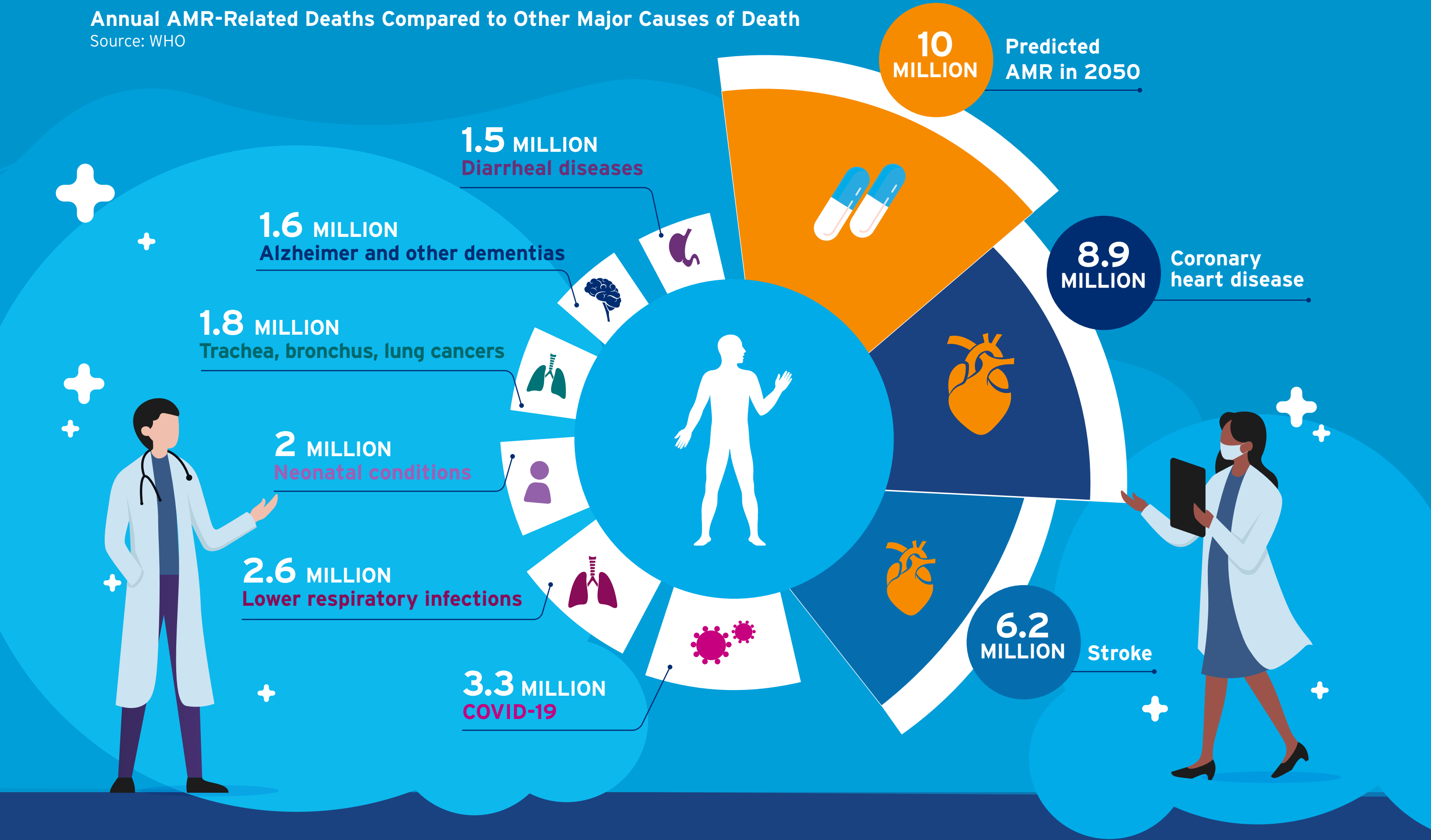
Based on discussions with experts throughout the report, policymaking appears to be the single most effective starting point in tackling AMR. The report summarizes their views and provides key recommendations for policymakers.

The Tragedy of the Commons

WHY IS ANTIMICROBIAL RESISTANCE (AMR) IMPORTANT?

If we fail to protect the current suite of antibiotics and invest in research and development into new antibiotics, we could find ourselves in a scenario where most, if not all, antibiotics no longer work. This would limit our ability to treat common infections. In 2019, an estimated 1.27 million deaths globally were directly attributed to AMR and by 2050 up to 10 million may die from AMR-related illnesses.

Annual AMR-Related Deaths Compared to Other Major Causes of Death
Source: WHO



DRIVERS OF ANTIMICROBIAL RESISTANCE

Overuse and misuse in humans

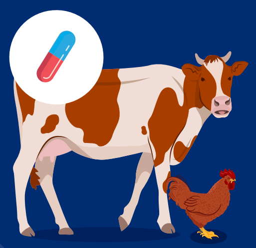
66%
of antibiotics used in U.S. are likely non-prescribed

30%
of antibiotics prescribed in U.S. are likely unnecessary

Overuse and misuse in animals

70%-80%
of global antimicrobial consumption is by animals

75%-90%
of antibiotics are excreted by animals unmetabolized and leak into the environment.



Poor hygiene and sanitation

Almost **50%** of the global population lacked access to adequate sanitation in 2020

Better sanitation in low-income countries could reduce antibiotic use to treat diarrhea by
60%

Lack of research and innovation to develop antimicrobials

Only 5%
of venture capital invested in pharmaceutical R&D went to antimicrobials research between 2003 and 2014

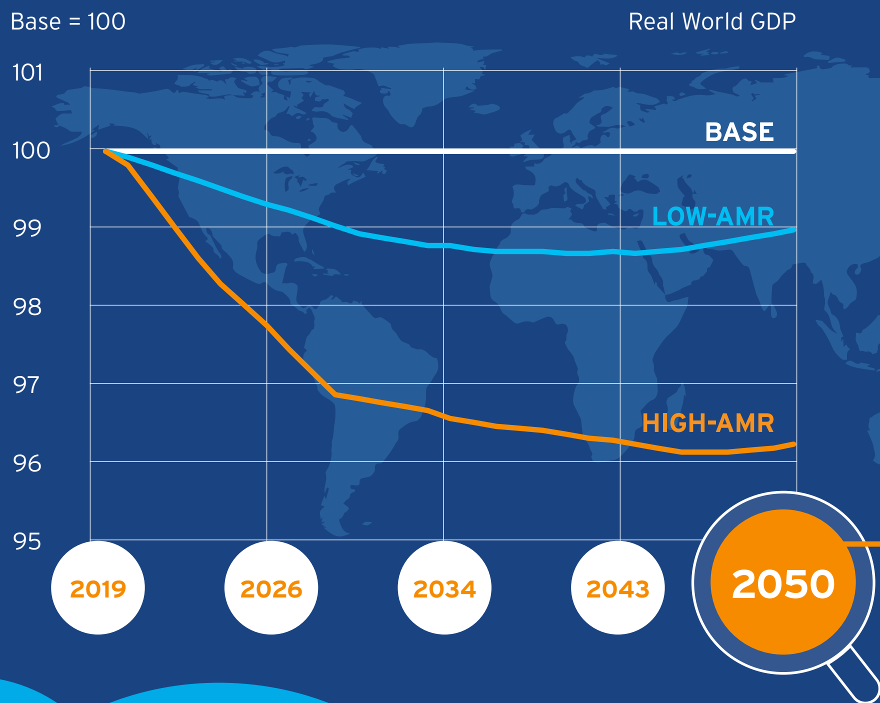
1.2%
of grant funding by the U.S. National Institutes of Health went to AMR-related research between 2009 and 2013

CONSEQUENCES OF ANTIMICROBIAL RESISTANCE

Using two scenarios corresponding to low and high AMR impacts, World Bank simulations have quantified the potential economic losses from AMR globally between 2017 and 2050.

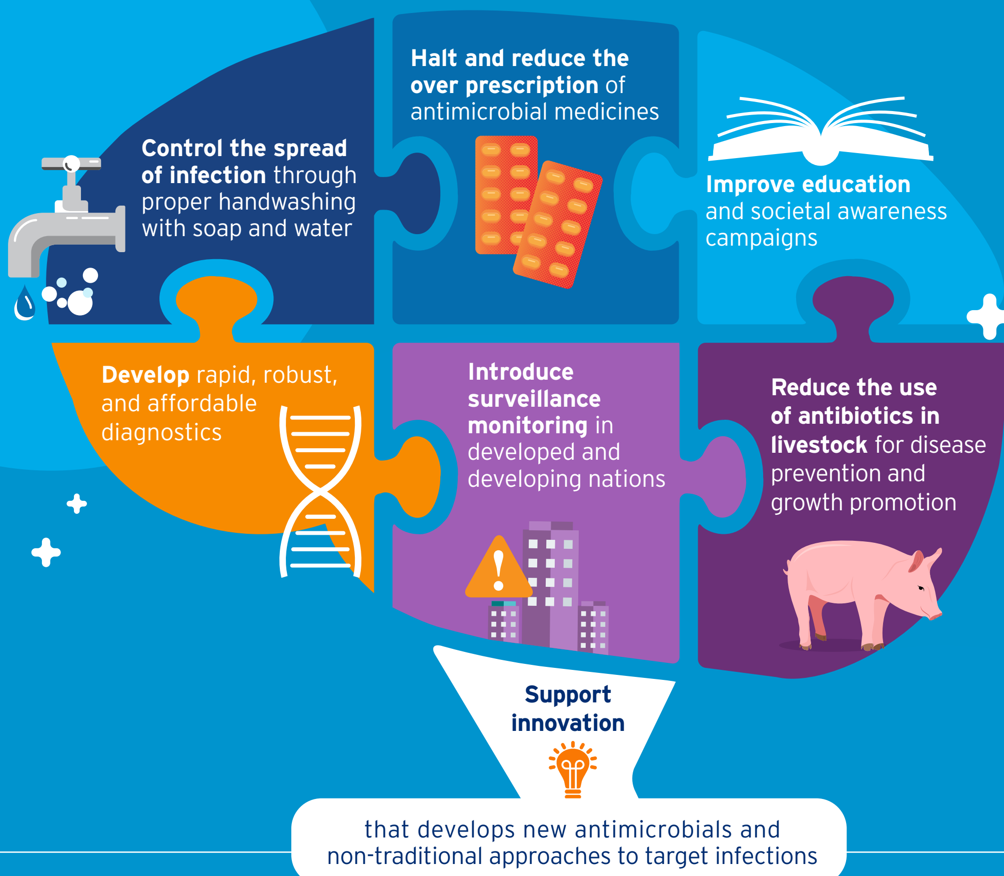
Source: The World Bank

By 2050, the high-AMR scenario would cause:



- **Annual global** GDP to fall by 3.8%
- 28 million more people to fall into **extreme poverty**
- Global real **exports** to fall 3.8%
- **Global healthcare** costs to inflate by $1 trillion a year
- **Annual livestock** production to fall by 7.5% globally

ACTIONS TO PREVENT ANTIMICROBIAL RESISTANCE



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Professor Timothy R. Walsh
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Prof. Tim Walsh has been studying AMR mechanisms for over 25 years and publishes regularly in *Nature* and *The Lancet* journals. Notably, in his career he has discovered and named two of the most notorious antibiotic resistant genes — NDM-1 and MCR-1. His work also helped discover the mobile tigecycline genes.

He is director of BARNARDS, a Gates Foundation project on AMR, prospectively examining the burden of neonatal sepsis in Pakistan, India, Bangladesh, Rwanda, South Africa, Nigeria (Abuja and Kano), and Ethiopia.

Prof. Walsh co-established the Ineos Oxford Institute of Antimicrobial Research (with a £100 million gift from INEOS) where he is IOI Director of Biology. Walsh has been appointed to the Fleming Fund expert advisory panel — a rolling U.K. government AMR capacity building program in LMICs. In 2020, he was awarded an O.B.E for "Microbiology and International Development" and in 2022 was awarded his DSc.

In addition to the above, he holds an honorary chair at the China Agricultural University in veterinary microbiology. He is advisor to the Fleming Fund, WHO, Médecins Sans Frontières and several publicly funded drug discovery initiative programs.

Foreword

AMR Is a Collective Responsibility

The COVID-19 pandemic has taught us, as a global community, that the planet is deeply interconnected economically, culturally, and socially with the ultimate consequence that what happens in one country soon appears in another.

Antimicrobial resistance (AMR), like COVID-19, knows no boundaries — it can spread via humans, animals (both domestic and wild), water, and air. Every time a country is flooded, such as the recent tragic events in Pakistan, not only is cholera and shigellosis an issue, but the unimaginable spread of AMR bacteria from animal and human feces is vast, contaminating potable water throughout numerous communities.

AMR is a critical public health crisis and an example of a "One Health" priority. COVID-19 could be described as an earthquake, but AMR is a silent pandemic and, unlike COVID-19, cannot be negated by vaccination programs. Bacteria are complex creatures and have a highly impressive system for responding to their immediate environment — either by creating mutants or, more impressively, by sharing large chunks of DNA that can encode for a variety of different functions, not least, AMR.

A 2022 article in *The Lancet* claims that drug-resistant infections directly caused by AMR killed 1.27 million people in 2019 — more than HIV/AIDS (864,000 deaths) or malaria (643,000 deaths). As data is lacking from many low-middle income countries (LMICs), these numbers are likely to be an underestimation and there is no doubt that the bulk of the clinical burden will be borne by LMICs.

Out of the 17 UN Sustainable Development Goals (SDGs), AMR is directly related to 16 and indeed should be considered to have its own SDG platform. The negative impact of AMR extends beyond the hospital environment, with severe negative implications for poverty and inequality, animal welfare, the environment, as well as food security.

While more than 150 countries have developed AMR national action plans (NAPs), only around 20% are costed or budgeted and therefore the implementation of these NAPs is an ongoing challenge. As a result, the response at the country level is sometimes fragmented without rational prioritization. The commitment to public health expenditure from gross domestic product (GDP) varies significantly by country and region.

An ongoing challenge is to provide AMR diagnostics across all health centers involving tractable, reliable, and cost-effective diagnostic tools ensuring sustainability. Cost-benefit analysis models have rarely been applied to AMR in LMICs and therefore development programs to tackle AMR have seldom been sustainable. Each country has different capacities in terms of economy, knowledge, diagnostics, and investment in facing these challenges.

AMR is a collective responsibility, and we are all ultimately responsible for the AMR challenge — across all countries and all sectors. While AMR should be our focus, ensuring appropriate antibiotics are given to critical patient populations (neonates with sepsis in LMICs) without the burden of cost deferment to extremely poor families must be a key priority.

A stronger health system is important to address AMR and ensure that antimicrobials remain effective for future generations. In 2022, we still use more than 100,000 metric tons of antibiotics in meat production (and crops), and it seems counterintuitive that governments and pharma will spend billions in creating the next “wondermycin” without the global community addressing antibiotic use across the planet.

Surely, the solution is to look for disease-protective molecules/therapies that are not “antibiotic-like” and will not enhance AMR in the human sector? It is now established that the use of ampicillin in animals maintains carbapenem —a World Health Organization (WHO) reserve antibiotic for humans — resistance. The same is also known for tetracycline (an antibiotic widely used in animals) and tigecycline (a WHO critical antibiotic used for humans).

In 2022, with the immense knowledge we have gained since the 1950s and 1960s when these farming practices began, one would hope for better. But apparently not. AMR has many similarities to climate change and indeed they are inextricably linked. Yet, while the public has engaged with the debate around climate change and global warming, few know about AMR.

The language we use to describe AMR is often laced with jargon and the subject is, by its nature, highly complex. Yet, its impact across the globe will mirror that of climate change. Perhaps, AMR requires a dedicated Conference of Parties (COP) summit? There is little doubt that for the last three years COVID-19 has occluded AMR, but there is now hope AMR can return to center stage as a public health priority and be afforded the attention it richly merits.

Executive Summary

Antimicrobial resistance (AMR) is regarded as one of the biggest threats to human health, animal health, sustainable development, and food security. It has been compared to other large-scale problems such as the global pandemic, climate change, and biodiversity loss. The reliance on antimicrobials such as antibiotics is a major issue for modern medicine and global food production, particularly given slow development and investment into new medicines by the pharmaceutical industry.

What can we learn from the economics of climate change and biodiversity loss? In 2006, Lord Nicholas Stern published his seminal work on *The Economics of Climate Change*.[1] The Review concluded that strong and early action will outweigh future costs and that scientific evidence points to increasing risk of serious, irreversible impacts.

Estimates at the time of publication suggested that 1% of global GDP would be required to stabilize greenhouse gas levels at between 500 and 550 parts per million (ppm) CO_2, if supported by policies to encourage the development of low-carbon technologies.[2] Lord Stern warned that there was still time to act to avoid the worst impacts of climate change, but it would require strong and collective action.

In February 2021, Professor Sir Partha Dasgupta published *The Economics of Biodiversity*.[3] The Dasgupta Review, as it is commonly called, outlined the collective failure to engage with nature to limit excess demand of natural resources, which has resulted in reduced resilience to future shocks. The collective failure to manage the global portfolio of natural assets has impaired the quality and quantity of those assets, thereby reducing the ability of ecosystems to regenerate.

The unprecedented decline in biodiversity has undermined productivity, resilience, and adaptability and is pushing ecosystems towards imminent tipping points, underpinning both the human ecosystem and financial health of the global economy.

Dasgupta describes the loss of biodiversity as the "tragedy of the commons" where people, thinking only of their own self-interest, deplete a shared resource.[4] In Dasgupta's case, this referenced biodiversity loss and in the case of this report we use the same language to describe the overuse of antibiotics critical to human health.

In 2016, the final report from the Review on Antimicrobial Resistance, chaired by Lord Jim O'Neill, was published. The Review estimated that 10 million people could die each year by 2050 as a result of AMR-related illnesses.[5]

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[1] Nicholas Stern, *The Economics of Climate Change; The Stern Review*, Cambridge University Press, 2007. Originally published by Her Majesty's Treasury of the U.K. Government in October 2006.
[2] Ibid.
[3] Partha Dasgupta, *The Economics of Biodiversity: The Dasgupta Review*, UK Government HM Treasury, February 2021.
[4] Ibid. In referencing the "tragedy of the commons" Dasgupta cites the 1968 work of Garret Hardin.
[5] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016. Estimates were first released in The Review on Antimicrobial Resistance, Chaired by Jim O'Neill,

According to the Review, the projected economic loss related to AMR by 2050 could be a staggering $100 trillion and to avert the worst outcomes it identified ten different intervention areas.[6] Among the most important were the need for robust, rapid, and affordable diagnostics, support of modern technology, and a drastic reduction in the injudicious use of antibiotics in livestock bred for human consumption.

In 2022, a study published in *The Lancet* indicated that the burden on human health is likely to be much higher than previously thought and in 2019, the deaths of 4.95 million people were associated with drug-resistant bacterial infections.[7]

To keep ahead of antimicrobial resistance, the world needs highly innovative products to prevent, diagnose, and treat the most dangerous drug-resistant infections. Much has been written about the lack of progress of affordable, state-of-the art diagnostics. This Citi GPS report shines a spotlight on the work of CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), which is focused on the most significant bacterial threats to human health, primarily those identified as "Urgent/Serious" in the Centers for Disease Control and Prevention (CDC) Threat Assessments or "Critical/High" in the WHO Global Priority Pathogens List.

This report engages with a core group of highly focused medical practitioners, scientists, and microbiologists working on infectious diseases. Based on these conversations, we find that while innovation is not lacking from the early stages of AMR research and development, these initiatives require an increase in the number of highly skilled practitioners and investment to achieve scale. Examples of areas seeing new investment include bacteriophage, peptide, and anti-virulence therapeutic strategies.

By applying learning from the intersection of climate change and biodiversity loss, we adopt similar language to tackle the global economic problem of AMR. Like climate change and biodiversity loss, the incentives for individual decision makers do not consider the economic costs to society at large. AMR represents an impending "tragedy of the commons" and there is a need for collective action to prevent negative societal impacts.

New products and investment into robust, rigorous, and affordable diagnostics will provide hope and can save millions of lives. This in turn can drive a public return on investment while also potentially being profitable for private investors. This will contribute to their further development towards the patients who desperately need them, as well as the UN Sustainable Development Goals and human and planetary health over the longer term.

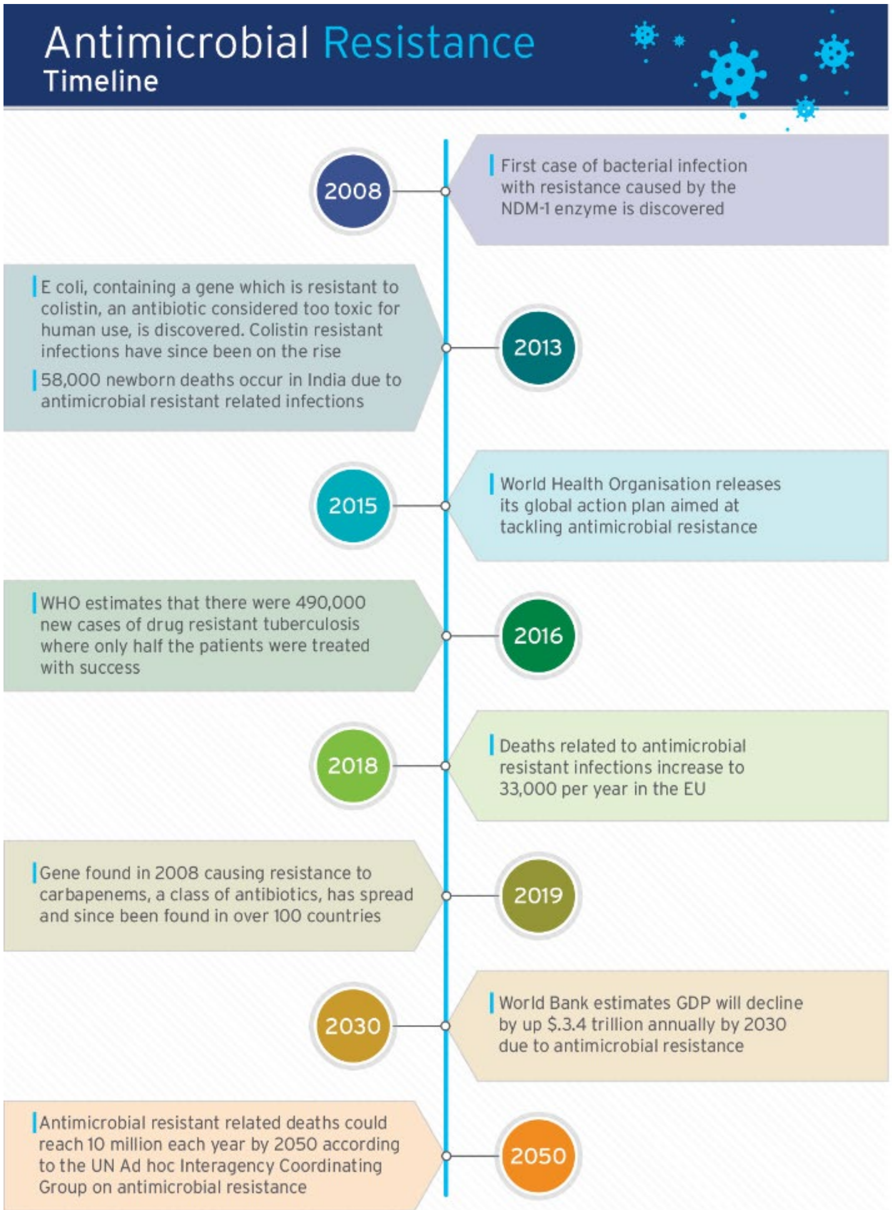
Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations, December 2014.

[6] Ibid.

[7] Christopher J. L. Murray et al., "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," *The Lancet*, Vol. 399, Issue 10325, February 2022.

[7] Editorial, "Antimicrobial Resistance: Time to Repurpose the Global Fund," *The Lancet*, Vol. 399, No. 10322, January 22, 2022.

Figure 1. The Emergence of Antimicrobial Resistance Timeline



Source: Adapted from Healthcare in Europe, Citi GPS

Expert Contribution: Lord Jim O'Neill

Lord O'Neill of Gatley

Lord O'Neill is a crossbench peer in the House of Lords. He is a member of the panel of Senior Advisors to Chatham House and recently became Chair of Northern Gritstone. His previous roles include: joint head of research at Goldman Sachs (1995–2000), its chief economist (2001–10), and chairman of its asset management division (2010–13); creator of the acronym BRIC; chair of the City Growth Commission (2014); chair of the Review on Antimicrobial Resistance [AMR] (2014-16); and commercial secretary to the U.K. Treasury (2015-16). He is a board member, and one of the founding trustees of educational charity SHINE.

Lord O'Neill was created a life peer in 2015 and serves as a crossbench member of the House of Lords. He is an honorary professor of economics, University of Manchester, and holds honorary degrees from the University of Sheffield, University of Manchester, University of London and from City University London. He received his PhD from the University of Surrey and is now a Visiting Professor there.

Are We Serious About AMR?

It has been six years since we published the final report on combating AMR including 29 specific recommendations. If these recommendations were not followed, it was likely that by 2050, 10 million people a year would die from AMR-related illnesses, and over the 34-year period, an accumulated loss of $100 trillion of economic potential would be squandered.

The AMR Review received considerable attention for these dramatic estimates and our proposed remedies. In the six years since, two things are worth pointing out strongly. Firstly, the world has gone through a COVID-19 pandemic in which millions of lives have been lost and the decline in global GDP was close to $8 trillion. Arguably, some of the subsequent global economic challenges are a consequence of the pandemic, especially as it is far from over and supply and labor shortages persist in many nations. Fewer people now would think our Review projections are quite so wild.

Secondly, detailed research published in *The Lancet* in 2022 suggests that at least two times as many people died in 2019 from AMR than the 700,000 we had initially assumed, possibly more. This is not necessarily because of the passage of three years but more detailed research undertaken over many years. So, if anything, the estimates we undertook, if based on these current numbers, could be even higher. If it were reflecting the passage of time, obviously a linear progression would mean troubling consequences. Either way, it makes us believe that AMR is a serious problem.

So, what about progress on our ideas? I often try to describe the broad thrust of our specific recommendations as the "Ten Commandments" of how to stop this terrifying problem. As an economics and finance person, I led the team to explore potential solutions in terms of supply and demand interventions.

It appears what needs to happen is: (1) a reduction in the demand for antibiotics, especially their inappropriate use; and (2) a boost in the supply of useful antibiotics and alternative treatments. Of our recommendations, five and a half might be seen as demand reducing interventions, three and a half as supply boosting ones, with the other — global policy — focused on coordination and implementation.

Let's briefly discuss where we stand today, as well as other ideas we might have proposed if I knew then what I know now, and what investors can do to help. On the supply side, one recommendation was more researchers needed to be attracted into the field, as well as for them to be remunerated better compared to other health researchers. I am not sure about the latter nor statistically the former, but my impression is that the number of academic research organizations focused on AMR has risen in the U.K. purely based on many asking me to speak there or help them in some way. The Ineos Oxford Institute is admirable and ambitious in this respect.

The second area relates to so-called push incentives with more money available to stimulate early stage research and development. In the immediate aftermath of our Review, there was a notable increase in such funding especially from the Biomedical Advanced Research and Development Authority (BARDA) in the U.S., the EU, and a small number of foundations including the Wellcome Trust in the U.K.[8] The $1 billion industry-wide AMR Action Fund should probably be regarded as a push-type fund, although it is aimed at helping take early stage research along the S-curve of progress. In finance jargon, some might think of it in terms of "valley of death" type money akin to beyond seed funding.

Funding may become very important as evidence is accumulating that without a huge development in the third area, so-called pull funding, early stage companies disappear as there is no one to support their growth or indeed, survival. This is a particularly worrying development. It also means the continued slow disappearance of so many pharmaceutical companies from the antibiotics business — it is all the more troubling as their business model simply isn't flexible enough to eagerly produce low-priced antibiotics at scale, especially when the costs entailed are high and some policies are aimed at reducing demand.

This is clearly where investors can help if they are serious about Responsible Investment — by not investing in firms that fail to participate in antibiotics, so the leadership understands there is a price to their absence. An alternative is for philanthropic investors as well as governments to give sizable rewards such as our recommended Market Entry Rewards to participate.

The most depressing thing for me personally has been the endless talk about pull-market incentives relative to the actual development. This obviously needs to change. The U.K. has shown some leadership with its own initiative to pay pharmaceutical companies upfront for two antibiotics, but without the U.S. or EU and probably leading Asian nations doing the same, pharmaceutical companies are unlikely to change their reluctant ways. Ultimately, perhaps my Review's controversial idea of Pay or Play may need to be imposed by governments to help shift the risk/reward thinking in the leadership of big pharmaceutical companies.

Vaccines (and alternatives) are a very interesting area as they straddle both the supply-boosting and demand-reducing side. We eagerly proposed ideas for greater use of vaccines for this reason, especially in animals. Indeed, if animal vaccine illness prevention were strongly adopted, the need to use antibiotics would fall dramatically. Needless to say, very little has happened here. In some ways this is even more amazing given the COVID-19 pandemic and the evidence that vaccines can be usefully developed quickly.

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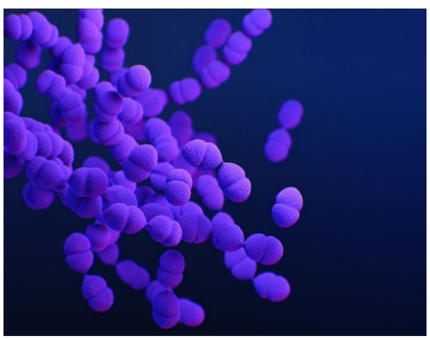
[8] Medical Countermeasures, "We Are BARDA," accessed November 16, 2022; Wellcome, "Science to Solve the Urgent Health Challenges Facing Everyone," accessed November 16, 2022.

I was a member of the U.K. G7 Carbis Bay task force that was asked to find ways of even faster vaccine development to allow even quicker response rates to pandemics that might appear in the future.[9] What would be an obvious way to keep pharmaceutical firms permanently interested in the vaccine business would be to advance vaccine usage in other areas, in particular AMR. Of our 10 million estimated deaths, one-third are because drug resistant tuberculosis (TB) is rising sharply in the emerging world.[10] More vaccine development here is urgently needed.

On the demand side, progress is less encouraging, with the possible exception of agricultural reduction. To our surprise, evidence is mounting of a decline in usage in at least the developed world, especially the U.S. This is a reflection of both policy development and consumers choosing to be tougher about what they will eat.

We used to call this the "Shake Shack factor" as evidence the younger generation were attracted to antibiotic-free meat and seemed to be attracting business away from more established players, resulting in most of them claiming, at least with chicken, a similar approach. It is also the case that some big emerging countries, such as China, have banned the use of Colistin, a crucial "last in line" antibiotic for human use, in animals. I can't understand why all such vital antibiotics are not banned in the developed world. Obviously, the goal of the Ineos Oxford Institute to support animal-only antibiotics is a very welcome development. But a speedier decline in usage would be fantastic.

S. pneumoniae



Let me discuss the others. We called for additional public awareness campaigns, as knowledge about the AMR problem was scant. It still is. Indeed, because of COVID-19 it might even have receded as how much can our citizens take, especially when they have seen the staggering disruption we all have suffered, and are still being warned about fresh COVID-19 outbreaks? But if we don't increase public awareness, how can policymakers find the determination to act? It is unfortunately needed. Hopefully, this Citi GPS report will help.

On hygiene, you would hope the pandemic should help the most basic needs at least at the margin, especially basics like washing hands. Ex U.K. Chief Medical Officer Professor Dame Sally Davies used to say, washing hands in warm soapy water while singing along to Happy Birthday twice, would help reduce infection spread. Surely, what we all have learned from COVID-19 will partially help?

A fourth demand intervention we called for was vastly superior surveillance. We were shocked as to how poor knowledge of incidence and infection rates were across the world and obviously if we don't really know what kind of AMR problems there are, and the scale of them, how can we solve the problem?

[9] U.K. Government, "Carbis Bay G7 Summit Communique," PDF, July 12, 2021.
[10] Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. Tuberculosis is curable and preventable. TB is spread from person to person through the air.

One of our early successes is that the U.K. government announced the launch of the Fleming Fund, a bold initiative to improve surveillance in parts of the emerging world.[11] We were very pleased. But years later, while it has progressed and there are some countries benefiting, AMR needs a truly global preventive health infection warning system. Yet again, the pandemic showed the obvious need, and our Carbis Bay team recommended this to be a focus for G7 agreement and development, but nothing has happened. I shall discuss the international cooperation aspects, or lack of, below

A big disappointment, as much as the behavior of pharmaceutical companies, is the lack of progress of affordable state-of-the-art diagnostics — the fifth demand intervention and definitely one of our biggest recommendations. Seen as an economist, we need to permanently reduce the demand for antibiotics, especially unnecessary usage.

If we use mobile phones and similar technology every day in our lives, why can't we use these things for our doctors to legitimately tell us whether we need an antibiotic or not? It is extremely silly that we pressurize doctors and allow them to have an educated guess. Our most aggressive recommendation was to force all developed countries to ban antibiotic prescriptions unless they have been deemed necessary through approved diagnostic tests.

The problem centers on the obsession with cheap antibiotics and our faith in the judgment of medical professionals, which makes it hard to find affordable antibiotics and also, therefore, fund diagnostic research. Financial participants might be able to help by encouraging the growth of venture capital (VC) diagnostic businesses. Indeed, due to the importance I attach to this factor, I am trying to support some early stage businesses. We need huge progress here.

Let me finish with a few words on AMR and global policy cooperation. One of our most gratifying aspects of the Review was that it helped us play a role in driving for the September 2016 UN High Level Agreement — a rare time the UN has had any such health policy focus. We also, with the help of the U.K. Treasury, forced AMR onto the G20 agenda, which persisted from 2016 until the COVID-19 pandemic, and in 2017 and 2018, many features of our recommendations were included. But, as I now discover yet again, words can be cheap and action more challenging, especially when money and international politics are involved.

Since the near collapse in any policy coordination between the U.S. and China, even before COVID-19, many crucial issues for genuine global cooperation have fallen by the wayside. Sadly, this includes global health and any efforts to truly progress AMR global cooperation. There is, to be fair, continued focus on AMR of sorts, from the U.K. and among G7 Health Ministers and to their credit, Finance Ministers. But AMR is a truly global challenge.

Bugs become resistant wherever they are, and AMR is truly a global challenge and needs true focus and determined solutions. Personally, AMR has become one of the most interesting things I have ever been asked to focus on. I am captured by its challenge. But we need others. AMR needs much more galvanizing. I am proud of the role our Review played and the initiatives that followed. But we need more. Hopefully, this Citi GPS report on AMR can help.

[11] The Fleming Fund, "Aims & Values," accessed November 16, 2022

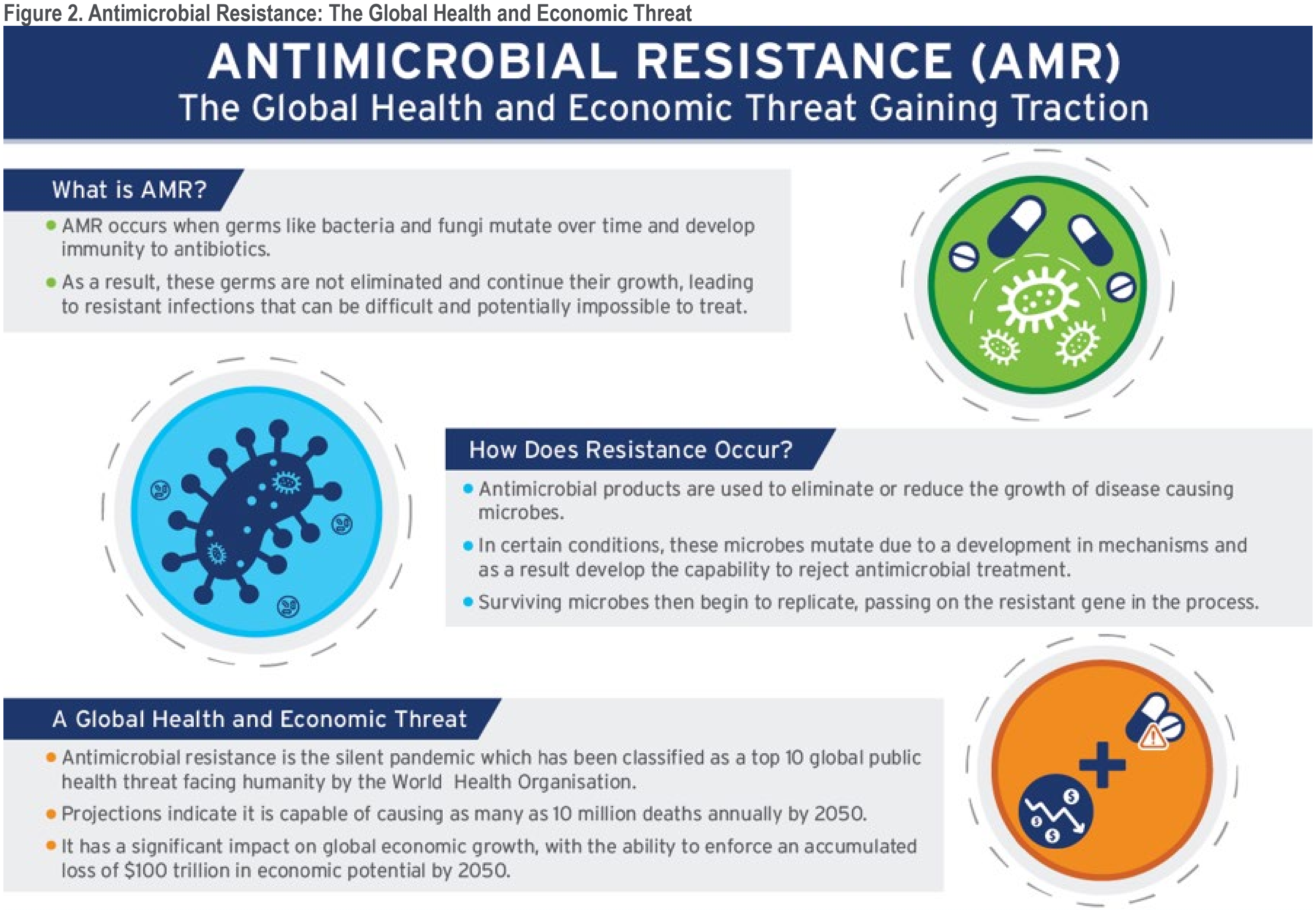
Chapter 1: Why Antimicrobial Resistance Is a Problem

What Is Antimicrobial Resistance?

Antimicrobials are medicines mainly prescribed to tackle infections (e.g., antibiotics, antivirals, antifungals, and anti-parasitic medicines). These medicines are used in humans, animals, and plants; in some cases, the exact same medicines are used in both humans and animals. Antimicrobial resistance (AMR) describes the process by which these medicines become ineffective as pathogens build up resistance to them. This makes infections initially more difficult and eventually impossible to treat, resulting in an increased risk of severe illness and, potentially, death.

In this chapter, we discuss why AMR is important, what causes it, and what is driving its growth. In the next chapter, we discuss how rising temperatures and increased incidences of extreme weather events, such as hurricanes and floods, make infection and bacteria spread more likely and increase the chances of AMR.

Figure 2. Antimicrobial Resistance: The Global Health and Economic Threat



Source: Citi GPS

Why Is Antimicrobial Resistance Important?

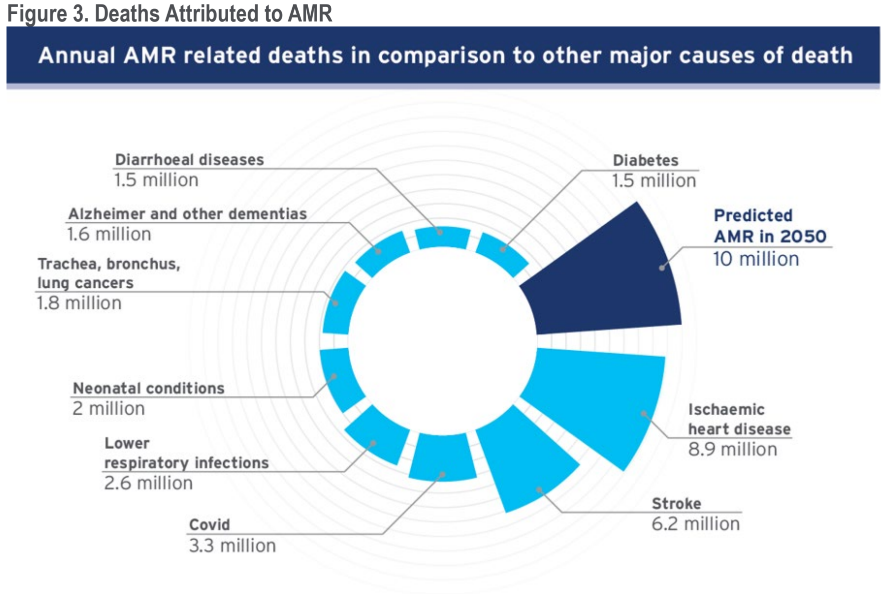
Drug resistance is the result of microbes changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents to cure or prevent infections.

AMR has vast implications for modern medicine. It represents one of the world's greatest public health threats, as treatment of infections — both common and complex — with antibiotics becomes increasingly ineffective due to bacteria evolving and becoming resistant to available medicines. A proliferation of AMR would raise the risk of infection for routine medical procedures, such as hip replacements and cesarean sections. If we fail to protect the current suite of antibiotics and to invest in research and development (R&D) for new antibiotics, we could find ourselves in a scenario where most, if not all, antibiotics "*no longer work and we are cast back into the dark ages of medicine*," as then U.K. prime minister David Cameron warned in 2014.[12]

By 2050, drug resistance could lead to 10 million deaths per year and cost the world $100 trillion in global economic losses, according to the final 2016 report by the Review on Antimicrobial Resistance, chaired by the economist Lord Jim O'Neill. The Review also estimated that 700,000 people die each year from bacteria, viruses, fungi, and parasites resisting treatment.[13]

[12] Alona Ferber, "Sally Davies: 'Anti-Microbial Resistance Could Kill Us Before the Climate Crisis Does'," New Statesman, October 17, 2022.
[13] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016. Estimates

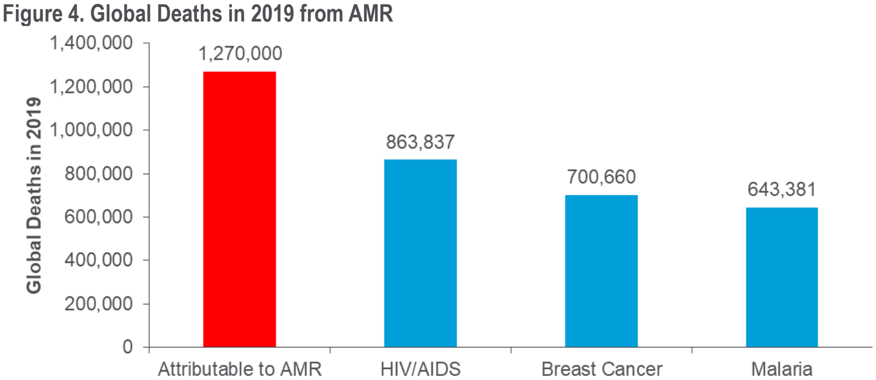
Figure 3. Deaths Attributed to AMR



Source: World Health Organization, Citi GPS

More recently, a 2022 study published in *The Lancet* estimated that in 2019 "there were 4.95 million deaths associated with bacterial AMR, including 1.27 million deaths directly attributable" to it. This makes AMR the third leading cause of death after heart disease and stroke based on the higher estimate. Based only on deaths directly attributable to it, AMR is the 12th leading cause of death, surpassing HIV/AIDS, breast cancer, and malaria (see Figure 4).[14]

Figure 4. Global Deaths in 2019 from AMR



Source: The Lancet (2022), Citi GPS

were first released in The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*, December 2014.

[14] Christopher J. L. Murray et al., "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," *The Lancet*, Vol. 399, Issue 10325, February 2022.

Antibiotics are a type of antimicrobial agent, either made from mold of bacterium, or synthetically produced that kills or slows the growth of other bacteria. Examples include penicillin and streptomycin.

Vertical gene transfer is the transfer of genetic information from parent to offspring cells.

Horizontal gene transfer is when bacteria share mobile DNA with one another, including between diverse genera of bacteria.

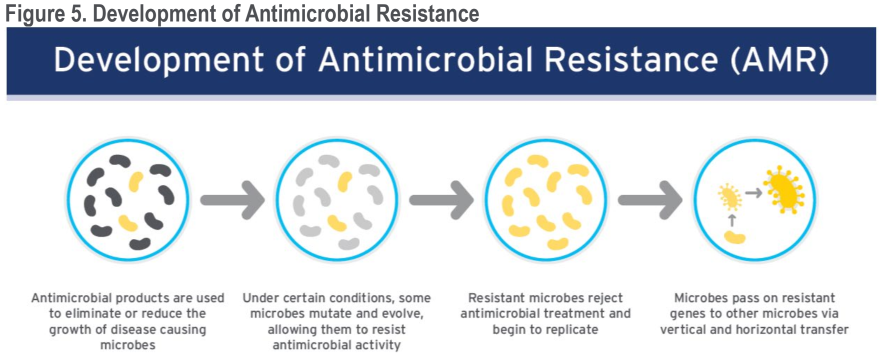
Multi-drug resistance is a property of a bacterial pathogen that is resistant to two or more different classes of antimicrobial agents.

What Causes Antimicrobial Resistance?

At the level of microbiology, resistance builds up through two mechanisms: first, bacteria mutate as they reproduce and some of these mutations provide an advantage in resisting antibiotics.[15] Through natural selection, the resistant bacteria multiply and pass on this resistance to their descendants. This is vertical gene transfer: Advantageous genetic mutations are transferred from parent to offspring cells.

Second, bacteria share DNA with one another through horizontal gene transfer, including between diverse species of bacteria. As a result, bacteria which were previously susceptible to a given antibiotic, or tranche of antibiotics, become resistant.[16] This is considered more consequential because it allows the determinants of resistance to spread between different species of bacteria and the mobile DNA (called plasmids) can mediate multi-drug resistance.[17]

Figure 5. Development of Antimicrobial Resistance

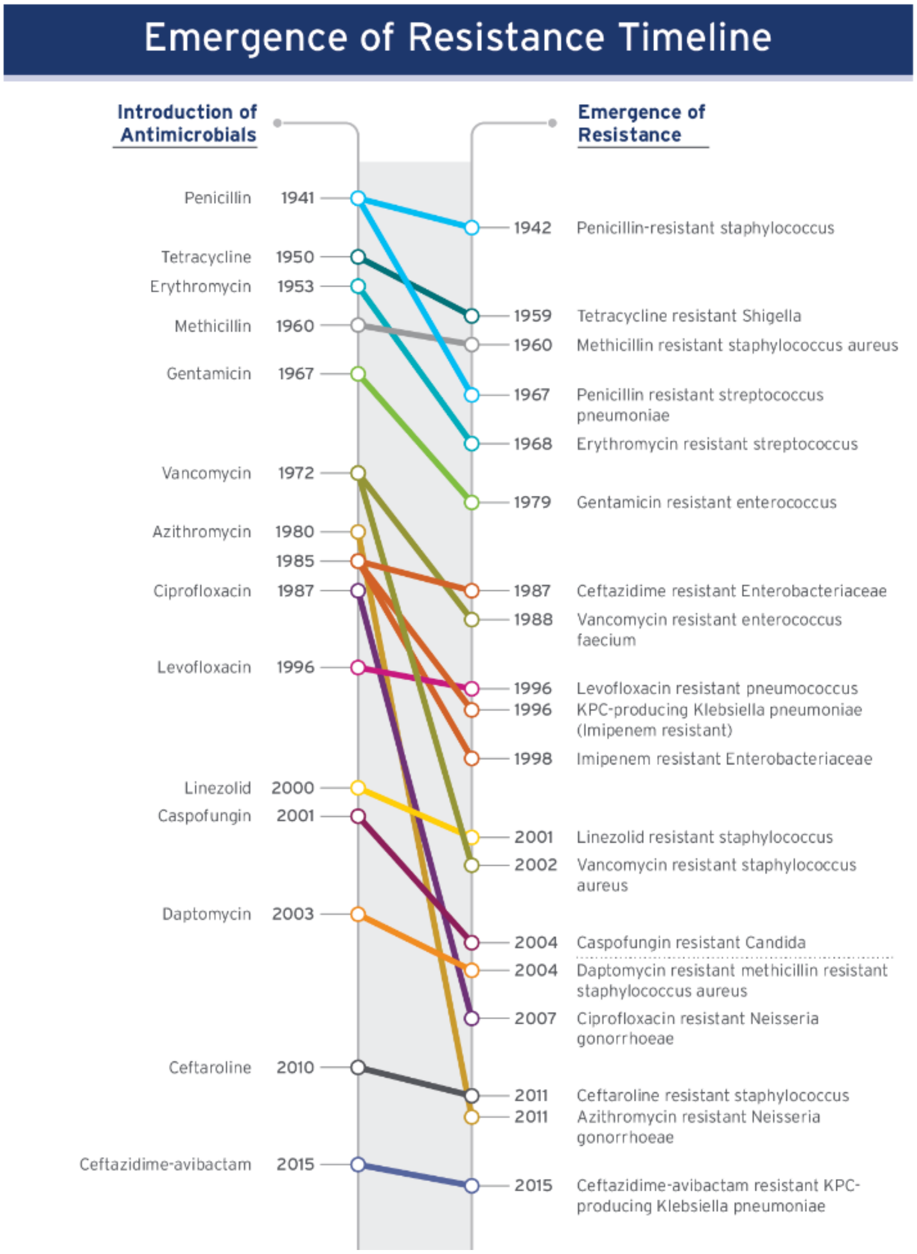


Source: Adapted from American Society of Microbiology, Citi GPS

The potential for pathogens to become resistant was recognized as a threat even before penicillin entered common use. In his Nobel lecture, Alexander Fleming noted that "*It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body*."[18] Previously, there was always another antibiotic on the shelf, but now many factors are accelerating the emergence of resistance, which outpaces the development of novel drugs.

[15] Research has focused on antibiotic resistance, but there is growing concern around antivirals (e.g., HIV drugs), antifungals, and antiparasitics (e.g., malaria treatments). See World Bank Group, *Pulling Together to Beat Superbugs: Knowledge and Implementation Gaps in Addressing Antimicrobial Resistance*, October 2019.
[16] Dongchang Sun et al., "Editorial: Horizontal Gene Transfer Mediated Bacterial Antibiotic Resistance," *Frontiers in Microbiology*, August 27, 2019.
[17] Mario Gajdacs et al., "Antimicrobial Resistance in the Context of the Sustainable Development Goals," *European Journal of Investigation in Health, Psychology and Education*, Vol. 11, No. 1, 2021.
[18] Sir Alexander Fleming, "Penicillin," PDF, Nobel Lecture, December 11, 1945.

Figure 6. Emergence of Resistance Timeline



Source: CDC (2013), CDC (2019), Adapted from FERN: Imagining the Post-Antibiotics Future, Citi GPS

What Is Driving Increased Antimicrobial Resistance?

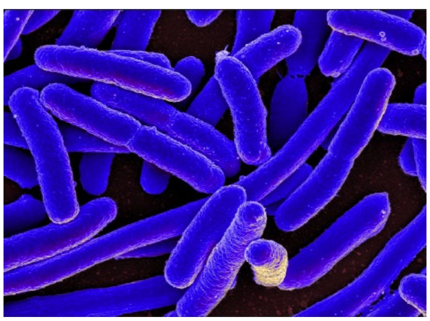
The drivers of AMR can be categorized into four groups: (1) overuse and misuse in humans, (2) overuse and misuse in animals, (3) poor hygiene and sanitation, and (4) a lack of research and innovation to develop novel antimicrobials.

Figure 7. Causes of Antimicrobial Resistance

Source: Citi GPS

1. Overuse and Misuse in Humans

E. coli



First, non-prescription use of antimicrobials is a significant challenge. A 2019 study in the U.S. found that the prevalence of non-prescription use of antibiotics was as high as 66% for some parts of the population.[19] The situation is expected to be even worse in low- and middle-income countries, where one study suggests that self-medication is "highly prevalent."[20] Healthcare costs and inaccessibility are key drivers here. Another is the lack of public awareness about when antimicrobials are an effective treatment: For example, a 2018 survey of the EU found that almost 50% of people thought antibiotics could kill viruses, when of course they are only effective against bacterial infections.[21] Yet another is illicit sales of antimicrobials outside medical contexts, including Internet sales and purchases from veterinary health sources.[22]

[19] Larissa Grigoryan et al., "Use of Antibiotics Without a Prescription in the U.S. Population: A Scoping Review," *Annals of Internal Medicine*, Vol. 171, No. 4, 2019.
[20] Adeel Aslam et al., "Evidence of Practice of Self-Medication With Antibiotics Among the Lay Public in Low- and Middle-Income Countries: A Scoping Review," *Antibiotics*, Vol. 9, No. 9, 2020.
[21] European Commission, *Special Eurobarometer 478 Report: Antimicrobial Resistance*, November 2018.
[22] Mario Gajdacs et al., "Antimicrobial Resistance in the Context of the Sustainable Development Goals," *European Journal of Investigation in Health, Psychology and Education*, Vol. 11, No. 1, 2021.

Over-prescription is a related issue. A World Bank study simulated a young female presenting to a pharmacy with symptoms of a lower urinary-tract infection in six low- and middle-income countries. More than 60% of visits resulted in dispensing antimicrobials without clinical diagnosis.[23] This is not only a challenge for primary care: One study found that 30% of the antibiotics prescribed in U.S. emergency departments were unnecessary.[24]

Prophylaxis (prophylactic) is the use ofantimicrobials to prevent an infection, for example in animals housed in unsanitary conditions or in high-risk human patients.

Moreover, antimicrobials are often given prophylactically (i.e., to prevent infections) in hospitals, including before surgery and for patients receiving chemotherapy. A survey in Australia found that up to 40% of these prescriptions were inappropriate.[25] The COVID-19 pandemic is expected to have exacerbated this problem: A U.S. report notes that between March and October 2020, 80% of patients hospitalized with COVID-19 received an antibiotic.[26]

2. Overuse and Misuse in Animals

Animals constitute 70%-80% of total antimicrobial consumption.[27] Moreover, a 2015 study expects this consumption to increase by 67% by 2030, including almost doubling in Brazil, Russia, India, China, and South Africa, driven by intensification of farming. Much of this consumption is not to treat infection but to maximize the productivity of the agricultural industry by increasing the growth of animals and allowing them to be kept in smaller, less sanitary conditions without illness. This accounts for a high share of antimicrobial consumption in animals:

- One study of the Mekong Delta region of Vietnam found that 84% of total antibiotic use in animal agriculture is used for prophylaxis.
- In a 2018 study of China, growth promotion accounted for 53% of antimicrobial consumption among animals.[28]

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[23] World Bank Group, *Drug Resistant Infections: A Threat to our Economic Future*, March 2017.
[24] Katherine E. Fleming-Dutra MD et al., "Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011," *JAMA*, Vol. 315, No. 17, 2016.
[25] National Centre for Antimicrobial Stewardship and Australian Commission on Safety and Quality in Health Care, *Antimicrobial Prescribing Practice in Australian Hospitals: Results of the 2015 National Antimicrobial Prescribing Survey*, 2016.
[26] Centers for Disease Control and Prevention (CDC), *2022 Special Report: COVID-19 U.S. Impact on Antimicrobial Resistance*, 2022.
[27] Mario Gajdacs et al., "Antimicrobial Resistance in the Context of the Sustainable Development Goals," *European Journal of Investigation in Health, Psychology and Education*, Vol. 11, No. 1, 2021.
[28] FAIRR Initiative, *Feeding Resistance: Antimicrobial Stewardship in the Animal Health Industry*, July 2021.

3. Poor Hygiene and Sanitation

P. aeruginosa

Poor hygiene and sanitation exacerbate demand for antimicrobials. According to a UN progress report, almost half the global population lacked access to adequate sanitation in 2020.[29] Increasing access to appropriate sanitation in households and care settings would reduce the spread of AMR bacteria, and subsequent infections, therefore lessening both the demand for antimicrobials and the growth of resistance.

Sanitation also concerns waste. Studies suggest that 75%-90% of antibiotics are still active when they are excreted by animals.[30] As a result, the active ingredients enter sewage systems and waterways resulting in low-dose exposure to pathogens. This accelerates the emergence of resistance by providing the perfect “training ground” for pathogens to develop resistance. Furthermore, bodies of water act as reservoirs and transmission mechanisms for resistant pathogens. As such, poor sanitation systems directly contribute to the growth of resistance.

4. Lack of Novel Antimicrobials

Few novel antimicrobials have come to market in recent decades and the pharmaceutical industry’s pipeline remains relatively small. For example, in 2019 only six of the 32 antibiotics in clinical development that address the WHO list of priority pathogens could be considered innovative.[31] Despite gains in recent years, an analysis of 17 of the world’s largest pharmaceutical companies in 2021 recorded only 92 active projects targeting infections caused by priority pathogens.[32] This includes both novel antimicrobials and AMR-relevant vaccines.

Other actors in the antimicrobial space have not filled this investment gap: Of the $38 billion venture capital invested into pharmaceutical R&D between 2003 and 2013, only $1.8 billion was invested into antimicrobials research, with total investments falling by more than a quarter over the period.[33] Similarly, antimicrobial research has not been a priority of the public sector: According to data from the U.S. National Institute of Health (NIH), just 1.2% of its grant funding went to AMR-related research between 2009 and 2014 versus over 18% to cancer-related research.

The causes of this underinvestment are multifaceted. First, there is a lack of economic incentives to create novel antimicrobials. The Office for Health Economics estimated that the net present value of a new antibiotic is $50 million compared to approximately $1 billion for a drug used to treat neuromuscular disease.[34] Moreover, any new drugs that do come to market may be held back by public health authorities to preserve their efficacy, cutting off their potential revenue stream.

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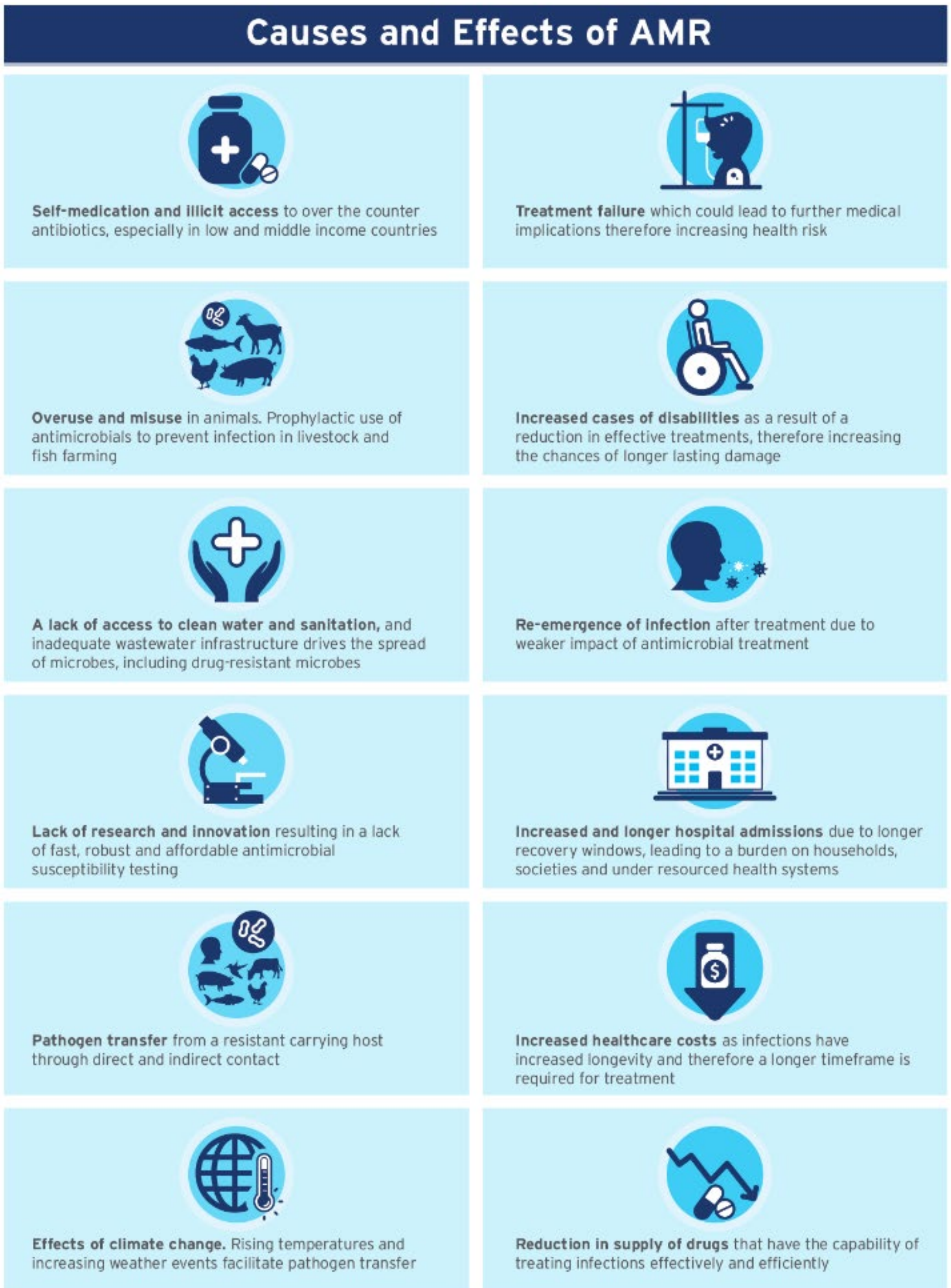
[29] WHO and United Nations Children’s Fund (UNICEF), *Progress on Household Drinking Water, Sanitation, and Hygiene 2000-2020: Five Years into the SDGs*, 2021.
[30] The Review on Antimicrobial Resistance, Chaired by Jim O’Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016.
[31] World Health Organization (WHO), “Antimicrobial Resistance,” November 2021.
[32] Access to Medicine Foundation, *Antimicrobial Resistance Benchmark 2021*, November 18, 2021.
[33] David Thomas and Chad Wessel, “Venture Funding of Therapeutic Innovation, Biotechnology Industry Organization, February 2015.
[34] Abigail Rhea Herron, *Superbugs and Super Risks: A Critical Assessment of Antibiotic Resistance as a Frontier Topic in Responsible and Sustainable Investment*, University of Cambridge Institute for Sustainability Leadership, December 2019.

Second, running clinical trials is often prohibitively expensive: More than 80% of the costs of bringing an antibiotic to market center around clinical trials.[35]

Antimicrobial resistance is clearly a complex issue with multiple drivers but, as many expert contributors note in this Citi GPS report on AMR, the solutions are also well known.

Figure 8. Causes and Effects of AMR



Source: Citi GPS

[35] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016.

The Discovery of Penicillin: Alexander Fleming

The discovery of penicillin ushered in a new era in medicine — but it was a chance discovery from a discarded Petri dish that brought about the antibiotic age.

In 1928, the British bacteriologist Sir Alexander Fleming returned from holiday to St. Mary's Hospital in London, where a number of discarded Petri dishes remained piled up on his workbench. As he rummaged through the pile, he came across one dish, on which a mold had grown and killed the *Staphylococcus aureus* that had previously been growing.

Seeing the potential of this mold to be the wonder drug that he had spent much of his career looking for, Fleming grew more of it in an attempt to determine what was killing the bacteria.

With the help of his colleagues, he observed it was a Penicillium mold, likely originating from the lab downstairs. Hence, Fleming called the antibacterial agent penicillin.

Running further experiments, Fleming found first, that the mold killed many other harmful bacteria and second, that it was non-toxic and could therefore be used as a medicine.

Fleming did not turn this discovery into a medicine that could be used in humans. That would have to wait until 1940, when the scientists Howard Florey of Australia and Ernst Chain of Germany turned the mold into a medicinal form that could be used in humans to treat bacterial infections.

Mass production started very quickly owing to the urgency of treating those wounded in World War II. Fleming, Florey and Chain were jointly awarded the Nobel Prize in Physiology in 1945 for their discovery of penicillin.

Chapter 2: Climate Change and AMR

AMR sits firmly within a nexus of broader sustainable development issues, including climate change, biodiversity loss, and food security. In this chapter, we focus on UN Sustainable Development Goal (SDG) 13 — Climate Action, SDG 14 — Life Below Water, and SDG 15 — Life on Land. By examining both the scientific and social consequences of climate change, we illustrate that the consequences of a lack of climate action risks intensifying the threat of AMR. We conclude that addressing AMR requires adopting a "One Health" approach to public health, recognizing the close links among animal, human, and environmental health.

In the Citi GPS report *Systemic Risk: Systemic Solutions for an Increasingly Interconnected World*, we noted that while antimicrobial resistance (AMR) is itself a significant risk, it is also deeply interconnected with many other global risks, including climate change and biodiversity loss.

Climate change is one of the most significant challenges of the 21st century. Its impacts are already being felt across the globe: 2022 alone has seen unprecedented heat stress in Northern Europe and significant flooding in Pakistan. On its own terms, climate change requires urgent action to avert a "Hothouse Earth" scenario, in which the global temperature settles between four and five degrees higher than pre-industrial averages.[36] But a lack of climate action is believed to also increase the threat of AMR.

We argue that tackling AMR requires equal effort to tackling climate change. We first illustrate that increasing temperatures are linked with the spread of infectious disease, the (re-)emergence of novel and ancient pathogens, and the accelerated emergence of antimicrobial resistance. We then show that other elements of climate change, like extreme weather events and the population displacement that often follows them, also increase the threat of AMR. Hence, tackling AMR is predicated on urgent climate action.

[36] Stockholm Resilience Centre, Stockholm University, "Planet At Risk of Heading Towards 'Hothouse Earth' State," accessed November 14, 2022.

Figure 9. AMR and the UN Sustainable Development Goals

Source: United Nations

Climate Change and Increasing Infectious Disease Burden

Climate change exacerbates many health challenges.[37] For example, the World Health Organization has estimated that the heat stress seen in Europe in 2022 caused the deaths of around 15,000 people.[38]

The evidence supporting a link between infectious diseases and climate change continues to mount. Long-run historical data compiled in 2020 suggest that climate change continues to create conditions that support the transmission of various infectious diseases, including some that are significant for global development, including dengue fever and malaria.[39]

Four paths mediate the relationship between climate change and an increased infectious disease burden:

1. **Rising temperatures increase the frequency and intensity of outbreaks** of some diseases. One paper examining the spread of helminths, a parasite harmful to both humans and animals, found that even modest increases in temperature could have a significant impact on the severity of an outbreak.[40]

[37] Jason P. Burnham, "Climate Change and Antibiotic Resistance: A Deadly Combination," *Therapeutic Advances in Infectious Disease*, February 15, 2021.
[38] World Health Organization. "Statement – Climate Change Is Already Killing Us, but Strong Action Now Can Prevent More Deaths," November 7, 2022.
[39] Nick Watts et al., "The 2020 report of *The Lancet* Countdown on Health and Climate Change: Responding to Converging Crises,' *The Lancet*, December 2, 2020.
[40] Naomi J. Fox et al., "Climate-Driven Tipping Points Could Lead to Sudden, High-Intensity Parasite Outbreaks," *Royal Society Open Science*, May 20, 2015.

2. **Rising temperatures increase the geographical scope of specific diseases and the vectors that transmit them** as more of the globe becomes an amenable temperature for transmission. For example, while sand flies are usually found only in Mediterranean Europe, one study concluded that climate change would see them spread as far as Northern Europe.[41]

3. **Climate change facilitates the (re-)emergence of both novel and ancient pathogens.** In 2016, the thawing of the permafrost in Siberia exposed the carcass of a reindeer that had died of anthrax. A subsequent outbreak of anthrax in the region is attributed to this event. Some have also suggested that climate change accounts for the pathogenicity of the fungus *Candida Auris*, which may not always have been harmful to humans.[42]

4. **As temperatures rise** and levels of precipitation and flooding increase, the **intensity of pathogen transfer and disease outbreak is expected to increase**. The World Economic Forum in its 2022 Global Risk Report highlighted the massive spread of bacteria that could result in an epidemic or pandemic placing further burdens on the global economy.[43]

There is a feedback loop here: As outbreaks of infectious diseases become more severe and larger in scale due to climate change, more antimicrobials will be required for treatment and the emergence of resistance will accelerate. Curtailing the number of infections is critical to addressing AMR.

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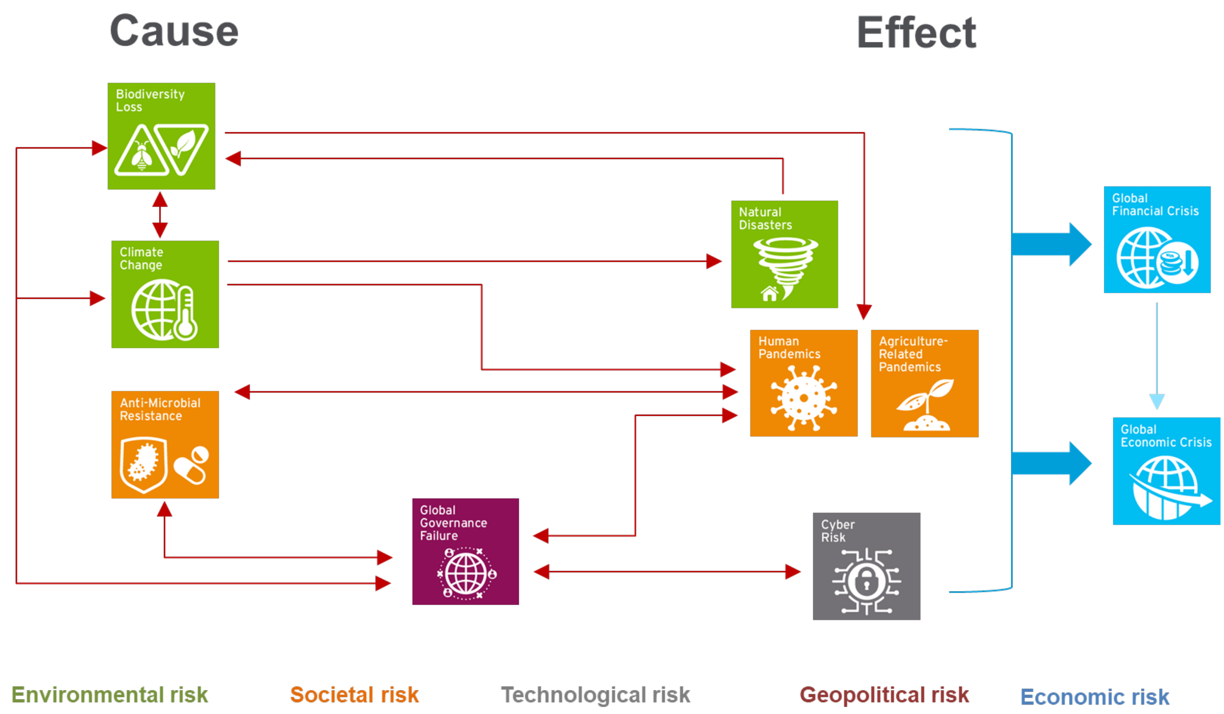
[41] Lisa K. Koch, Judith Kochmann, Sven Klimpel, and Sarah Cunze, "Modeling the Climatic Suitability of Leishmaniasis Vector Species in Europe'. *Nature Scientific Reports,* 2017.
[42] Arturo Casadevall, Dimitrios P. Kontoyiannis, and Vincent Robert, "Environmental Candida Auris and the Global Warming Emergence Hypothesis" *mBio*, March 16, 2021.
[43] World Economic Forum, "The Global Risks Report 2022," January 2022.

Figure 10. AMR Sits in a Close Nexus with Other Global Challenges



Source: Citi GPS

Climate Change and Increasing Resistance

Climate change can also be connected directly with resistance. MacFadden et al. (2018) explore the impact of climate change on the distribution of antibiotic resistance across the U.S.[44] Their data suggest that for multiple common pathogens, including *E. Coli, K. Pneumoniae*, and *Staphylococcus Aureus*, an increase in temperature is associated with an increase in resistance.

This finding is of global significance in understanding the threat that AMR presents. Estimates of the human and economic impact of AMR, including the calculations that AMR could be responsible for up to 10 million deaths per year by 2050 and a $100 trillion impact on GDP by 2050, do not account for the link with climate change and the impact it could have on accelerating resistance.[45] The true figures may be much higher unless significant action is taken to limit climate change.

Extreme Weather Events and Pathogen Exchange

So far, we have considered only the scientific effects of an increasing temperature on AMR. Broader issues of climate change, such as the increasing frequency of extreme weather events like flooding and water scarcity, together with their social consequences, also pose a threat of increasing AMR.

[44] Derek R. MacFadden et al., "Antibiotic Resistance Increases with Local Temperature,' *Nature Climate Change*, May 21, 2018.
[45] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016.; [45] World Bank Group, *Drug-Resistant Infections: A Threat to Our Economic Future*, March 2017.

- **Flooding facilitates the increased transmission of both water- and vector-borne diseases:** One review calls attention to the significant outbreaks of cholera and *E. Coli* that were seen in Bangladesh following periods of flooding.[46] The risk of spreading disease is particularly high where agricultural run-off or sewage contaminate floodwaters. Where resistant pathogens are found in a body of water, flooding enables their wider dissemination and can lead to greater incidences of urinary tract infections in female populations.

- **Both flooding and water scarcity can lead to an increased infectious disease burden:** Flooding and water scarcity disrupt the infrastructure of sanitation systems, especially in low- and middle-income countries where those systems may already be weak.[47] Droughts bring a second challenge to sanitation as a larger population is forced to use the same water source, increasing the potential scale of any outbreak of waterborne diseases.

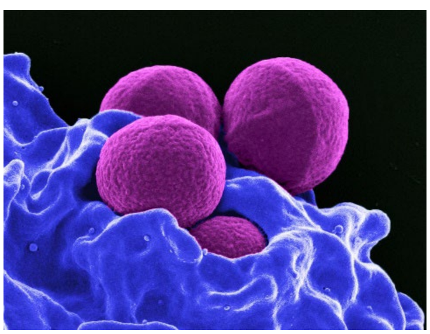
Zoonotic diseases (also known as zoonoses) are caused by germs that spread between animals and people. Animals sometimes carry harmful germs that can spread to people and cause illness. Scientists estimate that more than 6 out of every 10 known infectious diseases in people can be spread from animals, and 3 out of every 4 new or emerging infectious diseases in people come from animals.

- **All kinds of extreme weather events contribute to population displacement:** Extreme weather makes homes become uninhabitable and threatens access to potable water. The sanitary conditions of displaced persons are often more challenging than for the broader population, especially where there is significant crowding resulting in increased pathogen exchange. Furthermore, in some cases, displaced people may move closer to animal habitats, leading to an increased risk of novel zoonotic diseases (i.e., diseases that spread between humans and animals) emerging.

On each of these counts, an increase in the prevalence and severity of extreme weather events contributes to an increased infectious disease burden and, therefore, accelerates the emergence of resistant pathogens.

Resistant Bacteria in the Environment

S. aureus



Antimicrobial waste is a pollutant that, on the one hand, contributes to the emergence of resistance, and on the other, can have a deleterious impact on local biodiversity and ecosystem integrity.

Waste is produced in the manufacture of antimicrobials, from the run-off of intensive livestock production, and some is also due to the biological fact that when animals and humans consume antibiotics, some of the ingredients are still active upon excretion.[48] As a result, active pharmaceutical ingredients find their way into our waterways. Yet, waste sanitation systems do not adequately remove these active ingredients.

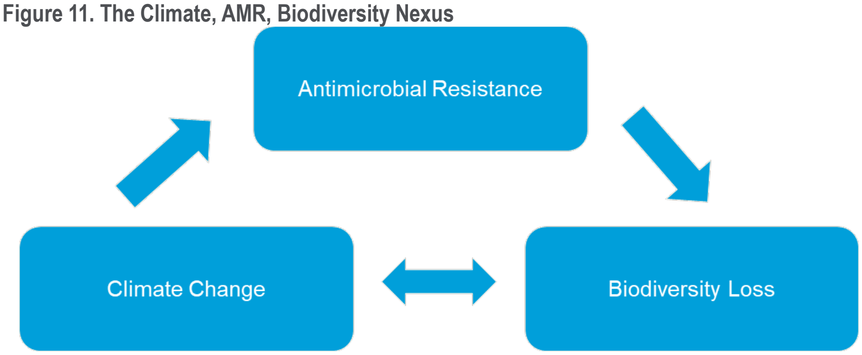
Above a critical threshold, the presence of these antimicrobials in bodies of water presents a training ground for bacteria to develop resistance. By needlessly exposing bacteria to antimicrobial waste, we present bacteria with an opportunity to evolve and become resistant, “learning” from their interaction with waste antimicrobial ingredients in wastewater.

[46] David L. Paterson, Hugh Wright, and Patrick N A Harris, “Health Risks of Flood Disasters,” *Clinical Infectious Diseases*, October 15, 2018.
[47] Jason P. Burnham, “Climate Change and Antibiotic Resistance: A Deadly Combination,” *Therapeutic Advances in Infectious Disease*, February 15, 2021.
[48] University of Exeter, “Stemming the Tide of AMR in the Natural Environment,” December 5, 2020.

Moreover, the contamination of water and solid waste by these antimicrobials can affect water and soil quality and have further negative consequences for marine and terrestrial ecosystem integrity, impacting freshwater fish and the animals that eat them, marine wildlife near the mouths of rivers, and the essential fungi and bacteria that make the soil productive, including the soil's carbon sequestration potential.

We noted in the 2021 Citi GPS report, *Biodiversity: The Ecosystem at the Heart of Business*, that biodiversity loss is inextricably linked to climate change, calling specific attention to the fact that building and maintaining the resilience of ecosystems plays a central role in mitigating emissions. This illustrates the final leg of the tight-knit nexus among AMR, climate change, and biodiversity: Just as preventing climate change decreases the threat of AMR, climate change is itself worsened by biodiversity loss, which in turn becomes more challenging by contributing factors to AMR like the presence of active pharmaceutical ingredients in the environment.

Figure 11. The Climate, AMR, Biodiversity Nexus



Source: Citi GPS

A One Health Approach to AMR

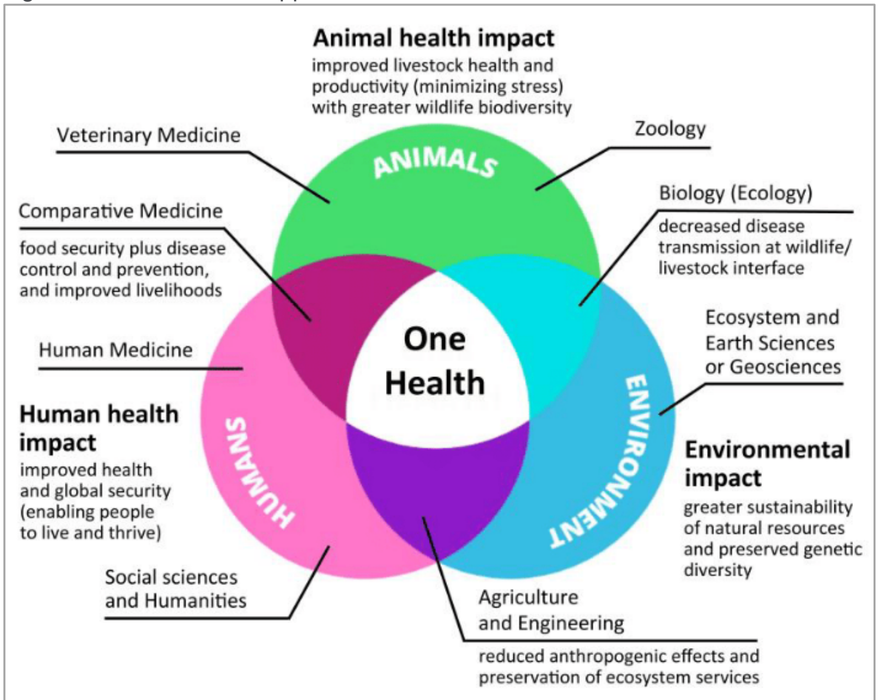
The nexus among AMR, climate change, and biodiversity loss is closely aligned to the "One Health" approach. The One Health approach is not entirely new: It has been recognized since the 19th century that many diseases have similar impacts on both humans and animals. The term first emerged in discussions of severe acute respiratory syndrome (SARS) when the spilling over of viruses from animals into humans, known as zoonotic disease, came sharply into focus.[49]

One Health approaches to public health start from the recognition that animal, human, and environmental health are all closely linked and are best considered holistically. In practice, the guiding principle of the One Health approach is that professionals from human, animal, and environmental health must communicate, coordinate, and collaborate on their shared priorities.

[49] John S. Mackenzie and Martyn Jeggo, "The One Health Approach – Why Is It So Important?" *Tropical Medicine and Infectious Disease*, June 2019.

> AMR is not just a medical problem. It's also a threat to crops, to food security, and to animals. This interconnection between people, animals, plants, and their shared environment demands a collaborative, trans-disciplinary One Health approach to finding solutions.
>
> – PROFESSOR NEIL GOS, PROFESSOR OF MICROBIOLOGY, UNIVERSITY OF EXETER

Figure 12. A One Health Approach



Schematic representation of the One Health approach finalized to ensure the well being of people, animals and the environment through collaborative problem solving -locally, nationally and

Source: Barcaccia et al. (2020)

Expert Contribution: Professor Dame Sally Davies

What Next for AMR?

Professor Dame Sally Davies
UK Special Envoy on Antimicrobial Resistance

Dame Sally Davies was appointed as the UK Government's Special Envoy on AMR in 2019. She is also the 40th Master of Trinity College, Cambridge University.

Dame Sally was the Chief Medical Officer for England and Senior Medical Advisor to the UK Government from 2011-2019. She is a leading figure in global health, having served as a member of the World Health Organization (WHO) Executive Board 2014-2016, and as co-convener of the United Nations Inter-Agency Co-ordination Group (IACG) on Antimicrobial Resistance (AMR), reporting in 2019.

In November 2020, Dame Sally was announced as a member of the new UN Global Leaders Group on AMR, serving alongside Heads of State, Ministers and prominent figures from around the world to advocate for action on AMR.

In the 2020 New Year Honours, Dame Sally became the second woman to be appointed Dame Grand Cross of the Order of the Bath (GCB) for services to public health and research, having received her DBE in 2009.

The COVID-19 pandemic was a wake-up call on the impact of an initially untreatable infection on lives and livelihoods. Antimicrobial resistance (AMR) is also a pandemic, which currently kills almost 1.3 million people annually globally. As the world continues to emerge from the darkest days of the COVID-19 pandemic, we must seize this wake-up call and learn the lessons of the pandemic, bringing the same energy and focus to addressing the silent pandemic of AMR. The past two years have shown us what is possible — when scientists, policymakers, the public, and investors quickly mobilize to focus on prevention, diagnosis, and effective treatments.

Antibiotics are critical infrastructure for modern health systems, food systems, and the planet. This is why the threat of AMR is both global and complex, with drivers, impacts, and risks from across different sectors. As such, everyone has a role to play in addressing it. The bottom line is simple: we must prevent, control, and treat infections. We, the world, can choose to produce and consume differently to preserve our antibiotics. Investors, in particular, have an important role to play as antibiotic stewards, advocating for sustainable innovation, production, and use of antibiotics.

Global demand for antibiotics is high and increasing, having almost doubled globally between 2000 and 2018. But our valuation and payments for these drugs is at an all-time low, with the proliferation of generics driving a race to the bottom in pricing. As a result, the financial and societal as well as the environmental value of antibiotics has plummeted.

Less than half of the new chemical entities developed between 1999 and 2014 were even available in more than ten countries — including in some instances, G7 economies. As it stands, the weak market and lack of access leaves the public paying — through premature death, expensive treatments, or higher taxes — for our collective inability to anticipate or act on risks. But the benefits of coordinated action are high.

Staying one step ahead of superbugs requires global leadership from the G7, G20, and G77 — with Health and, importantly, Finance Ministers leveraging the investments and approaches that we needed for COVID-19. Under the UK G7 Presidency in 2021, Finance Ministers made commitments to strengthen antibiotic development through exploring "pull" incentive mechanisms.

The leadership from Finance Ministers of the AMR agenda marks a monumental step forward as it underlines the fact that, as they learned during the COVID-19 pandemic, infectious disease presents an economic threat alongside risks to health.

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

The first steps towards positive action are being taken by some countries across the world that are exploring ways to pay for antimicrobials in a way that reflects their value to healthcare systems. For example, in the U.K., the world's first subscription-based model is paying for the availability of antibiotics to National Health Service (NHS) patients, including cefiderocol and avibactam, rather than paying for the number of antibiotics consumed working with Shionogi and Pfizer.

Other countries have taken up a similar model. For example, Germany aims to transition to value-based pricing through innovation in reimbursement structures. These schemes will collectively give a meaningful incentive for investing in antibiotics.

The PASTEUR Act (2021) in the U.S., which aims to tackle the shortcomings of market-led antimicrobial development and ensure the availability of novel, effective antimicrobials for patients, would be a global step forward in addressing the challenge of AMR. The Act would establish a subscription-based payment mechanism to encourage innovation and protect the health system's ability to treat resistant infections.

The sheer scale of the U.S. market would both make this a watershed moment in addressing the challenge of AMR and send a signal to other economies on the importance of changing our approach to antimicrobial consumption. It gives us a glimpse of how the future might look, with a level playing field, so that it makes as much sense for companies to develop a new antimicrobial treatment as it would to pursue a new cancer therapy.

What comes next in addressing the AMR challenge? The PASTEUR Act sets the stage for future multilateral action. AMR cannot be solved once and moved on from — it requires ongoing action over many years. It is only by sustained, global action that the world can address the threat of AMR.

As a member of the UN Global Leaders Group on Antimicrobial Resistance, I have noted the importance of a coordinated response to this threat and the need for action at a global scale. This global governance mechanism will catalyze political action, including through the High-Level Meeting that will take place at the United Nations in 2024, where the world will look to countries for their leadership and ambition on AMR. It will also be vital that the private sector has a voice in the run-up to this meeting.

Investors can lead the way in mitigating AMR risks and create long-term value. AMR should be integrated into investment decision-making, with investors stewarding antibiotics. Alongside FAIRR, the UN Principles for Responsible Investment, and the Access to Medicine Foundation, the U.K.'s Department of Health and Social Care launched the Investor Action on AMR initiative.

Together, we have galvanized some of the world's leading asset managers and development finance institutions to demonstrate that AMR does represent a material risk. Over 16 investors with a collective asset portfolio exceeding $11 trillion are aligning with global best practices on AMR by incorporating AMR into their ESG standards. We welcome additional investors to join us in this effort.

The World Bank, European Bank for Reconstruction and Development, and the CDC Group are all supporting AMR interventions through technical partnership, financing, and training. A one-size-fits-all approach will not sufficiently address the challenge of AMR, but global collaboration and collective learning are both vital in protecting this precious resource for global health.

Chapter 3: Interventions to Tackle Antimicrobial Resistance

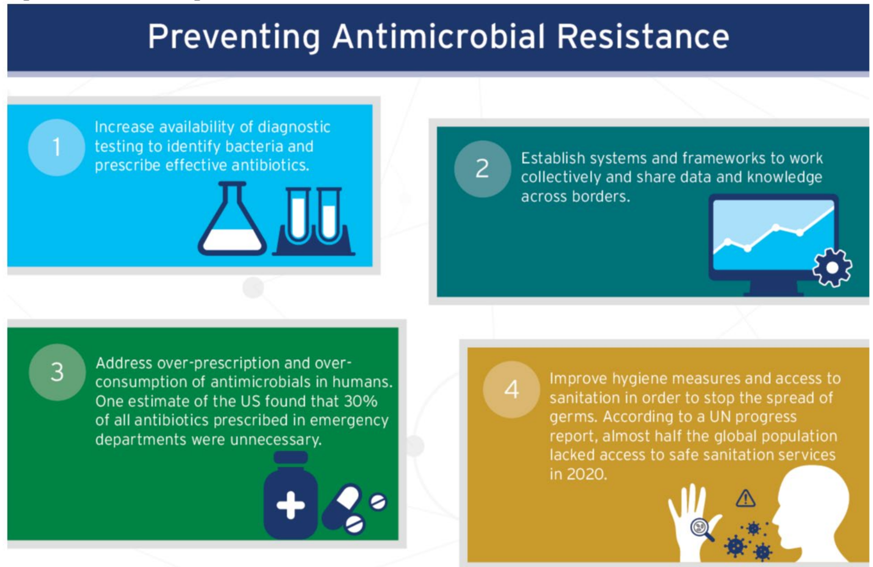
The projected economic losses related to AMR between 2015 and 2050 could reach a staggering $100 trillion — currently eightfold the global cost of COVID.[50] The solutions are just as well understood as the costs, and they are achievable.

This chapter summarizes the possible interventions to avert the worst outcomes, among the most important of which are rapid, robust, and affordable diagnostics; the support of modern technology; and a drastic reduction of antibiotics consumption in the production of animal protein (meat and dairy) bred for human consumption.

AMR is a significant global problem, but many of the solutions are within reach. As Professor Dame Sally Davies puts it, "*this is not insurmountable, this is doable.*" In this chapter, we explore some of the interventions and solutions that can help address the global challenge of AMR and catalogue them under four headings: (1) reducing the burden of infectious disease, (2) reducing the use of antimicrobials, (3) innovating for novel antimicrobials, and (4) curtailing the spread of resistance where it has already emerged. These solutions require the collaboration of a broad range of stakeholders, including the public and private sectors together with civil society.

[50] *Reuters*, "IMF Sees Cost of COVID Pandemic Rising Beyond $12.5 Trillion Estimate," January 20, 2022; The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016.

Figure 13. Preventing Antimicrobial Resistance



Source: Citi GPS

1. Reducing the Burden of Infectious Disease

One of the first steps in addressing AMR is reducing the burden of infectious disease. This would feed through to reductions in the antimicrobials required to treat infections and hence slow the emergence of resistance. Multiple interventions are required to achieve any reduction in the transmission of infectious diseases. These include improved sanitation systems, especially in low- and middle-income countries (LMICs), developing vaccines for both human and animal populations, and implementing biosecurity strategies in the livestock sector to maintain animal health.

Improving Sanitation to Prevent Spread of Infection

Infrastructure to support good hygiene includes access to handwashing stations and facilities utilizing soap and clean water for communities and households, safe disposal of human waste (feces and urine), the collection and management of industrial and household waste, and the treatment of wastewater and solid waste.

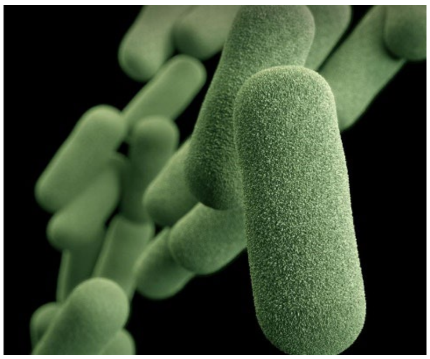
Improving sanitation, hygiene, and access to safe water is a key sustainable development goal; according to Macintyre et al. (2017), the link with antimicrobial resistance is "multifaceted and complex."[51] Populations that do not have access to infrastructure supporting good hygiene practices and sanitation are at higher risk of contracting infectious diseases. The COVID-19 pandemic issued a reminder that good hygiene and regular hand washing are a vital and cost-effective intervention to reduce the burden of infectious diseases.[52]

[51] Alison McIntyre, Megan Wilson-Jones, and Yael Velleman, "Prevention First: Tackling AMR Through Water, Sanitation AND Hygiene," AMR Control, July 31, 2017.
[52] UN Water, "Summary Progress Update 2021: SDG 6 – Water and Sanitation for All," July 2021.

Illustrating the point with reference to diarrheal disease, a March 2016 report concluded that access to sanitation could reduce the burden of these diseases by between 69% and 72%.[53] The same report estimates this could feed through to a reduction in antimicrobial consumption due to diarrheal disease of between 47% and 72%. Complementary measures such as educating clinicians and increasing vaccination coverage, which are discussed elsewhere in this chapter, could further add to this reduction in antibiotic consumption.

Development and Use of Vaccines and Alternatives

H. influenzae



Vaccines also play a significant role in reducing the burden of infectious diseases by preventing infections in immunized populations. This applies equally to both human and animal populations, where vaccines can reduce reliance on antimicrobial medicines.

However, just as novel antimicrobials are difficult and expensive to develop, many of the same challenges plague vaccine development. The Review on Antimicrobial Resistance, commissioned by the U.K. government, notes that developing vaccines can take over a decade and very few of the products that enter early stage research ever come to market. This has resulted in a situation in which multiple priority pathogens, including those that the CDC has designated in need of "urgent" innovation to produce novel antimicrobials, have no corresponding vaccine that could reduce the number of infections.[54]

As a result, in its final 2016 report, the Review on AMR concludes that increased vaccine coverage in both human and animal populations should be pursued and greater investment is required to support the development of vaccines with a particular focus on priority pathogens.[55]

Biosecurity

Biosecurity: Biosecurity refers to measures aimed at preventing the introduction and/or spread of harmful organisms (e.g., viruses, bacteria, etc.) to animals and plants in order to minimize the risk of transmission of infectious disease.

Improving sanitation and increasing vaccine coverage could feed into a biosecurity strategy. In the context of AMR, the term biosecurity refers to the steps taken either to avoid the introduction of pathogens, like bacteria and viruses, to animal and plant populations, or to reduce their spread.[56]

As this section suggests, reducing the disease burden feeds through to a reduction in the number of antimicrobials required for treatment should infection occur. Indeed, multiple studies have shown that farms with high biosecurity compliance require fewer antimicrobials. Moreover, better farm management both strengthens productivity and improves measures to prevent disease. As a result, adopting a biosecurity strategy and investing in compliance with it constitutes a cost-effective intervention in tackling the overuse of antimicrobials.

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[53] Pablo Araya et al., "The Impact of Water and Sanitation on Diarrhoeal Disease Burden and Over-Prescription of Antibiotics," *Review on Antimicrobial Resistance*, March 2016.
[54] U.K. Government, "Vaccines and Alternative Approaches: Reducing Our Dependence on Antimicrobials," February 15, 2016.
[54] Teja Sirec and Tomasz Benedyk, "One Health: 10 Ways to Tackle Antimicrobial Resistance," Federation of European Microbiological Societies, September 19, 2017.
[55] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016.
[56] A survey article on the definition and evolution of this term shows that it has also been applied to humans and used in the specific context of biological weapons. See Véronique Renault, Marie-France Humblet, and Claude Saegerman, "Biosecurity Concept: Origins, Evolution and Perspectives," *Animals*, December 28, 2021.

2. Reducing the Use of Antimicrobials

S. baumannii

A second cluster of interventions aims at reducing the use of antimicrobials in both humans and animals. There is a significant opportunity here because many antibiotic prescriptions, even in humans, are unnecessarily administered. One U.S. statistic suggests that as many as 30% of antibiotic prescriptions may be unnecessary.[57] Appropriate deployment of antimicrobials may be even worse in LMICs where a World Bank study of six countries found that in 60% of cases, a young woman reporting to a pharmacist with symptoms of a lower urinary tract infection was administered with antibiotics without a prescription.[58]

Government regulation has already started to address this pillar significantly: In 2015, the White House released a National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB), which set a goal of reducing inappropriate outpatient antibiotic use in the U.S. by at least half by 2020.

Raising Awareness: Education on Antimicrobial Resistance

Behavioral change is critical to improving the stewardship of antimicrobials. This can only be achieved by education to improve awareness and understanding of antimicrobial resistance, particularly among two key audiences:

1. **Patients and consumers of antimicrobial products**, where public awareness campaigns have previously reduced the number of antimicrobials prescribed by up to 36%.[59]

2. **Professionals across the fields of human and animal health**, where AMR could be included in certifications and continuing professional development.[60]

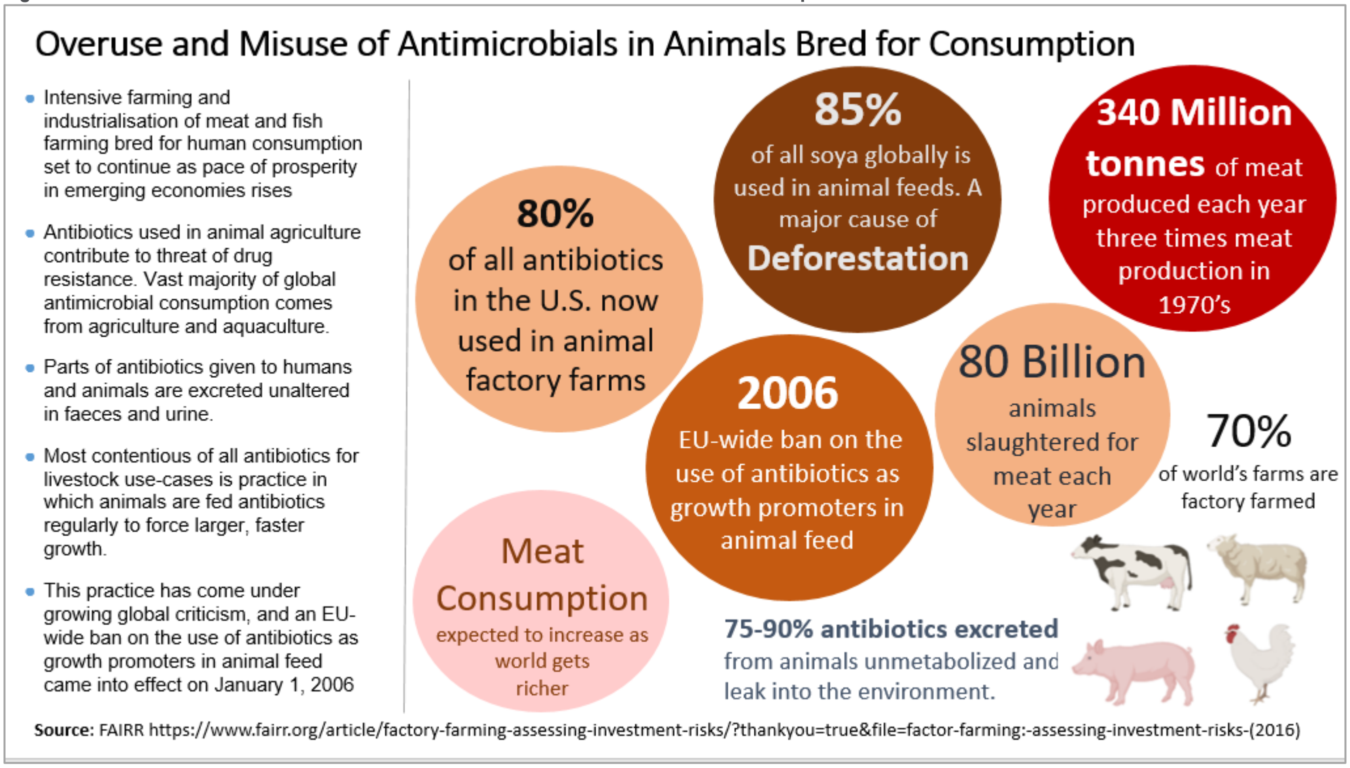
One element of this public awareness campaign will involve public education on the role of antimicrobials and what they are effective in treating. There is a significant lack of knowledge here with one report on the EU finding that almost half of the population thought antibiotics would be effective against a virus, when of course they only target bacterial infections.[61]

Reduce Unnecessary Antimicrobials in Agriculture and the Environment

We highlight in Chapter 4 the imprudent use of antimicrobials in food production and call for better governance of antimicrobials across the industry by both farmers and veterinarians. Antimicrobials are routinely used in food production both to prevent infection and, which has proven somewhat more contentious, to promote the faster growth of animals in intensive farms. Figure 14 reminds us of some key statistics on the use of antimicrobials in food production.

[57] CDC, "CDC: 1 in 3 Antibiotic Prescriptions Unnecessary," updated January 1, 2016.
[58] World Bank Group, "Drug Resistant Infections: A Threat to our Economic Future," March 2017.
[59] The Review on Antimicrobial Resistance, Chaired by Jim O'Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016.
[60] WHO, "Raising Awareness and Educating on Antimicrobial Resistance," accessed November 14, 2022.
[61] European Commission, "Antimicrobial Resistance," November 2018.

Figure 14. Overuse and Misuse of Antimicrobials in Animals Bred for Human Consumption



Source: FAIRR (2016), Citi GPS

Regulation has already started to move here: The use of antimicrobials for growth promotion was banned in the EU as early as 2006 as part of a strategy aimed at slowing the emergence of antimicrobial resistance.[62] However, in LMICs, the politics of such a ban are challenging. As the population in these countries gets larger and richer, increased demand for animal protein (meat and dairy) is expected to follow. In the short term, over-reliance on antimicrobials supports attempts to address food insecurity, which is likely to remain a significant issue in growing lower-income countries. In Chapter 4 we explore in more detail what is needed to facilitate reducing the use of antimicrobials in food production.

Modern Tools for Rapid Diagnostics

In a paper on modern tools for rapid diagnostics by Vasala et al. (2020), the authors call for "fast, robust, and affordable antimicrobial susceptibility testing."[63] Where pathogens have been inaccurately identified, patients can be prescribed antibiotics to treat a believed bacterial infection when the infection is actually a viral infection and, as a result, unresponsive to antibiotics. Inaccurate prescriptions could be minimized by using rapid diagnostic tools.

[62] European Commission, "Ban on Antibiotics as Growth Promoters in Animal Feed Enters Into Effect," December 2005.
[63] Antti Vasala, Vesa P. Hytonen, and Olli H. Laitinen, "Modern Tools for Rapid Diagnostics of Antimicrobial Resistance," *Frontiers in Microbiology*, Vol. 10, Article 308, 2020.

We have witnessed the powerful impact of rapid COVID-19 tests which admittedly test for fewer infection markers but have been instrumental in helping patients understand if their symptoms are viral or bacterial. Similar investment into rapid diagnostics for pathogen identification to better treat the presentation of infection in human and animal patients (companion pet and livestock) could result in more effective deployment of the correct antibacterial treatment.

Similar rapid diagnostics also offer visibility into the susceptibility of pathogens to antibiotic treatment. From a clinical perspective this is referred to as “antibiotic susceptibility testing” rather than “antibiotic resistance testing.”

3. Innovating for Novel Antimicrobials

Improvements to tackle an over-reliance on antimicrobials are a vital first step in addressing AMR and without better stewardship, novel antimicrobials would be only a temporary solution to the challenge. However, innovation is also critical to replenish the clinical pipeline of new medicines. Facilitating innovation requires investment into early stage research and drug discovery, where emerging technologies may also have a role to play. Another element of this involves building the pipeline of talent to ensure that scientists continue to be attracted into AMR-relevant fields.

Incentivizing Drug Discovery in the Pharmaceutical Industry

We discuss holistically the role of the pharmaceutical industry in addressing the challenge of AMR in Chapter 7. For now, it is sufficient to note that the development of novel antibiotics has presented difficulties for the pharmaceutical sector and more must be done at the level of policy to alter the economics of research and development in AMR-relevant fields. Opening up the research capacity of the pharmaceutical industry to this space would constitute a significant step in tackling AMR.

Many of the recommendations presented in the 2016 AMR Review still apply at this stage: The regulatory hurdle for bringing novel antimicrobials to market is still very high and there are limited economic incentives to enter the anti-infectives market at all. In his commentary, Lord Jim O’Neill notes that more progress is needed here and suggests again a “Pay or Play” funding scheme, which would require pharmaceutical companies either to invest in the research and development of novel antimicrobials or to pay a charge.

Public Sector and Philanthropic Funding for Early Stage Research

There is likely to remain an investment gap in early stage drug discovery, even if the pharmaceutical industry can be incentivized to take more action on AMR. This is because of the risks involved in earlier stage research. As a result, funding from alternative sources, including the public sector and philanthropists, plays a significant role in supporting drug development.

Case Study: Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

CARB-X is a non-profit organization with global support from a range of institutions, including the U.K. government and the Bill & Melinda Gates Foundation. The organization exists to accelerate and support scientific research to create novel antimicrobials, vaccines, and diagnostic tools that tackle AMR-relevant pathogens.

Figure 15. How CARB-X Works

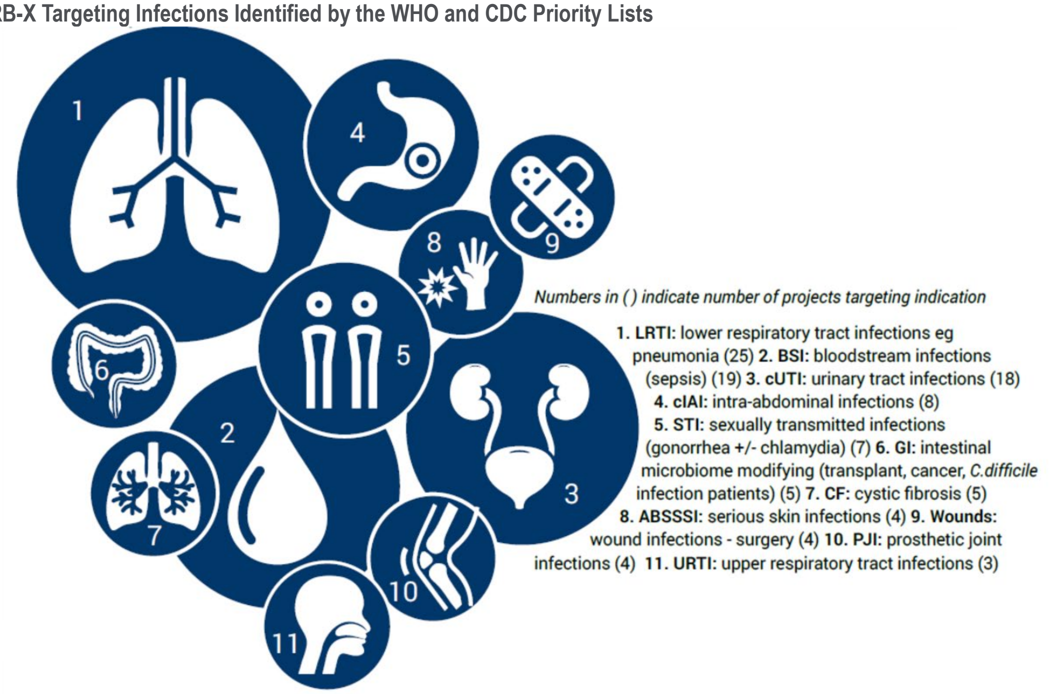
How CARB-X works

CARB-X fills a critical gap to help stem this crisis. Beginning with competitive funding calls to address unmet medical needs, CARB-X provides non-dilutive funding as well as scientific, regulatory and business support to product developers. CARB-X focuses both on the most serious drug-resistant bacteria identified by the World Health Organization and the US Centers for Disease Control and Prevention and on the syndromes with the highest degrees of mortality and morbidity. Diagnostics are supported from feasibility through prototype development, while therapeutics and preventatives are supported from finding potential leads for new drugs through preclinical development and into a demonstration of safety in human clinical trials.

Source: CARB-X

In its *Annual Report 2020-2021*, CARB-X reported on the diverse portfolio of innovative antibacterial products moving toward clinical development and regulatory approval with funding, expert support, and cross-project initiatives.[64] CARB-X focuses on the dangerous bacteria identified by the WHO and CDC priority lists, see Figure 16 below.

Figure 16. CARB-X Targeting Infections Identified by the WHO and CDC Priority Lists

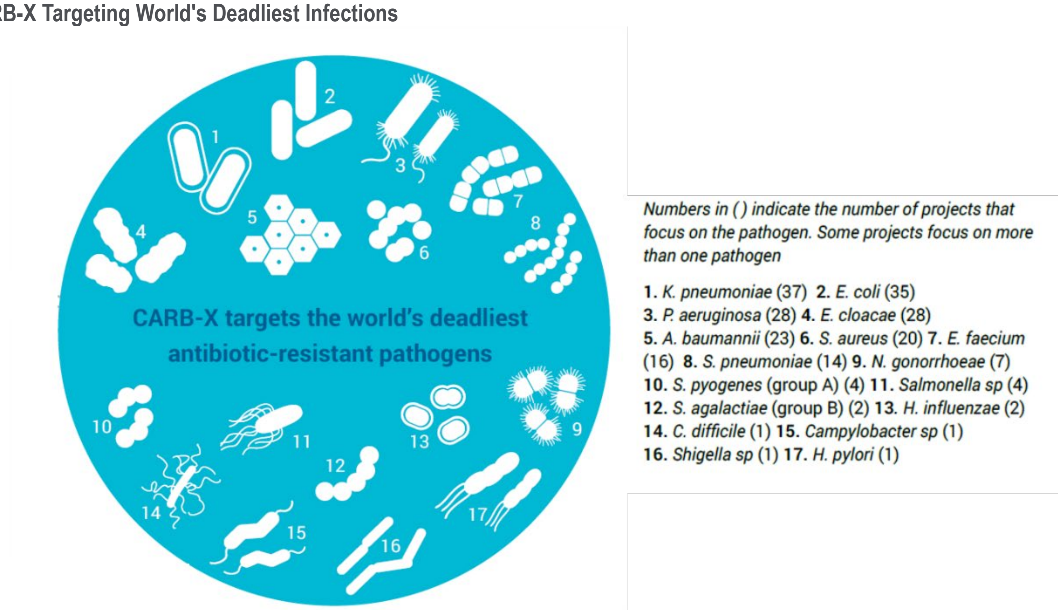


Source: CARB-X Annual Report 2020-2021

In its annual report, CARB-X claims it is pursuing “radically innovative classes, targets, and non-traditional approaches” compared to existing research methods that build on the “the extension” of well-known classes” of antibiotics.

[64] CARB-X, *Annual Report 2020-2021: Preparing the World Against Antibiotic-Resistant Bacteria*, October 2021.

Figure 17. CARB-X Targeting World's Deadliest Infections



Source: CARB-X Annual Report 2020-2021

Highlights from the 2020-2021 CARB-X annual report include the development of:[65]

- A **differentiated oral combination of a novel broad-spectrum inhibitor of Class A and C beta-lactamases** with cefpodoxime to treat complicated urinary tract infections (UTIs) including carbapenem resistant Enterobacteriaceae (CRE).
- An oral, **rationally designed microbiome consortium for the prevention of breakthrough antibiotic-resistant bacterial infections** and graft-versus-host disease in patients following solid organ and allogeneic stem cell transplantation.
- A **novel class, broad-spectrum antibiotic to target multi-drug resistant Gram-negative bacteria**.
- **An orally bioavailable small-molecule drug** that targets an adhesion protein found on the surface of *Escherichia coli* bacteria called FimH. *E. coli* is a key causative pathogen resulting in UTIs.
- An **innovative "soft drug" polymyxin antibiotic** that targets clinically important therapy of **multidrug-resistant** infections including *E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Acinetobacter baumannii*.
- **An orally active small molecule with activity against *N. gonorrhoeae***, including multidrug-resistant forms.
- An **oral cyclic-boronate as a penicillin-binding protein (PBP) inhibitor** for third-generation cephalosporin-resistant gonorrhea.

Emerging Technologies Support Drug Discovery

Advances in technology might support the discovery of novel antimicrobials. Some companies working on emerging technologies have explained that technology can be deployed not only to search out those that might have antimicrobial properties from known molecules more efficiently than human researchers, but these technologies can even learn the underlying structures of antimicrobial medicines and generate new molecules that have not yet been synthesized.[66]

[65] Ibid.

[66] World Economic Forum, "Tackling Antibiotic Resistance with AI and Quantum Computing," August 2, 2022.

> Combining powerful emerging AI techniques could be the most promising route to successfully tackling antibiotic resistance.
>
> – ALESSANDRO CURIONI, VP EUROPE AND AFRICA DIRECTOR, IBM RESEARCH EUROPE[67]

Two examples illustrate the potential of these technologies:

- In 2020, a group of academics from North America trained a deep neural network to predict which molecules might have antibacterial properties and published their findings. Their investigations predict that Halicin, a molecule found in the Drug Repurposing Hub, would have antimicrobial properties. Trials in mice then provided confirmation that Halicin does show antimicrobial properties.[68]

- A 2021 paper proposes a fully offline mobile application capable of analyzing antibiotic susceptibility testing.[69] While the system will still require basic microbiology, the proposed AI-based model is designed to partially alleviate need of expert human resources, highly relevant in LMICs, to make, for example, disk-reading more reliable and potentially enable faster interpreted results.

Deploying these technologies to support drug discovery does stand to significantly reduce the costs of replenishing the clinical pipeline and the time it would take to do so compared with traditional research, which is significantly more labor intensive. However, this is not a panacea: Computational techniques do not always predict the toxicity of novel molecules, and this is a key factor in the suitability of antimicrobials as medication that can limit their progression to clinical trials.

Number and Recognition of People Working With Infectious Disease

Surveillance systems involve the ongoing systematic collection, collation, and analysis of information related to public health (animal and human) and the timely dissemination of information so that action can be taken. The information is used, for example, for actions that prevent and control infectious disease.

We know the challenge of AMR will require continuous monitoring for as long as we have the need of antimicrobials and keeping the pipeline of novel antimicrobials replenished will be an ongoing task. Hence, part of the solution requires ensuring there is a qualified workforce to support surveillance systems and innovation efforts going forward.

The broader problem of an under-resourced global health workforce persists: The WHO expects that there will be a shortage of 10 million workers by 2030, with the majority of this shortfall experienced by LMICs.[70] Moreover, attracting workers into the infectious diseases specialty remains challenging: The 2016 AMR Review suggested that the specialty had among lowest earnings of all medical specialties in 2012 and, according to Medscape data, infectious disease remains in the five lowest-paid specialties in the U.S.[71]

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[67] Ibid.
[68] Jonathan M. Stokes et al., “A Deep Learning Approach to Antibiotic Discovery,” *Cell*, Vol. 180, No. 4, February 20, 2020.
[69] Marco Pascucci et al., “AI-Based Mobile Application to Fight Antibiotic Resistance,” *Nature Communications*, Vol. 12, No. 1173, February 19, 2021.
[70] WHO “Health Workforce,” accessed November 16, 2022.
[71] Leslie Kane, *Medscape Physician Compensation Report 2022: Incomes Gain, Pay Gaps Remain*, Medscape, April 15, 2022..

4. Curtailing the Spread of Resistance

The final set of solutions aims at curtailing the spread of resistance that has already emerged. The first stage must be to improve surveillance systems, especially in LMICs, and to understand the current state of resistance and target actions appropriately. Second, treating wastewater will be critical to halting the spread of resistant pathogens as well as preventing the emergence of further resistance.

Global Surveillance of Drug Resistance

Shigella

Surveillance involves tracking both the emergence of AMR in humans, animals, and the environment, as well as the use of antimicrobial medicines. Without this information, it is impossible to develop a targeted and informed strategy to curtail resistance. This must also be complemented by an understanding of the microbiological mechanisms by which resistance emerges.

Figure 18. Global Surveillance of Drug Resistance

Source: Citi GPS

Many surveillance systems are attempting to build a global picture of the current state of AMR. One example is the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS), launched in 2015.[72] The global approach aims to facilitate data sharing globally by setting out a standardized methodology for collection and interpretation at the level of individual countries.

In addition to GLASS, there are other noteworthy initiatives on AMR surveillance data including ACORN (A Clinically-Oriented Antimicrobial Resistance Suveillance Network) and the Fleming Fund.[73] The former is a tractable reporting system designed to collect accessible information in LMICs; the latter is a laboratory building initiative/surveillance system across 24 countries in LMICs funded by the British government. Other surveillance systems such as BARNARDS focus on antimicrobial use and resistance in neonates from Africa and South Asia.[74]

[72] WHO, "Antimicrobial Resistance," November 17, 2021.
[73] ACORN, "Development, Implementation, and Assessment of Enhanced Antimicrobial Resistance (AMR) Surveillance," accessed November 14, 2022; The Fleming Fund, "Aims & Values," accessed November 14, 2022.
[74] Kathryn M. Thomson et al., "Effects of Antibiotic Resistance, Drug Target Attainment, Bacterial Pathogenicity and Virulence, and Antibiotic Access and Affordability on Outcomes in Neonatal Sepsis: an International Microbiology and Drug Evaluation Prospective Substudy (BARNARDS)," *Lancet Infectious Diseases*, Vol. 21, No. 12, August 2021; Kirsty Sands et al., "Characterization of Antimicrobial-Resistant Gram-Negative Bacteria that Cause Neonatal Sepsis in Seven Low- and Middle-Income Countries," *Nature Microbiology*, Vol. 6, April 2021.

Improving Treatment of Wastewater With Attention to Antimicrobials

Calabria de Araújo et al. (2020) highlight the role of wastewater treatment plants in mitigating AMR.[75] Wastewater, including water used in both domestic and industrial contexts, is treated in a multi-stage process at wastewater treatment plans. These stages start with the manual removal of large objects and progress through to using bacteria that consume much smaller contaminants.

With a high prevalence of both pathogens and antimicrobials, these treatment plants are among the most important reservoirs of antibiotic resistance in urban environments. The combination of the two presents an opportunity for the emergence of AMR and the scale at which these treatment plants operate presents an opportunity for the widespread dissemination of resistance.[76] Yet, improving the treatment of wastewater is also an opportunity to limit the spread and emergence of AMR.

Figure 19. Wastewater Treatment Plant

Source: Shutterstock

To prevent the emergence and dissemination of resistance at wastewater treatment plants, stricter requirements should be set on the level of antimicrobials and pathogens permitted in wastewater when it is released into other bodies of water, including rivers, lakes, and coastal regions, or into the sewage system.

Regulation is an important element of the solution here, but it cannot act alone. Innovation to help meet these stricter requirements is also vital. The current landscape of new technologies, including nature-based solutions, includes:

[75] Juliana Calabria de Araújo et al., "Antibiotic Resistance, Sanitation, and Public Health," *Antibiotic Resistance in the Environment*, Vol. 91, March 25, 2020.
[76] Johannes Alexander, Norman Hembach, and Thomas Schwartz, "Evaluation of Antibiotic Resistance Dissemination by Wastewater Treatment Plant Effluents with Different Catchment Areas in Germany," *Scientific Reports*, Vol. 10, No. 8592, June 2020.

- Novel **treatment reactors** that convert contaminants in the water to carbon dioxide gas and biomass.[77]

- **Constructed wetlands**, which are artificial flooded ecosystems set up to capitalize on natural processes to treat wastewater, including the removal of antimicrobials. One study suggests that constructed wetlands can remove more than 60% of antibiotic-resistant genes.[78]

- **Biochar**, a form of charcoal that can also be used as a carbon sink, to filter antibiotics from the wastewater.[79]

All these solutions play a role in addressing the global challenge of AMR. Each requires coordinated action and, in some cases, significant investment. But one thing is certain: The solutions are well-known and achievable if there is sufficient motivation to act.

[77] Fateme Barancheshme and Mariya Munir, "Strategies to Combat Antibiotic Resistance in the Wastewater Treatment Plants," *Frontiers in Microbiology*, Vol. 6, No. 2603, January 2018.
[78] Lin Liu et al., "Response of Antibiotic Resistance Genes in Constructed Wetlands During Treatment of Livestock Wastewater with Different Exogenous Inducers: Antibiotic and Antibiotic-Resistant Bacteria," *Bioresource Technology*, Vol. 314, No. 123779, October 2020.
[79] Patrycja Krasucka et al., "Engineered Biochar – A Sustainable Solution for the Removal of Antibiotics from Water," *Chemical Engineering Journal*, Vol. 405, February 2021.

Expert Contribution: Dr. Damiano de Felice

Damiano de Felice, PhD
Director of Development and External Engagement, CARB-X

Damiano de Felice, PhD, is a non-profit executive with experience leading teams across multiple functions, including business development and fundraising, partnerships and external relations, strategy and impact, operations, and finance. He currently serves on the Executive Team of CARB-X, leading development and external engagement.

Damiano joined CARB-X from the Access to Medicine Foundation, where he served as Director of Strategy and a member of the management team. At the Access to Medicine Foundation, he trebled annual funding to the organization and coordinated one of the world's largest impact investing initiatives.

He serves as an expert for the WEF Global Future Council on Human Rights, SASB Advisory Group for the pharmaceutical sector, the Global AMR R&D Hub Stakeholder Group, and Expert Committee for the UN Sustainable Procurement Index for Health. Damiano holds a PhD in international relations from the London School of Economics and Political Science.

Replenishing the Clinical Pipeline

To keep ahead of antimicrobial resistance (AMR), the world needs highly innovative products to prevent, diagnose, and treat the most dangerous drug-resistant infections. For example, in 2016, the Review on AMR chaired by Lord Jim O'Neill set the target of developing 15 new antibiotics a decade, of which "at least four should be breakthrough products, with truly novel mechanisms of action or novel therapeutic profiles targeting the bacterial species of greatest concern." More recent reports suggested that the number of new approvals should be even higher, with consensus among experts coalescing around the target of six high-impact therapeutics over 10 years.

Unfortunately, the existing global clinical pipeline cannot be expected to deliver these much-needed products. According to a detailed analysis of the antibacterial agents in clinical development in 2021 by the World Health Organization (WHO), "overall, the clinical pipeline and the recently approved antibacterial agents are insufficient to tackle the challenge of increasing emergence and spread of AMR." Out of the 27 antibiotics under development against WHO bacterial priority pathogens, only six fulfill at least one of the WHO innovation criteria.

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) was created in response to this problem. We support the early development of innovative products so that the global clinical pipeline will be replenished with the R&D projects that the world needs to address AMR. With financial contributions of up to $800 million until 2032 from our five funders (the U.S., German, and U.K. governments, plus the Wellcome Trust and the Bill & Melinda Gates Foundation), our job is to identify, select, and fund, in a nondilutive manner, high-quality and differentiated science from around the world, irrespective of either the geographical location of the applicant or the size of the organization.

Our portfolio is laser-focused on the most significant bacterial threats to human health, primarily those identified as "Urgent/Serious" in the CDC Threat Assessments or "Critical/High" in the WHO Global Priority Pathogen List. We fund the stages of development from hit-to-lead through the initial Phase 1 clinical trials (or feasibility demonstration through the verification for diagnostics).

The profile regarding size of the organizations applying to CARB-X shows a crucial feature of the global antibacterial R&D ecosystem. Out of a total of 1,163 applications, 44% (n = 511) originated from companies that had ≤10 employees, and a further 25% (n = 294) were from small companies with ≤50 employees. This means that, while numerous large pharmaceutical companies have left this area, especially with respect to therapeutics, there remains a core of passionate scientists working on infectious diseases.

These small organizations often lack the breadth and depth of larger pharmaceutical companies in all disciplines that are required to successfully transition programs through the different stages of preclinical and clinical development. This is why, in addition to financial support, CARB-X provides R&D as well as business mentoring services through an accelerator network of partners, an extensive list of advisory board members and consultants, and an internal R&D team.

What we can confidently say is that innovation is not lacking from the early stages of AMR research and development. While the antibacterials developed and approved for commercial use over the past few decades have been extensions of well-known classes, at CARB-X we aim higher. This includes embracing non-traditional modalities for which there is neither a well-trodden preclinical nor a well-defined clinical history, requiring us to work with the broader community to forge new ground for these novel technologies.

A few examples of areas where we invested significantly in recent years include bacteriophage, peptides, and anti-virulence:

- Also known as “phage,” bacteriophage are viruses that infect bacteria with their DNA or RNA and replicate among bacteria. Typically, they are species-specific and as such are considered harmless to the gut microbiota.
- Peptides are naturally occurring antibiotics that target bacteria. They are appreciated for their broad-spectrum coverage of Gram-negative bacteria. However, owing to their typical chemical composition, they often have off-target activities that result in toxicities to humans.
- Anti-virulence blocks and disarms the bacterial pathogen’s ability to cause infectious diseases. Whether anti-virulence agents can be used as standalone therapies, which would therefore be an antibiotic-sparing approach, or whether they will be given on top of an antibiotic is something we will learn.

One measure of success for us is the number of products we have supported into First-in-Human trials, and 12 is an extraordinary achievement in six years. The future holds even more promise, as more than 50 patents and invention disclosures have been filed for products in our portfolio. However, the funding and support provided by CARB-X is not sufficient, in isolation, to ensure a viable pipeline of products available commercially to tackle the AMR challenge.

Significant other changes are also required to create an end-to-end sustainable ecosystem for innovation in this therapeutic area, including the creation of an effective global system of pull incentives that delink R&D rewards from the volume of sales, while providing AMR product developers with appropriate returns on their investments in case their R&D programs are successful.

Against the business challenges experienced by many AMR product developers in the past years (see, for example, the cases of Achaogen and Melinta), we welcome the fact that global investors have started to recognize that drug-resistant infections can be material to the profitability of their long-term holdings and are willing to engage with policymakers in support of bolder reimbursement reforms.

We are also grateful that some biotech and impact investors (e.g., the Novo Holdings’ REPAIR Impact Fund) have already decided to play the long-term game. They are co-investing in the product developers within the CARB-X portfolio on the basis of the expectation that governments will soon redress the current market failure.

We share the optimism that new products (within and outside CARB-X portfolio) will save millions of lives (providing a public return on the public investments from our current funders) while being profitable for the private investors that are contributing (or will contribute) to their development toward the patients who desperately need them.

Chapter 4: Human Antimicrobials and Food Production

Salmonella

More than 73% of global antimicrobial consumption is directed at food production. As a result, reducing the farming sector's consumption of antimicrobials is critical to curbing resistance. Yet, this will require financial support and radical intervention programs to prevent increasing poverty. Developing alternatives to antimicrobials is also critical to ensuring both animal welfare and food security.

Reducing the inappropriate use of antimicrobial drugs in food systems is a key priority for the Global Leaders Group on Antimicrobial Resistance (GLG).[80] Access to high-quality antimicrobials is important for animal and plant welfare, but global leaders recognize that preventing the existential threat of antimicrobial resistance will not be possible without reducing, if not fully eliminating, the use of human antibiotics relied on for decades, in global farming.

Antibiotic Use in Food Systems Expected to Increase

Antibiotic use in food systems is common practice and projections suggest it will increase by 11.5% from 2017 through 2030.[81] The link between the use of antimicrobials in food systems and the development of AMR to those drugs is well established, at least within the farming sector, as exemplified by the detection of the first plasmid-mediated polymyxin resistance (MCR-1) in Enterobacteriaceae in animals and humans in China.[82]

[80] 'Global Leaders Group on Antimicrobial Resistance website, accessed November 14, 2022.
[81] Kate Tiseo et al., "Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030," *Antibiotics*, Vol. 9, No. 12, 2020.
[82] Yi-Yun 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, No. 2, 2016.

Since the discovery of mobilized colistin (polymyxin) resistance (MCR) gene, the link between the use of antibiotics in farming and resistance in human infections has been furthered with the discovery of both tigecycline and carbapenem resistance — the former by the use of tetracycline on farms and the latter by the use of ampicillin on farms.[83]

Both antibiotics are on the World Health Organization's critically important antimicrobial list.[84] The worrying aspect of these observations is that a common and cheap antibiotic (e.g., tetracycline) used by the many thousands of metric tons per year in farming is selecting for resistance to high-end antibiotics (e.g., tigecycline) that are reserved to treat highly resistant bacteria causing life-threatening infections in critical patients (e.g., neonatal sepsis).[85]

Medically Important Antimicrobials Used for Growth Promotion

Metaphylaxis is the treatment of a group of animals that do not show disease but are in close contact with other animals that do show evidence of contagious diseases.

The GLG have called on all countries to: (1) end the use of medically important antimicrobials for growth promotion entirely, (2) limit antimicrobial prophylaxis and metaphylaxis and ensure strict regulatory oversight, (3) eliminate the use of antimicrobials to compensate for inadequate agricultural practices, and (4) markedly reduce the use of antimicrobials — particularly those on the Highest Priority Critically Important list.[86]

However, while these notions may be palatable and even potentially implementable in high-income countries (HICs), in low- and middle-income countries (LMICs), their implementation will result in higher meat prices and an inevitable increase in poverty through lack of income.

Recently, China has taken these concerns very seriously by introducing a ban on all antimicrobials as an animal growth promoter in 2020.[87] European Union regulation came into force in January 2022 to prohibit routine use of antimicrobial drugs in farming.[88]

[83] WHO, "Critically Important Antimicrobials for Human Medicine," 2019; He Tao et al, "Emergence of Plasmid-Mediated High-Level Tigecycline Resistance Genes in Animals and Humans," *Nature Microbiology*, Vol. 4, 2019; 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, June 2020.
[84] WHO, "Critically Important Antimicrobials for Human Medicine," 2019.
[85] He Tao et al., "Emergence of Plasmid-Mediated High-Level Tigecycline Resistance Genes in Animals and Humans," *Nature Microbiology*, Vol. 4, 2019; 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, June 2020.
[86] Global Leaders Group on Antimicrobial Resistance website, accessed November 14, 2022; World Health Organization (WHO), "WHO Model List of Essential Medicines – 21st List 2019," July 23, 2019.
[87] Jessika Hu Yanhong and Benjamin John Cowling, "Reducing Antibiotic Use in Livestock, China," *Bulletin of the World Health Organization*, Vol. 98, 2020; Timothy R. Walsh and Yongning Wu, "China Bans Colistin as a Feed Additive for Animals," *The Lancet Infectious Diseases*, Vol. 16, No. 10, 2016.
[88] Eur-Lex, "Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on Veterinary Medicinal Products and Repealing Directive 2001/82/EC," PDF, 2019.

In the U.K., the use of antibiotics in the animal health sector fell by 40% between 2013 and 2017 and the U.K. government has recently pledged to include commitments to tackle AMR in the published negotiating objectives of all future independent trade agreements.[89]

However, whether in HICs or LMICs, the issue is where prophylaxis meets metaphylaxis — i.e., how many animals in a flock or herd must be ill before you treat the entire flock or herd.

For financial reasons, a farmer is likely to set this bar very low. Ensuring family income will surely eclipse any ethereal notion of safeguarding global AMR, however persuasive the GLG, World Health Organization, Food and Agriculture Organization, or World Organisation for Animal Health may be.

The Need for Infrastructure and International Interdisciplinary Implementation

C. difficile

The GLG's steps should be applauded, and countries should be encouraged to implement the recommendations in the GLG's statement on antimicrobial use in food systems. However, a lack of good husbandry practice (e.g., bird-rearing conditions) and international interdisciplinary implementation may prevent these actions from achieving their desired goals across all countries. Furthermore, as argued above, there must be financial support, both local and national, to encourage such incentives without increasing local poverty — a key Sustainable Development Goal.[90]

We do not fully know the long-term consequences of banning antibiotics in animal feed for animal welfare and food production efficiency. The initiatives are unprecedented and monitoring their impact will be crucial to understanding how similar policies can be enacted across the world, particularly in LMICs. While these interventions are noteworthy and noble, the international trade of antibiotics used in animal feeds (primarily prophylaxis and metaphylaxis) continues unabated and many LMICs are the recipients of, for example, cocktails of ampicillin, oxytetracycline, and colistin. Therefore, global governance of antibiotic sales, particularly in animals where tonnage vastly exceeds that used in humans, is long overdue.

Population Growth Will Drive Global Meat Consumption

The world's population is forecast to increase by 2.2 billion by 2050, and the majority of the rise will occur in middle-income countries where meat is considered an indispensable food source for the wealthy.[91] Accordingly, global meat consumption is projected to increase by 14% in 2030, and LMICs in particular will need to continue to adjust farming practices to meet the needs of rapidly growing populations. Consequently, by 2030, antibiotic use is also forecast to increase by 12% to meet this demand.[92]

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[89] U.K. Department for International Trade, "Government Response to the Final Trade and Agriculture Commission Report," 2021.

[90] UN Department of Economic and Social Affairs, Sustainable Development, "The 17 Goals," accessed November 14, 2022.

[91] UN Department of Economic and Social Affairs, "World Population Projected to Reach 9.8 Billion in 2050, and 11.2 Billion in 2100," June 21, 2017.

[92] Kate Tiseo et al., "Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030," *Antibiotics*, Vol. 9, No. 12, 2020.

Farmers in LMICs will need support to make the necessary improvements in farm hygiene, management, and animal husbandry that enable restrictions on the use of antimicrobials while still protecting animal welfare and avoiding catastrophic losses of livestock from disease.

Vaccination programs have been suggested as a means of protecting animals against major pathogenic strains, but delivery and affordability is challenging on a global scale.[93] Moreover, the use of phages (viruses that specifically attack bacteria) is unproven on a large scale, and besides, phages have been shown to be vectors of AMR genes themselves, which will diminish the appetite for large scale production.[94] Thus, the support needed to significantly reduce or eliminate human antibiotics from use in farming is currently lacking and will take time to mobilize globally, as well as to secure appropriate financial backing.

Farming in Low-Middle Income Countries

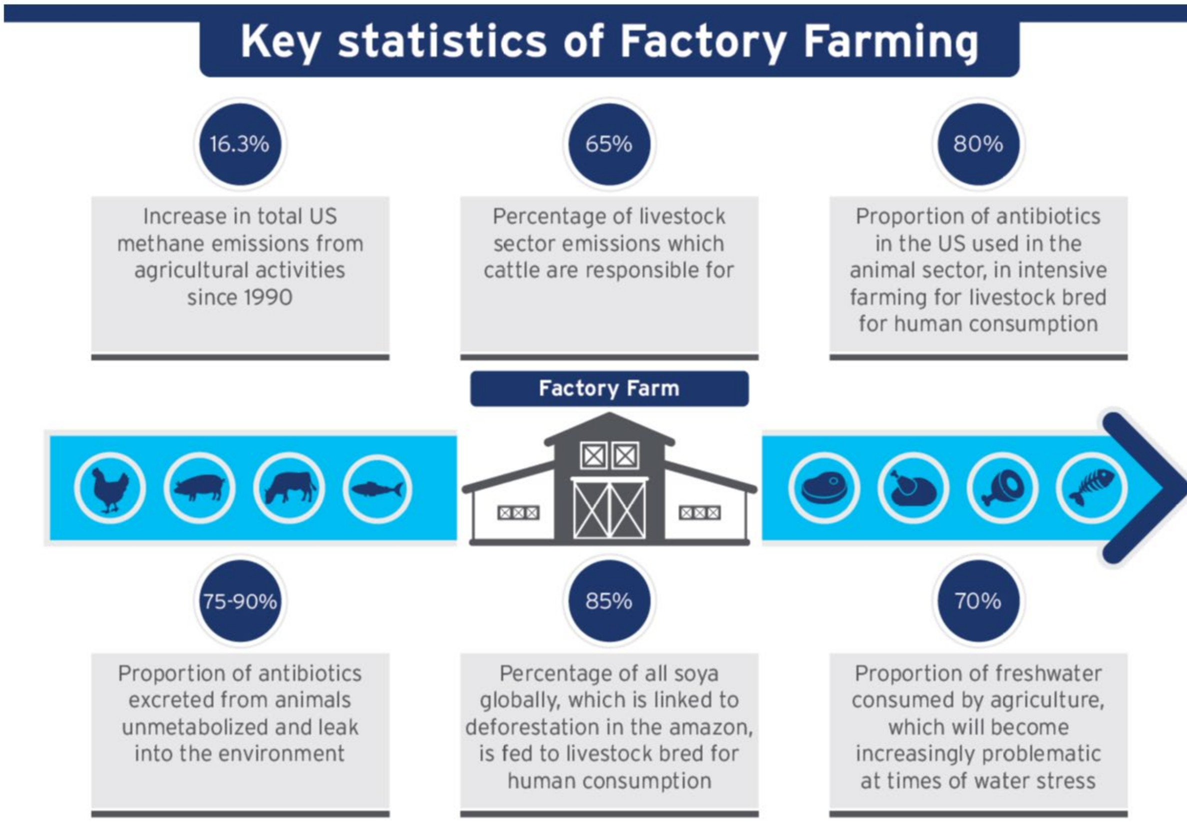
Cross-resistance is when something, e.g., bacteria, develops a tolerance for substances with similarly acting mechanisms, e.g., a class of antibiotics.

Asking farmers in LMICs to reduce antimicrobial usage will be challenging when there is nothing of similar efficacy to replace them. They will see their flock or herd wilt and with it, their livelihood to support their families. Therefore, alongside reduction, or even elimination, we need to find alternative antimicrobial-like therapies that protect animal welfare, imbue efficient farming, and do not risk cross-resistance to precious drugs crucial for human medicine, such as oxytetracycline (used in farms) and tigecycline (used in human medicine).

Compared to the development of human antimicrobials, which takes up to ten years and can exceed $1 billion, designing completely new "protective therapies" for animals has many distinct advantages, such as that requirements for toxicity and tissue residue are more easily achievable. However, other aspects such as environmental half-life and cost (e.g., tetracycline, for example, is similar in price to sugar, which is why its global use is more than 60,000 tons per year), are challenging but not insurmountable hurdles, as long as desire and financial backing exists to support this unique approach to this immense problem and ensure the longevity of human medicines for future generations.[95] To this end, the hope is that one day all supermarkets when selling meat, whether HIC or LMIC, will proudly bear the label "NHA" — no human antibiotics.

[93] World Organisation for Animal Health, "Vaccination" in *Terrestrial Animal Health Code: Volume One*, 2019.
[94] Amit Vikram et al., "Phage Biocontrol for Reducing Bacterial Foodborne Pathogens in Produce and Other Foods," *Current Opinion in Biotechnology*, Volume 78, 2022.
[95] Fabio Granados-Chinchilla and Cesar Rodríguez, "Tetracyclines in Food and Feedingstuffs: From Regulation to Analytical Methods, Bacterial Resistance, and Environmental and Health Implications," *Journal of Analytic Methods in Chemistry*, 2017.

Figure 20. Key Statistics Around Factory Farms



Source: Adapted from FAIRR Initiative, Factory Farming: Assessing Investment Risks (2016), Citi GPS

Global Action Points:

1. Enhance public awareness on antibiotic use in farming — both agriculture and aquaculture.
2. Investment in the production of new “animal only” drugs with no cross-class resistance to human antibiotics.
3. Funding of alternative disease-preventing therapies, such as vaccines.
4. Educate companies that trade in antibiotics for animal use on the medium-term risk of this use, both to animals and to humans.

Chapter 5: The Role of Investors in Addressing the AMR Threat

The growth of responsible investment has been catalyzed by increasing regulation, asset owner demands for greater transparency, and the ambition to align investment to the 2030 UN Sustainable Development Goals. The enormous economic and societal impact from antibiotic failure is not just a concern for responsible investment and impact investment strategies but a concern for all sectors and all investors. AMR is a societal issue, and as we have become comfortable talking about the social cost of carbon, we now need to consider the social cost of antibiotic resistance. This chapter expands on why investors should care about AMR and, at the end, highlights the role investors can play.

Sustainable Investing on the Rise

This chapter defines and charts the growth of environmental, social, and governance (ESG) investing and responsible investment. Labels used to describe ESG investing include sustainable investing, socially responsibility investing (SRI), responsible investing (RI), values-based investing, impact investing, thematic investing, green investing, and mission-driven investing.[96]

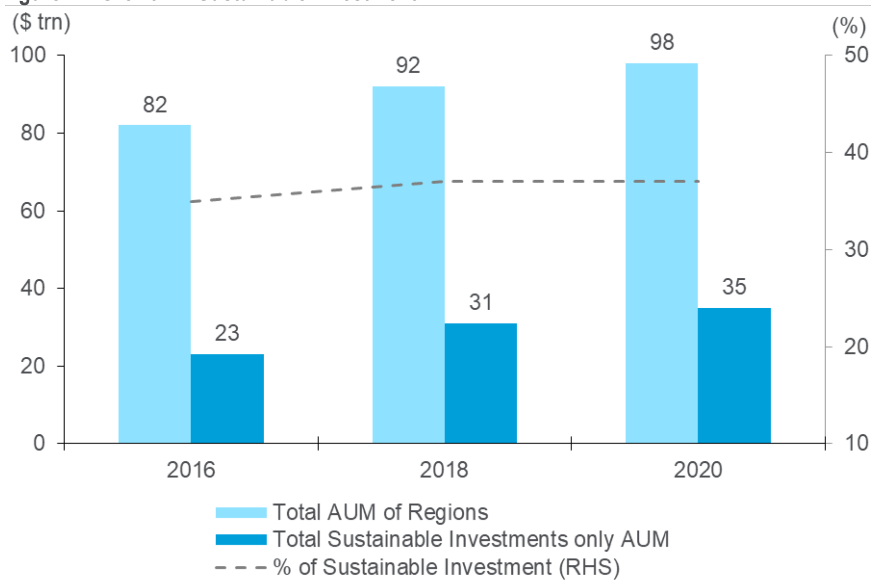
The UN Principles for Responsible Investment (UNPRI) define responsible investing as a "*strategy and practice to incorporate environmental, social, and governance factors in investment decisions and active ownership.*"[97]

[96] James J. Tucker III, PhD, CPA and Scott Jones, PhD, "Environmental, Social, and Governance Investing: Investor Demand, the Great Wealth Transfer, and Strategies for ESG Investing," *Journal of Financial Service Professionals*, Vol. 74, No. 3, April 2020.
Principles for Responsible Investment (PRI), "An Introduction to Responsible Investment: What is Responsible Investment?" accessed November 14, 2022.

Integration of ESG is defined as the explicit and systematic inclusion of ESG issues in investment analysis and investment decisions.[98] To avoid confusion, we use both ESG and responsible investing in this report. The underlying premise is the identification of, integration of, and alignment to ESG criteria. There is a body of evidence to suggest that firms with strong ESG disclosures exhibit stable financial returns in the form of dividend payouts, benchmark outperformance, and mitigation of downside credit risk.[99]

Adopting a structured and integrated approach to ESG investment offers the potential to deliver a more comprehensive investment analysis, which should result in better-informed investment decision making.[100] Approaches to ESG integration are typically a combination of two overarching areas: ESG incorporation and active ownership.

Figure 21. Growth in Sustainable Investment



Source: Global Sustainable Investment Alliance, Citi GPS

[98] PRI and CFA Institute, *ESG in Equity Analysis and Credit Analysis*, 2018.

[99] Robert G. Eccles, Ioannis Ioannou, and George Serafeim, "The Impact of Corporate Sustainability on Organizational Processes and Performance," Management Science, Vol. 60, Issue 11, February 2014; Pedro Verga Matos, Victor Barros, and Joaquim Miranda Sarmento, "Does ESG Affect the Stability of Dividend Policies in Europe?" *Sustainability*, Vol. 12, No. 21, 2020; Rob Bauer and Daniel Hann, *Corporate Environmental Management and Credit Risk*, Maastricht University European Centre for Corporate Engagement (ECCE), 2010.

[100] Amir Amel-Zadeh and George Serafeim, "Why and How Investors Use ESG Information: Evidence From a Global Survey," *Financial Analysts Journal*, Vol. 74, No. 3, 2018.

Why Investors Care About Responsible Investment

The UN PRI identify three reasons responsible investors care about ESG integration: (1) financial materiality, (2) client demand, and (3) regulation. A CFA Institute (2020) survey of more than 4,400 investors uncovered further motivations pursued by investors in relation to ESG integration: fiduciary duty, reputational concerns, investment opportunity, and as a proxy for management quality.[101]

Using data from mainstream investors, Amir and Serafeim (2018) discovered that the opportunity to effect change, develop new investment strategies, understand the impact of future materiality, and asset owner client mandates all influence how responsible investors integrate ESG issues into the fund proposition.[102]

The impact of future financial materiality from the negative impacts of climate change, biodiversity loss, and food insecurity are increasingly part of the dialogue with investors in 2022 as they seek to understand how resilient their portfolio companies are.

Investors Not Currently Prioritizing AMR

At the start of 2022, Citi Research conducted a survey of 150 investors across asset classes, geographies, and assets under management. Investors were asked to name their priority ESG topics for the year ahead.

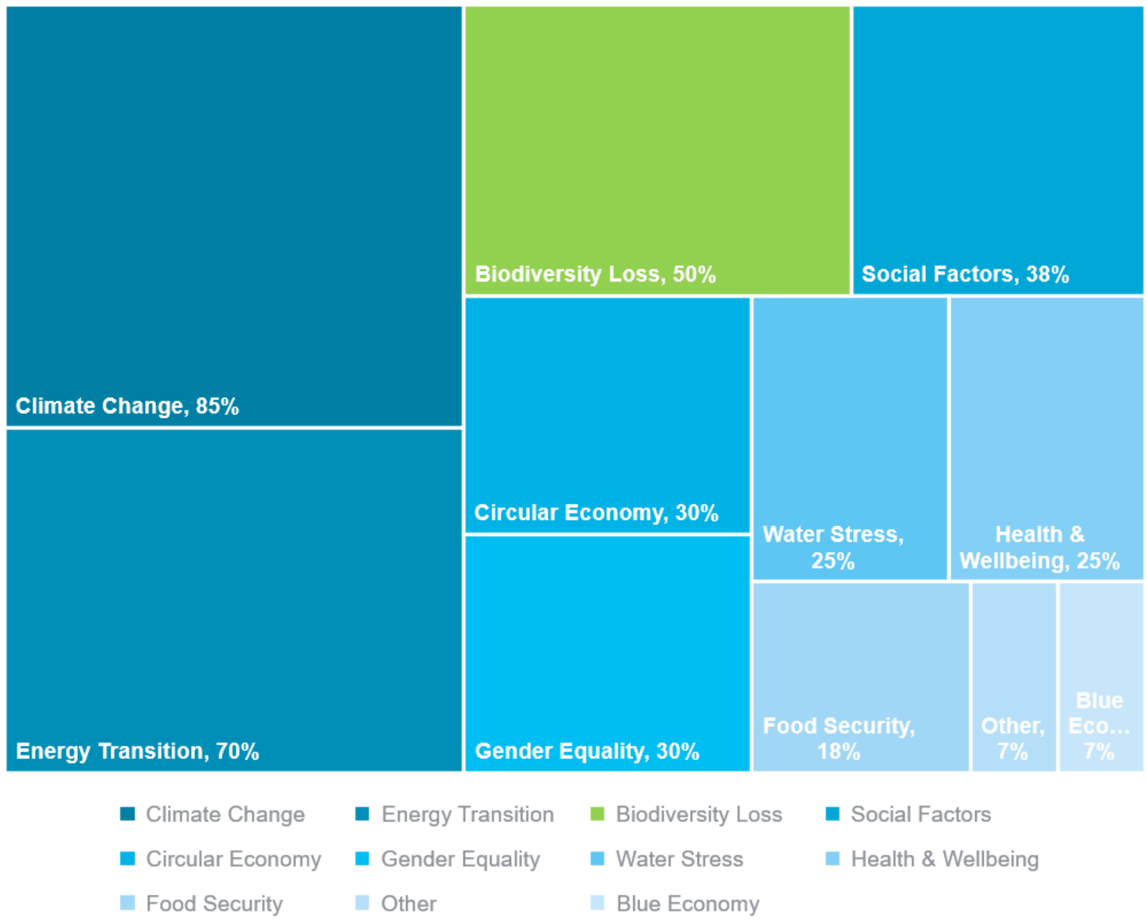
This survey was conducted in advance of the invasion of Ukraine and the extreme heat stress experienced across the U.K. and Europe, as well as six months before the devastating floods that caused major disruption to Pakistan. These events have had a negative impact on human security, disrupting and displacing communities, and worsening the health outcomes for the elderly, young, immuno-suppressed, and other at-risk categories.

The top three ESG areas of focus for the survey respondents were climate change, energy transition, and biodiversity loss (see Figure 22). In an open text box, investors responding to the survey were invited to list other priority investment themes. The survey uncovered a small group of investors that had identified AMR as an area of focus for the year ahead but otherwise, AMR remains poorly understood for the majority of investors.

[101] CFA Institute, *Future of Sustainability in Investment Management: From Ideas to Reality*, 2020.

[102] Amir Amel-Zadeh and George Serafeim, "Why and How investors Use ESG information: Evidence From a Global Survey," *Financial Analysts Journal*, Vol. 74, No. 3, 2018; Amel-Zadeh and Serafeim's survey precedes launch of Sustainable Finance Disclosure Regulation (SFDR), which has had an impact on investor behavior. This is a limiting factor when interpreting their results.

Figure 22. Citi Research Investor Sentiment Survey Key Trends 2022 Outlook



***Other includes** *Anti-Microbial Resistance (AMR), First Nation Rights and Cultures, Sustainable Digitisation, Board Effectiveness, Corporate Governance, Human capital, Diversity, Equity and Inclusion (DE&I), Supply Chain, Methane*

Source: Citi GPS

The Role of Responsible Investment in Tackling AMR

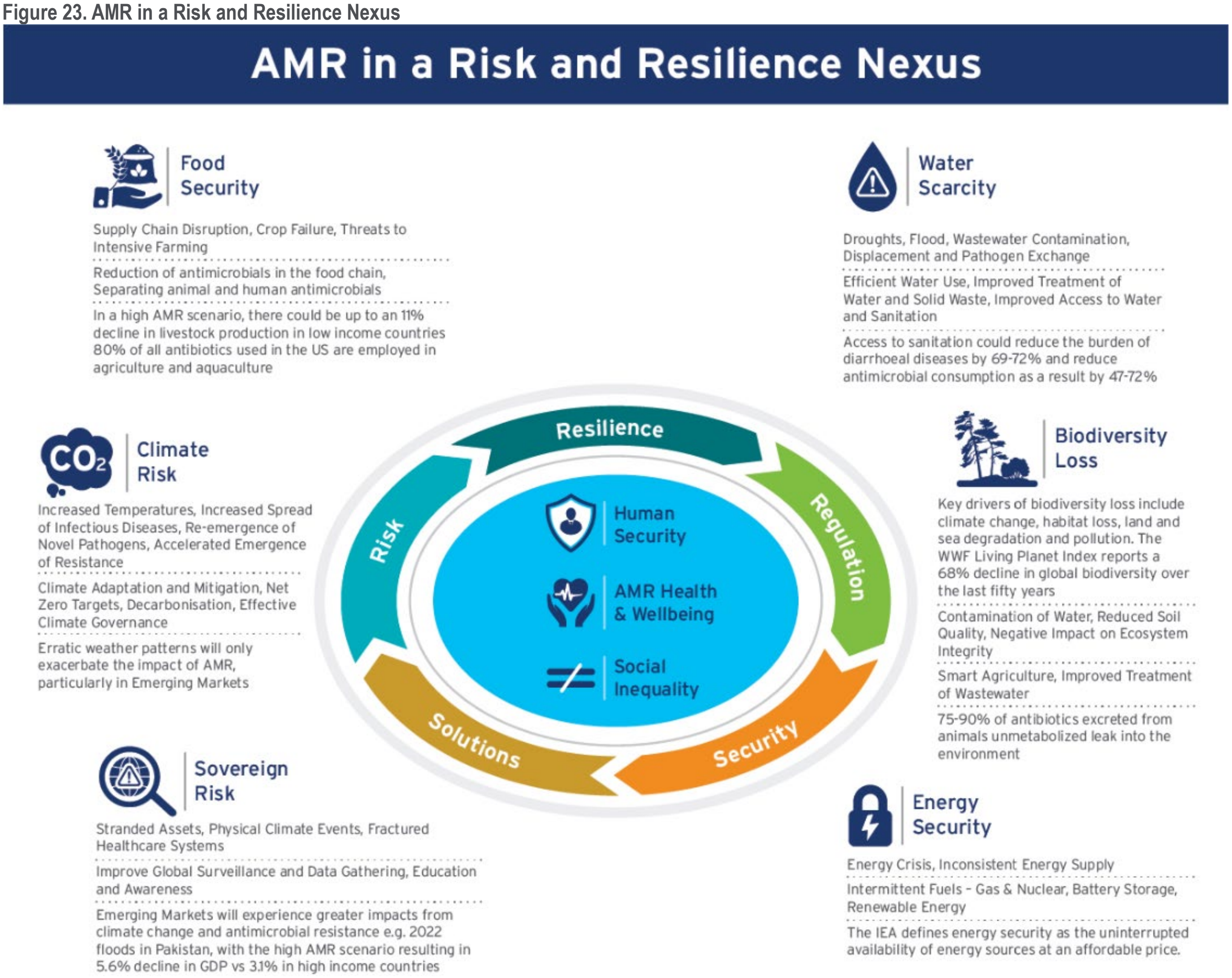
This Citi GPS report makes the case for AMR to be a responsible investment consideration by highlighting the link between extreme weather events, (e.g., hurricanes and floods), contaminated drinking and bathing water, poor sanitation, and the impact of accelerated pathogen transfer on human health.

Human security and health and well-being sit at the nexus of a long-term sustainable investment strategy. AMR is closely linked to many of the issues identified by the UN SDGs such as food insecurity, where reduced susceptibility of pathogens to antimicrobial treatment threatens intensive livestock farming practices. AMR is also linked to water scarcity because improved access to water and sanitation is critical to reducing the burden of AMR. We have made the case elsewhere (see Chapter 2) that AMR, biodiversity loss, and climate change are inextricably linked to human, animal, and ecosystem health.

This has a long-term impact on human security, as displaced people escape or migrate away from conflict, climate stress or land use change. The UNHCR estimated that "forcibly displaced people" number over 100 million globally.[103] Deteriorating and cramped living conditions with reduced access to clean and safe drinking water, and limited access to health facilities and medical assistance, reduce immunity and aide pathogen transfer. In the U.K., a diphtheria outbreak, a highly infectious and potentially fatal upper respiratory tract bacterial infection, has been linked to overcrowding at an asylum center housing refugees.

This directly impacts human security, which sits at the core of a resilience nexus. This finds that drivers, such as climate change, biodiversity loss, food insecurity, and water scarcity are linked to energy security and sovereign risk, as noted in Figure 23.

Figure 23. AMR in a Risk and Resilience Nexus



Source: Citi GPS

[103] UNHCR, "Refugee Data Finder," accessed November 27, 2022.

Investors Lack Necessary Tools to Evaluate Impact of AMR

As of today, current investment frameworks and ESG tools to assess the financial materiality of AMR are mostly lacking. In recent years, we have seen the arrival of an enormous amount of ESG data for investors to assess, for example the carbon footprint of portfolio companies based upon their disclosure of greenhouse gas emissions. This was once considered "non-traditional data" but with the arrival of the Task Force on Climate-Related Financial Disclosures (TCFD), we are now witnessing an evolution from such disclosures moving from voluntary to mandatory in a few jurisdictions.[104]

What does this mean for AMR? In a world that demands greater transparency and traceability from companies about future risks that might become financially material, the pressure to disclose such risks is increasing.

This is directly comparable to the progress investors are now making on issues such as biodiversity loss. No more than two years ago, biodiversity loss was a poorly understood topic by the responsible investment community. Admittedly, there is much more work to be done, but in the last 12 months we have seen the arrival of the Task Force on Nature-Related Financial Disclosures (TNFD). Citi Research has also witnessed upskilling within investment teams in response to the investor sentiment survey, reflecting pressure from asset owner and regulatory demands (see Figure 24 below).

Figure 24. Responsible Investment Skills Evolution — Survey Respondents to Citi Research

Source: Citi Research

Today, investors may lack the necessary tools and skills to evaluate the impact of AMR, but if the rapid upskilling in biodiversity supported by frameworks is any indicator, we could expect more active engagement by the investment community in AMR in the years ahead supported by the necessary skills.

[104] Financial Stability Board, "2022 TCFD Status Report: Task Force on Climate-Related Financial Disclosures," accessed November 16, 2022.

Subset of Investors Reveal AMR Focus

A review of publicly available investor statements on AMR uncovered a small subset of responsible investors that acknowledge the impact of AMR. Disclosures link poor stewardship of antibiotics in healthcare and farming to the potentially destabilizing impact on sectors such as health services, antibiotic manufacturers, pharmaceutical companies, animal health companies, farmers, and the food industry.

"*We are looking at how we can engage most effectively with investee holdings in the pharmaceutical and animal husbandry industries to promote a "One Health"' approach. We work collaboratively with our peers and encourage other investors to take action on AMR within their investee holdings. Where appropriate we will engage with policymakers too.*"

Legal & General Investment Management

"*AMR is the new frontier of ESG — a massive missing piece from crucial multilateral agreements such as the UN Sustainable Development Goals (SDGs) and the European Sustainable Finance Disclosure Regulation (SFDR). Looking at the SDGs, many of the goals are almost impossible to achieve against a backdrop of antibiotic resistance.*"

Abigail Herron, Global Head of ESG and Strategic Partnerships at Aviva Investors

"*We support development of new antibiotics by investing in pharmaceutical companies and by engaging with companies where appropriate. Our engagement topics include AMR, affordable product pricing, product safety, clinical trial data, product pipeline, and lobbying.*"

Eden Tree

"*AMR can seem like a formidable opponent, but there are chinks in its armor. Via our engagement and research, we have identified a wide variety of initiatives aimed at overcoming the myriad underlying challenges.*"

BMO Global Asset Management

Collaboration with peers to engage with investee companies offers a potentially impactful way for investors to actively engage with the pharmaceutical and animal husbandry industries. Investors statements also highlight the absence of AMR within the UN SDGs and the European Sustainable Finance Disclosure Regulation (SFDR).

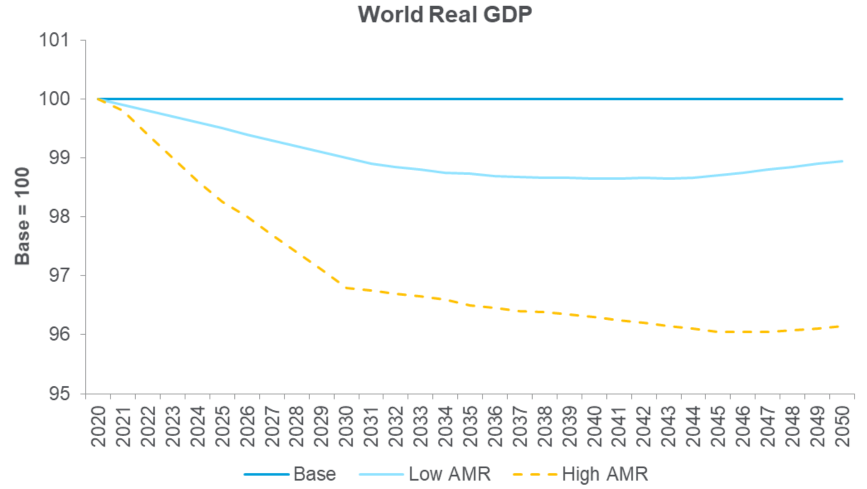
Why AMR Is an Investment Consideration

In a 2017 report, the World Bank ran some simulations to try to quantify the economic impact of AMR on the global economy. They used two scenarios in the simulation between 2017 and 2050 that corresponded to low AMR impacts (optimistic scenario) and high AMR impacts (pessimistic scenario).

In the optimistic case of low AMR impacts, the simulations found that, by 2050, annual global GDP would fall by 1.1% relative to a base-case scenario with no AMR effects. In the high AMR-impact scenario, the world could lose 3.8% of its annual GDP in 2050, with an annual shortfall of $3.4 trillion by 2030 rising to $6.1 trillion by 2050 (see Figure 25).

The study notes that in terms of order of magnitude, the reduction in global economic growth in the pessimistic AMR scenario would be similar in impact to the Global Financial Crisis. It also notes that the economic impacts from AMR are not equally distributed across economics, with low-income economies affected more than higher-income economies.[105]

Figure 25. Substantial and Protracted Shortfalls in Global Economic Output



Source: The World Bank, Citi GPS

UN SDGS: Making the Case for AMR

For investors who wish to align their investment strategies to the UN SDGs, we highlight how AMR impacts all 17 of the UN SDGs and propose a strengthening of the SDG language to accommodate AMR. AMR is affected by 16 of the 17 listed UN SDGs and sits at the very center, linking many of the established SDGs (see Figure 26).

We regard AMR as the greatest health threat facing humankind in the 21st century. However, as with so many SDGs and the consequences of climate change, it will be the LMICs that will bear the brunt of its impact, both clinically and financially.

As bacteria are an intrinsic and indelible part of human existence and an ancient example of symbiosis, AMR is equally part of this peculiar relationship but one that is tilting increasingly in favor of the bacteria due to the use and abuse of one of medicines most precious resources. Given the global importance of AMR and its deeply intertwined association with other SDGs, the case for strengthening AMR within the UN SDG framework is compelling.

[105] World Bank, *Drug-Resistant Infections: A Threat to Our Economic Future*, March 2017.

Figure 26. The UN SDGs and AMR

1 NO POVERTY	AMR is intrinsically and fundamentally linked to poverty and risk factors for AMR infections include over-crowding, lack of potable water, and basic sanitation. Access to healthcare systems is variable and in LMICs often dependent on deferred payment to the patient which will affect access to appropriate antibiotics.
2 ZERO HUNGER	AMR is not only an increasing factor in the intensive farming of livestock bred for human consumption, but antibiotics are also sprayed on crops to prevent bacterial infections, in addition to antifungals. If AMR continues to rise in crops and herds/flocks, sustainable farming may cease to exist affecting global food production.
3 GOOD HEALTH AND WELL-BEING	Antibiotics have enhanced the average human lifespan. When these precious drugs are compromised, common infections will progress unchecked, good health will diminish, and mortality will increase.
4 QUALITY EDUCATION	The fact that AMR is not openly discussed, but will impact us all, is a testimony to how difficult it is to discuss AMR as a subject. It is complicated and understanding the ramifications of antibiotic misuse across agriculture, communities, and hospitals and how this impacts our daily lives is a global priority.
5 GENDER EQUALITY	Girls and young women are more prone to cystitis, particularly in LMICs where access to clean water, hygiene, and sanitation may be lacking and exacerbated by local flooding, for example, the recent floods evidenced in Pakistan in 2022. Furthermore, pregnancy and labor too are a risk where premature rupture of membranes cannot only infect the newborn but further complications can cause maternal sepsis and death. If the women's normal flora is multi-drug resistant (MDR), then this is an additional risk of antibiotic failure, prolonged infection, and increased mortality.
6 CLEAN WATER AND SANITATION	Risk factors for the carriage of AMR bacteria are poor domestic sanitation and hygiene, and in LMICs can occur in babies only a few days old. As in the No Poverty SDG, lack of clean water is intrinsically linked to poverty. Furthermore, LMICs are far more prone to climate change where flooding will mix potable water and sewerage and contaminate large areas of a country.
8 DECENT WORK AND ECONOMIC GROWTH	If people cannot be appropriately treated for even a simple infection, they will spend time away from work which will impact their earnings and family livelihood. A country's ability to produce crops and meat supplies will impact on its national economic growth and GDP, particularly in LMICs.
9 INDUSTRY, INNOVATION AND INFRASTRUCTURE	Innovation in designing new and novel therapies for both humans and animals is desperately needed and therefore must be encouraged. Farming and agricultural industry is heavily dependent on antibiotics or disease-prevention therapies. If the basic infrastructure in a country is lacking, this will impact on supply chains of consumables for hospitals e.g., diagnostics and antibiotic supplies for appropriate treatments. Infrastructure is the cornerstone that supports government and private investment, and thus will indirectly but significantly impact on AMR.

Source: Citi GPS

Figure 27. The UN SDGs and AMR (continued)

10 REDUCED INEQUALITIES	Those people most affected by AMR are communities in LMICs and usually from the lower-social sector where illiteracy and poverty are unacceptably high. Equally, it is the same population that will buy sub-doses of over-the-counter antibiotics avoiding the expense of clinical consultation. Free access to adequate healthcare for low socioeconomic groups is critical but continues to remain elusive.
11 SUSTAINABLE CITIES AND COMMUNITIES	Sustainability is a crucial factor in the fight against AMR. Sustainable hospitals and diagnostic laboratories are fundamental to long-term clinical support. If there is a lack of sustainability, there can be no long-term governance healthcare facilities or country national action plans to tackle AMR.
12 RESPONSIBLE CONSUMPTION AND PRODUCTION	As the world population is set to increase by approximately an extra 2.2 billion by 2050, food will become scarcer and therefore consumption must meet production not visa-versa. How we engender sustainable farming to meet hunger and avoiding poverty will be a major challenge the use of antibiotics and AMR will be central to this issue.
13 CLIMATE ACTION	Climate change is indelibly linked to AMR. Bacteria are carried on winds and spread rapidly throughout communities via flooding. Erratic weather patterns will only exacerbate the impact of AMR, particularly in tropical LMICs who do not have adequate weather defences.
14 LIFE BELOW WATER	Aquaculture in the form of fish and shrimp farms contribute significantly to the GDP of many countries including Bangladesh, Thailand, Vietnam etc. The use of antibiotics in aquaculture is immense and unchecked, driving AMR into the human food chain.
15 LIFE ON LAND	As over 80% of antibiotics are used in farming and agriculture, this has become a critical issue. Moreover, MDR bacteria are spread by flies, birds, and other wildlife that have been associated with causing human infections. As "life on land" should also include humans, the link with AMR in patently obvious.
16 PEACE, JUSTICE AND STRONG INSTITUTIONS	War and conflict zones result in mass migration of refugees who are often housed in refugee camps that are over-crowded with poor sanitation and therefore the spread of AMR bacteria is unchecked. Moreover, medical care and antibiotic use is often high and unchecked during these periods. Human conflict also causes disruption to basic infrastructure and invariably disproportionately affects girls/women which also includes AMR through lack of basic hygiene.
17 PARTNERSHIPS FOR THE GOALS	Partnerships to tackling AMR are critical and needs to be founded on experience, financial support, complementary skills, and knowledge, and deliver impact to tackle AMR that is globally tractable and sustainable.

Source: Citi GPS

Expert Contribution: Aviva Investors and LGIM – The Financial Materiality of AMR for Investors

Abigail Herron
Global Head of ESG Strategic Partnerships, Sustainable Finance Centre of Excellence at Aviva Investors.

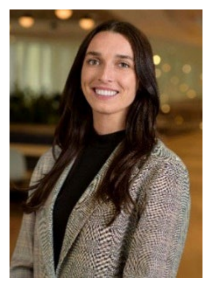
The scope of Abigail's work includes market reform activity to complement company engagement around antibiotic resistance, biodiversity, climate change, net zero, pollution, human rights, gender and diversity, and a just transition. Abigail completed a Master's degree focusing on antibiotic resistance 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 Master's thesis, 2020. She works with the Investor Action on AMR project to address the market failure of AMR.

Maria Larsson Ortino
Global ESG Manager, Investment Stewardship at LGIM

Maria joined Legal & General Investment Management Ltd (LGIM) in January 2019 where she is a Senior Global ESG Manager within the Investment Stewardship Team. She leads the team's efforts on health as well as being responsible for global engagement and voting activities for holdings within the pharmaceutical, biotech, healthcare and chemicals sectors. Maria is a member of the Access to Medicine Foundation's Expert Committee for the 2021 Antimicrobial Resistance Benchmark. Maria has an LLB from Queen Mary College, University of London and a Master's degree from the Graduate Institute of International Studies, University of Geneva, Switzerland.

Alexander Burr
ESG Policy Lead at LGIM

Alexander joined LGIM in 2019 and leads the ESG policy engagement across markets. Prior to this, he helped establish an impact fund that uses blended finance to invest in emerging markets. Before that, Alexander negotiated blended finance investments at the European Bank for Reconstruction and Development (EBRD) to support sustainable economic growth across Eastern Europe, Central Asia, and North Africa. He has held roles advising governments on alternative finance and established a nuclear safeguards organization. Alexander holds a BSc in Politics and International Relations from the University of Southampton, and completed further education at LSE, ICSA, CISL, and Birkbeck.



Emma Cameron
ESG Analyst at LGIM

Emma supports the Investment Stewardship team as an ESG Analyst in developing and running thematic ESG engagement campaigns. Emma joined LGIM America in 2019 as a Rotational Analyst before becoming a Strategy Analyst where she focused on client engagement and ensuring solutions continued to successfully achieve clients' long-term objectives.

Emma earned a BBA in Finance from the University of Miami.

Q: Why is increasing antimicrobial resistance financially material for companies and investors?

Aviva Investors: If nothing is done to stop it, the U.K. government predicts that by 2050, antibiotic resistance will be the number one cause of death in the U.K.[106] The macroeconomic implications of the antibiotic resistance crisis are significant. Levels of drug-resistant infections by 2050 are predicted to cost the world $100 trillion in lost output between now and 2050, which is more than the current global economy.

Some sectors are particularly at risk from AMR, including pharmaceuticals, food retailers and producers, and health and life insurance. Bans on the use of antibiotics could have material implications for companies that are unprepared for regulatory restrictions to farm antibiotic use. This could cause significant operational disruptions and reductions in livestock numbers due to the increased prevalence of disease in densely packed facilities.

LGIM: Investors around the world are becoming increasingly aware of the significant economic impact of AMR if it is not appropriately addressed. The World Bank estimates that by 2050, AMR could result in a 3.8% loss in global GDP, causing economic damage commensurate with the 2008 financial crisis.[107] In a worst-case scenario, additional healthcare expenditures globally could amount to $1.2 trillion on an annual basis.[108]

As a global investor, we have the responsibility to protect the value of our clients' assets and do so in part by engaging on systemic market risks. Given the significant financial implications of AMR, and as custodians of our clients' money, we are therefore actively seeking to mitigate the impact of AMR.

Q: What role can investors play in mitigating the risks of antimicrobial resistance? How do you engage with investee companies?

LGIM: Given the scale and geographic breadth of the issue, LGIM is taking a two-pillar approach in tackling AMR: (1) engaging with investee holdings (including using our voting power) and (2) undertaking policy and regulatory engagement. We employ these two levers bilaterally as well as collaboratively with our peers.

- **Pillar 1:** We have used our voting power to support shareholder proposals filed at McDonald's (twice), Hormel Foods, and Abbott Laboratories seeking disclosures around actions that the individual companies are taking to slow the growth of AMR. In some instances, we publicly declared how we intend to vote at the forthcoming shareholders' meeting.

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[106] Public Health England, "Health Matters: Antimicrobial Resistance," December 2015.
[107] World Bank, *Drug-Resistant Infections: A Threat to Our Economic Future*, March 2017, pg. 17.
[108] Ibid, pg. 22.

- **Pillar 2:** At a policy level, AMR is gradually making its way onto the agenda. It has been encouraging to see G7 leaders highlight AMR as a priority issue in recent years. Given the scale and global nature of the issue, we are working to ensure AMR is kept high on the agenda and approached across governments. We also continue to focus on policy areas that continue to be overlooked, encouraging a systems-level approach. For example, we recently published a blog on AMR and the water sector, which outlines four key recommendations that policymakers should adopt to strengthen the AMR policy both domestically and internationally, including how it can be integrated into existing sustainable finance regulation, be coordinated through the multilateral system, support emerging markets, and incentivize or penalize the laggards. We plan to send a briefing on this to relevant global policymakers.

Aviva Investors: AMR needs to be a key ESG issue for companies, for investors, for Whitehall, for Brussels, for the G7, for the G20, and for the UN. Working with the Investor Action on AMR group, set up by the UK's Department of Health and Social Care, FAIRR, the Principles for Responsible Investment, and the Antimicrobial Resistance Benchmark, is one powerful way for investors to raise AMR up the agenda.

As recognized by the previous Chief Medical Officer of England, Professor Dame Sally Davies, in a recent letter to Amanda Blanc and Mark Versey, the CEOs of Aviva plc and Aviva Investors, respectively, Aviva Investors has successfully used their influence to convince G7 finance ministers to commit to collaborating with investors, policymakers, and companies to mitigate AMR. In its G7 presidency priorities, published in early 2022, the German government confirmed this commitment, as did the EU Council’s presidency trio of France, Sweden, and the Czech Republic. This is notable.

Aviva Investors recently made a submission to the U.K. All-Party Parliamentary Group (APPG) on AMR’s joint inquiry into the links between antibiotic resistance and lack of access to clean water, hygiene, and sanitation facilities in healthcare settings across the least developed countries of the world and have been asked to give evidence in the House of Commons as the representative of the finance community.

For clients of Aviva Investors, we have organized an event in conjunction with our strategic partners the British Society for Antimicrobial Chemotherapy (BSAC) for World Antibiotic Awareness Week on November 24, 2022, to highlight how climate change and biodiversity loss exacerbate antibiotic resistance with a heavy focus on solutions.

Q: How can different pools of capital, from philanthropists to impact investors and foundations to pension funds, collaborate to tackle the challenge of antimicrobial resistance?

LGIM: Collaboration across different pools of capital, and particularly across stakeholders, is powerful and key to accelerating action on AMR. Foundations, academia, and civil society have a strong history of bringing together stakeholders from across the economy, and across multiple policy sectors, focusing voices behind areas that need reform and supporting a systems approach to change.

Philanthropists have often provided the helpful research funding to highlight where and how AMR is impacting our economies and demonstrating where there may be policy gaps for policymakers to respond to. Indeed, if all investors — impact, institutional, or philanthropists supporting blended finance investments in emerging markets — are requesting and requiring the same degree of information from companies, then it encourages companies to improve their disclosures.

Q: How do you think about which companies are relevant to addressing the challenge of antimicrobial resistance?

Aviva Investors: AMR impacts companies and supply chains from the farm to big pharma. ESG can help identify mispriced risks and opportunities and direct capital towards companies that have more sustainable business models. However, certain systemic risks are a result of market failures underpinned by fundamental gaps in the regulatory environment, which means mispriced assets may remain in perpetuity until regulation is addressed.

Therefore, the most impact an investor can have is to tackle market failures by advocating for sustainable regulatory reform, also known as macro stewardship, which in turn will cascade back into adjustments to business models, valuations, and asset allocations. This was the key take away from my Master's, which focused on how investors can best tackle AMR. Macro stewardship is the focus of the Aviva Investor's Sustainable Finance Centre for Excellence, which is building and delivering the world's most ambitious ESG agenda on market reform in collaboration with our colleagues, clients and stakeholders through thought leadership, advocacy, and education.

LGIM: Any companies within sectors relating to the production, use, or disposal of antimicrobials are relevant to addressing AMR. To mention specific sectors: pharmaceutical manufacturing, animal production and agriculture, veterinary medicine, hospitals and healthcare facilitates, and water and sewage utilities all have a role to play in mitigating AMR. Given the multi-sectoral nature of AMR, we believe taking a systems-level approach through policy and regulation will best encompass all of these sectors.

Q: Beyond pharma and food, water utility companies are also relevant. What role do they play in addressing antimicrobial resistance?

LGIM: Discharges from pharmaceutical production facilities are often linked to the uncontrolled release and disposal of antimicrobial agents into water systems around the world. While the infrastructure of wastewater treatment plants has improved over the past century, waste sanitation and management systems have not been designed to address AMR concerns.

We therefore took a first step to try to understand whether (or how much) water utility companies are aware of this critical issue by writing to over 20 investee companies across Asia, Europe (including the U.K.), and North and South America, setting out our concerns and seeking dialogue. We met and had open and frank discussions with several of these companies.

We were disappointed to learn that, for most companies, awareness was low and very little monitoring is undertaken in this area. We believe this is mainly due to the lack of national (or international) regulatory requirements or incentives to do so, and perhaps because there is little perception of any immediate to long-term potential risks to the individual company.

We did find that a few companies consider AMR. One utility company is seeking to understand what happens to emerging contaminants in the wastewater treatment process and what improvements in their systems would be required to address this. LGIM also noted that very little reporting and monitoring is taking place in this area, which is another huge barrier.

Moving forward, instead of focusing on one-off company engagement, LGIM will be engaging with policymakers globally to develop a comprehensive approach to regulating AMR risks in the water sector, to drive a more "enhanced and standardized approach to the problem." The collective voice of investors will be of value in advocating for tighter regulations.

Aviva Investors: A study of water utilities and wastewater factories in China found that antibiotic-resistant bacteria were not only escaping purification but also breeding.[109] For every bacterium that entered one waste treatment plant, four or five antibiotic-resistant bacteria were released into the water system, tainting water, livestock, and communities.

Clinically important AMR bacteria are in U.K. bathing waters at levels high enough for people to be at risk of swallowing them. It is estimated that over six million water sports sessions occurred that involved the ingestion of these AMR bacteria.[110] Moreover, it is estimated there are more than 123 million exposures to *E. coli* harboring one or more resistant genes in England alone each year.[111]

One solution in the U.K. could be to encourage the Department for Environment, Food & Rural Affairs (DEFRA) to accelerate consideration of the AMR Industry Alliance set of standards. Another solution would be to fast-track production of the wastewater standards that the U.K. 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.

Q: What action do policymakers need to take to address the market failure of AMR?

Aviva Investors: In the U.K., put One Health at the heart of government policymaking: Antimicrobial stewardship (AMS) should not just be a discrete task for the private sector. The government must also set best practice by embedding AMS into core health, economic, trade, and financial decision-making processes. This should include embedding AMR within U.K. regulatory and legislative architecture, such as integrating it into Sustainable Disclosure Requirements (SDR) and the U.K. Green Taxonomy, and requiring all principal financial regulators (Financial Conduct Authority, Prudential Regulation Committee, Monetary Policy Committee, Prudential Regulation Authority) to explicitly incorporate AMR risks in developing countries and at home into their activities.

[109] Abby Olena, "Resistant Wastewater," *The Scientist*, December 18, 2013.
[110] Anne F. C. Leonard et al., "Human Recreational Exposure to Antibiotic Resistant Bacteria in Coastal Bathing Waters," *Environmental International*, March 2015.
[111] Anne 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, No. 3, 2018.

In the G7, the Informal Consultation Group brought together industry and Heath and Finance Ministry representatives to remedy the issue of pull incentives. From an outcome perspective, this collaboration worked well, and we commend this collaborative approach to HM Treasury, DEFRA, the Department of Health and Social Care, and beyond to address AMR in a holistic manner.

Q: Is antimicrobial resistance urgent? In a world facing so many challenges, from climate change to a cost-of-living crisis, why should antimicrobial resistance be a priority for investors?

Aviva Investors: ESG is a crowded space with multiple urgent and important demands on a finite number of teams. That is one of the reasons why we are working on an initiative to demonstrate how AMR interplays with two other huge, and more established, ESG issues: biodiversity loss and climate change. That way the conversation shifts away from one topic crowding out another topic.

There's also the human element — no one wants to have their pension invested in something that shortens their life, and antibiotics add an average of 23 years to the average human lifespan in the U.K.[112] Antibiotics form an essential part of modern medical procedures such as chemotherapy, cesarean sections, hip and knee replacements, and organ transplants. AMR touches on almost every investor's life directly in a way that few other ESG topics do: Perhaps they or a member of their family has had chemotherapy, knee replacement surgery, or a C-section.

LGIM: Beyond the financial impact mentioned above, the human and societal impact is enormous. In January 2022 the Global Research on Antimicrobial Resistance (GRAM) Project published a report in *The Lancet*. The analysis found that in 2019 alone, 1.27 million deaths were directly attributable to bacterial AMR, with 4.95 million deaths being associated with drug-resistance — making it a leading cause of death around the world.[113]

The previously estimated number of deaths per year due to AMR was 700,000, demonstrating that the actual number is almost twice as high.[114] If no, or insufficient, action is taken, it is estimated that there will be 10 million deaths per year by 2050.[115] Considering the 2019 figure, it would appear to confirm that we are unfortunately on the trajectory of 10 million deaths per year by 2050.

[112] Matthew Hutchings, Andrew W. Truman, and Barrie Wilkinson, "Antibiotics: Past, Present, and Future," *Current Opinion in Microbiology*, Vol. 51, October 2019.
[113] Christopher J. L. Murray et al., "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," *The Lancet*, Vol. 399, Issue 10325, February 2022.
[114] Interagency Coordination Group on Antimicrobial Resistance, *No Time to Wait: Securing the Future From Drug-Resistant Infections*, Report to Secretary General of the United Nations, April 2019, pg. 1. This figure was already estimated in 2014 by Jim O'Neill in the Review on Antimicrobial Resistance, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, May 2016, pg. 1.
[115] Interagency Coordination Group on Antimicrobial Resistance, *No Time to Wait: Securing the Future From Drug-Resistant Infections*, Report to Secretary General of the United Nations, April 2019, pg. 1. The U.S. Centers for Disease Control and Prevention (CDC) estimates that each year at least 2.8 million people in the US get an antibiotic-resistant infection, and that more than 35,000 die of AMR per CDC, *Antibiotic Resistance Threats in the United States 2019*, revised December 2019.

Chapter 6: Investor Tools & Best Practice

There are many tools available to support investors in understanding how AMR impacts their investments and what their investee companies are doing to address the challenge of AMR. In this section, we profile four such tools: (1) the Access to Medicine Foundation's AMR Benchmark Report, (2) the FAIRR Initiative's tools, (3) Business Benchmark on Farm Animal Welfare (BBFAW), and (4) the AMR Industry Alliance Progress Report.

Antimicrobial resistance is a systemic portfolio risk that has the potential to have as great an impact on the global economy as the 2007-09 financial crash.[116] Shareholders, regulators, and policymakers must address AMR and improve the outlook. Some investors have already acted on the challenge of AMR: For example, Investor Action on AMR was launched at the World Economic Forum Annual Meeting in Davos in 2020 and now brings together 16 institutional investors and investor representatives.

Investors have several tools available to them to support their engagement and actions when leveraging their influence to curb AMR. These tools include reports examining the progress of the life sciences sector, detailed performance assessments of relevant pharmaceutical companies and animal protein producers, and best practice guidance and policies.

Access to Medicine Foundation's 2021 Antimicrobial Resistance Benchmark

The Access to Medicine Foundation is a non-profit, independent organization based in Amsterdam. The Foundation stimulates companies and mobilizes allies — including investors, policymakers in governments, and global health organizations — to expand access to medicines, vaccines, and other essential health products in low- and middle-income countries (LMICs).

[116] World Bank Group, *Drug-Resistant Infections: A Threat to Our Economic Future*, March 2017.

Investors use the Foundation's insights and analysis to better assess risks and opportunities related to access to medicine and antimicrobial resistance, and to inform direct engagements with investee companies.

The Access to Medicine Foundation publishes a periodic report evaluating the performance of 17 of the largest pharmaceutical companies in the anti-infectives space, including companies engaged in research and development and generic medicine manufacturers.[117] The **AMR Benchmark** reports where companies have the greatest opportunity and responsibility to limit AMR and compares the performance of these companies 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 (CRE).
- **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 antibacterial material in wastewater does not exceed safe limits.
- **Appropriate access**, including registering products in low- and middle- income countries, ensuring that medicines are affordable through equitable pricing structures, and building capacity to help lower-income countries build up knowledge and expertise in manufacturing.
- **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 Report provides specific actions that investors can take to curb antimicrobial resistance, for example, by considering whether a company manufactures responsibly as part of investment decisions. 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 specific opportunities for improvement. This provides an additional tool for investors to gain insight into company actions and commitments to date.

FAIRR Initiative: Research, Tools, and Engagement to Tackle AMR

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 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 $69 trillion in combined assets.

[117] Access to Medicine Foundation, *2021 Antimicrobial Resistance Benchmark*, November 18, 2021.

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**.[118] This is a publicly available resource on antibiotic stewardship that was 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 antibiotics for prophylactic and metaphylactic use, and set time-bound targets.

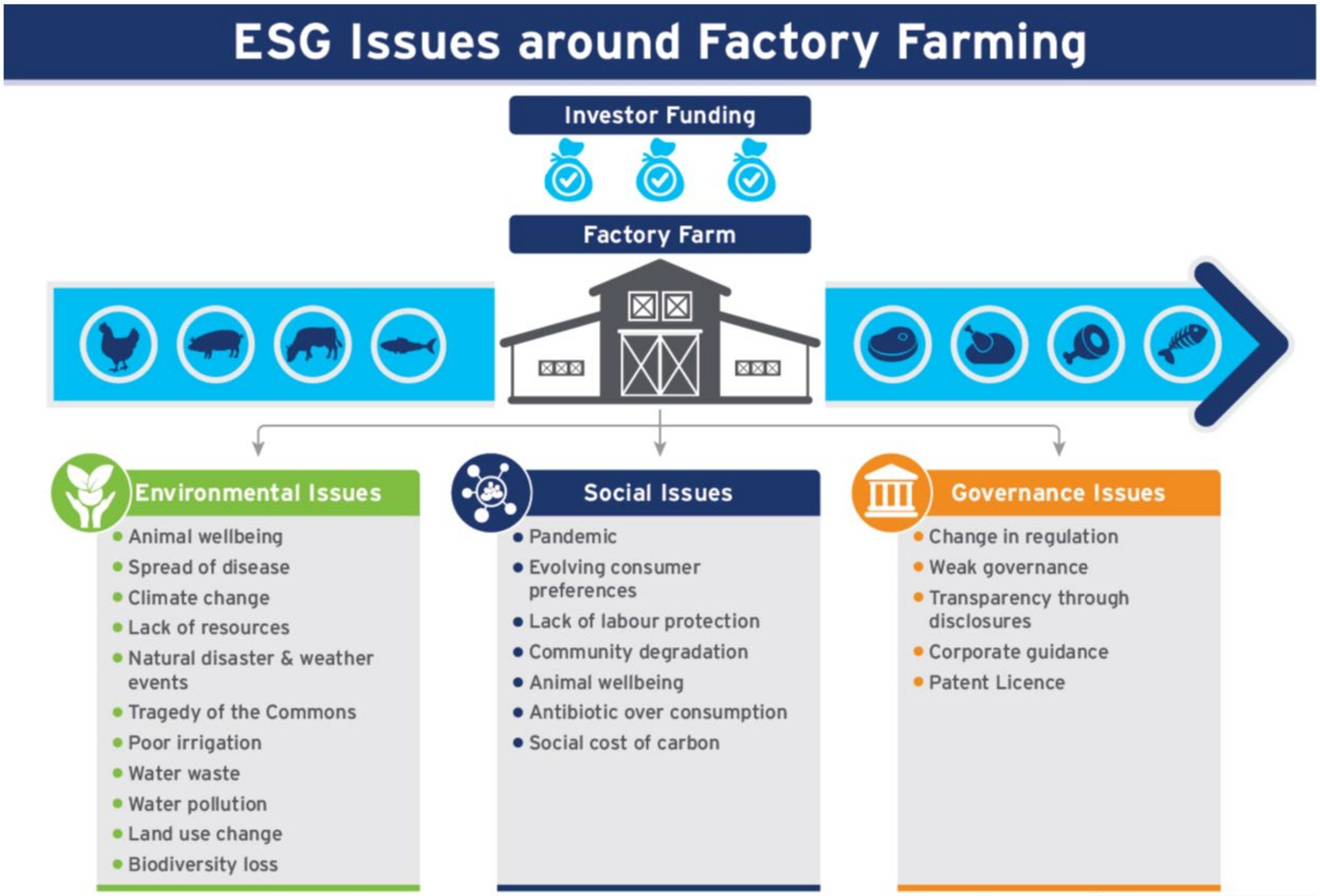
Second, the **Coller FAIRR Protein Producer** is a benchmarking tool that provides investors with a systematic assessment of the 60 largest animal protein producers on key strategic ESG issues within the industry, including antibiotic use and policies.[119] The tool enables investors to identify companies that are low, medium, or high risk according to the strength of their antibiotics policy and disclosure.

Finally, FAIRR has developed a comprehensive list of **Company Dialogue Questions** to provide investors with guidance and direction during dialogues with animal protein producers on several topics including antibiotic use.[120] 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.[121]

The engagement ran for three years and encouraged all 20 companies to implement policies to address AMR. FAIRR also launched an engagement in 2022 encouraging 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.[122] Collaborative engagements enable investors to leverage their influence to induce companies to enhance and improve their policies.

[118] FAIRR, "Best Practice Policy on Antibiotics Stewardship," PDF, October 2018.
[119] FAIRR, "Coller FAIRR Protein Producer Index," last modified December 1, 2021.
[120] FAIRR, "Company Dialogue Questions," accessed November 14, 2022.
[121] FAIRR, "Overuse of Antibiotics in Protein Supply Chains," accessed November 14, 2022.
[122] FAIRR, "Antimicrobial Stewardship in the Animal Pharma Industry," accessed November 14, 2022.

Figure 28. ESG Issues Around Factory Farming



Source: Adapted from FAIRR Initiative, Factory Farming: Assessing Investment Risks (2016), Citi GPS

Business Benchmark on Farm Animal Welfare (BBFAW) Report

N. gonnorrhoeae

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, in 25 different countries.[123] It allows investors to understand how investee companies are managing farm animal welfare, including in their supply chains, in order to compare the performance of different companies, to identify leaders and laggards, and to examine how farm animal welfare in the global food industry is changing.

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

- **Management Commitment**, which considers the 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 that farm animal welfare poses to a company and maintaining a policy setting out core principles and their implementation.

[123] Business Benchmark on Farm Animal Welfare (BBFAW), *The Business Benchmark on Farm Animal Welfare Report 2021*, March 2022.

- **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, both on a day-to-day basis and at the senior management level.

- **Leadership and Innovation**, including investment in projects to support and advocate for farm animal welfare. Here, best practice includes participating 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.

The Benchmark drives investor engagement around farm animal welfare: in 2015, more than 30 institutional investors managing a combined £2.5 trillion (about $3 trillion as of November 21, 2022) in assets supported the Global Investor Statement on farm animal welfare and the Global Investor Collaboration on Farm Animal Welfare.[124] These initiatives have contributed to real improvements in the management of animal welfare.

AMR Industry Alliance

In 2016, more than 100 companies and nine industry associations drafted and signed the Declaration on Combating Antimicrobial Resistance, also known as the Davos Declaration. This set out the global principles to support antibiotic conservation and the development of new drugs, diagnostics, and vaccines.[125] The following year, the AMR Industry Alliance was created at the G20 meeting in Berlin.

As the largest life-sciences coalition of its kind, the AMR Industry Alliance aims to provide sustainable solutions in the fight against AMR through broad industry momentum, public-private collaboration, and multi-sectoral action. The Alliance includes biotechnology, diagnostic, generics, and research-based biopharmaceutical companies and trade associations, and was formed to drive and measure industry progress to curb antimicrobial resistance.

Since the 2016 declaration, the AMR Industry Alliance has published three progress reports that reflect on the commitments, actions, and achievements of the life-sciences industry in curbing antimicrobial resistance in four core areas. These reviews go beyond the disclosures that each company publishes by surveying Alliance members about their activities to address the challenge of AMR and then reporting on aggregate sector-specific metrics.

[124] BBFAW, "Global Investor Statement on Farm Animal Welfare," PDF, accessed November 14, 2022.
[125] United Nations, "Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance," PDF, September 21, 2016.

The progress reports focus on four areas, which track the four elements of the 2016 declaration:

1. **Manufacturing and the Environment**, including reporting on the adoption of the Antibiotic Manufacturing Standard, which the Alliance published in June 2022 to provide clear guidance to manufacturers in the global antibiotic supply chain on ensuring that their antibiotics are made responsibly, helping to minimize the risk of AMR in the environment.

2. **Research and Science**, including reporting the cumulative investment by Alliance members in AMR-relevant R&D, surveying member sentiment regarding market conditions, and reporting members' outlook on the future state of the market.

3. **Access**, including reporting the percentage of members active in supporting access to AMR-relevant products and technologies, the percentage of Alliance members pursuing collaboration to support this, and the members' reported challenges in supporting access.

4. **Appropriate Use and Stewardship**, including how many members had appropriate-use and stewardship strategies in place (including across diverse geographies) and the ways in which members contributed to AMR stewardship and awareness raising strategies, especially strategies to align their promotional activities with stewardship aims.

The work of the Alliance in supporting progress on addressing AMR has been significant. For example, in support of the Alliance's progress on responsible manufacturing, the G7 Health Ministers formally recognized the Alliance's work towards a Standard in their 2021 communique.[126]

[126] U.K. Government, "G7 Health Ministers' Meeting Communique, Oxford," June 4, 2021

Expert Contribution: AMR Industry Alliance – Industry Steps

Steps Industry Should Take to Prevent the Spread of AMR in the Environment

Antibiotics are essential innovations that have revolutionized modern healthcare, but the rise of antimicrobial resistance (AMR) is threatening their effectiveness.

Today, AMR is a top 10 global public health threat according to the World Health Organization (WHO) and expected to get worse. Unchecked, it threatens to undermine the basis of modern medicine by rendering the antibiotics used to treat and prevent infections ineffective, making mainstream medical advances like chemotherapy, hip replacements, cesarean sections, and root canals risky, and even deadly. In 2019 alone, antimicrobial resistant bacteria accounted for 1.27 million deaths and contributed to another nearly 5 million deaths during the same year, according to IHME/*The Lancet*, far greater than the deaths caused by malaria and HIV collectively.

While there are many factors that contribute to the spread of AMR, the environmental dimension is a critical yet often overlooked component. AMR can spread in the environment from untreated wastewater from healthcare facilities, municipal wastewater, farms, and discharge from pharmaceutical manufacturing, among other sources.

Since its inception, the AMR Industry Alliance has been developing solutions to drive the antibiotic industry to minimize any contribution to antimicrobial resistance that may arise as a result of the processes used to make their important medicines. Together with the British Standards Institution (BSI), the Alliance formally announced an **Antibiotic Manufacturing Standard** to provide clear guidance to manufacturers in the global antibiotic supply chain and ensure that their antibiotics are made responsibly, helping to minimize the risk of AMR in the environment.

In 2023, the AMR Alliance and BSI will release a certification scheme that will enable antibiotic manufacturers to demonstrate, through independent third-party evaluation, that the requirements of the Standard have been satisfied. Widespread adoption of this environmental stewardship can bring about a new era of transparency and accountability in antibiotic manufacturing.

Once established, the certification scheme will allow consumers, procurers, and investors alike to more easily understand the environmental impact of their antibiotic provider's manufacturing processes and suppliers. The AMR Alliance's goal is that demand from the pharmaceutical industry's relevant stakeholders will ultimately drive antibiotic producers to adopt the certification scheme and thoughtfully approach their contribution to AMR spread in the environment.

We are already seeing evidence of these market forces at work. Norway, Sweden, and Britain, for example, provide market incentives to promote sustainable antibiotic manufacturing. In Norway, their government procurers offer a 30% weight to environment-friendly production in their procurement decisions.

AMR is a global, interconnected problem with many different contributing factors. The Alliance's Antibiotic Manufacturing Standard provides a tangible step forward for industry to combat the spread of AMR in the environment.

Chapter 7: The Role of Big Pharma and R&D Into Novel Anti-Infectives

The rise of antimicrobial resistance (AMR) undoubtedly represents a significant risk to human health over the next decade and has been recently coined "The Silent Pandemic." The misuse of antibiotics by patients (e.g., incomplete courses of treatment), as well as shortcomings by governments (e.g., poor education and awareness-raising) and physicians (e.g., over-prescription) over the past 30 years, have led to an increasing number of drug-resistant infections globally which in turn is leading to growing AMR-related mortality rates.

Big Pharma and Novel Antibiotics

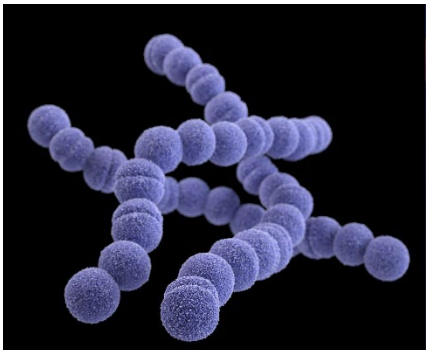
Despite the rise of drug-resistant infections worldwide, the major pharmaceutical companies have largely disengaged from investment in novel antibiotic discovery and development given historically high regulatory and commercial hurdles. Most of the multinationals have closed their discovery activities in the field, with GSK and Pfizer remaining among the few major companies with active programs in both research and development of novel anti-infectives.

From a regulatory perspective, several late-stage novel antibiotics such as Ketek have failed to meet stringent regulatory hurdles. Ketek, for example, was associated with concerns over submitting fraudulent safety issues to the FDA, inappropriate trial methods, and a rash of cases of hepatic toxicity (liver inflammation). The recent U.S. Inflation Reduction Act (IRA) is also unhelpful with companies highlighting that legislation, as written, will lead to significant challenges, particularly with regards to the development of small molecules, (i.e., low molecular weight compounds that are used as therapeutics since they can pass through cell membranes to reach targets within a cell).

According to the U.S. Centers for Disease Control and Prevention (CDC), each year in the United States at least 2.8 million antibiotic-resistant infections occur, and more than 35,000 people die as a result.[127] Combating AMR requires multifaceted efforts in both the healthcare and veterinary sectors.

A Dichotomy for the Pharmaceutical Industry

S. pyogenes



From a commercial perspective, returns for novel antibiotics to address multi-drug resistant (MDR) infections have been low owing to health policy and clinical practice among infectious disease physicians. This understandably encourages limiting the use of novel antibiotics to MDR patients in order to obviate the risk of emergent resistance to effective last line, or last resort, therapy.

There are also increasing incentives and awareness campaigns in place that promote more sparing use of earlier stage anti-infectives as AMR becomes an increasingly predominant health threat. As such, health policy and responsible clinical practice are leading to limited revenue potential presenting a dichotomy for the pharmaceutical industry when it comes to funding continued investment in anti-infective businesses.

Lack of Appropriate Incentives for Continued Development

There have been recent moves to ensure that AMR is at the forefront of public discourse with a report from the WHO and European Centre for Disease Prevention and Control (ECDC) published in January 2022 highlighting 2020 data on drug-resistant infections and AMR-related mortality in Europe.

At the same time, one of Europe's largest pharmaceutical companies, AstraZeneca, recently announced plans for the divestment of their anti-infective unit after reported difficulty securing an investor/partner interested in taking control of the assets. While there is global recognition that AMR is an increasing health treat, the pharma industry highlights the lack of appropriate incentives for continued development in this field.

A "Netflix Subscription Model"

There has been much active discussion to resolve the inherent paradox between the limited commercial use and the growing need for antibiotic research and funding. Most of these discussions revolve around the concept of a "Netflix subscription model" in which governments contribute an annual fee in exchange for access to a portfolio of innovative anti-infective products rather than paying in line with volume used. Such an agreement intends to ensure sufficient funding for the development of novel antibiotics for MDR disease while promoting responsible use of antibiotics. To date, we believe that only the U.K. government has committed and enacted such a program. In the U.S., there is strong bipartisan support for such a policy under the PASTEUR Act; however, it faces the risk of de-prioritization under a Republican-led majority in the House of Representatives.

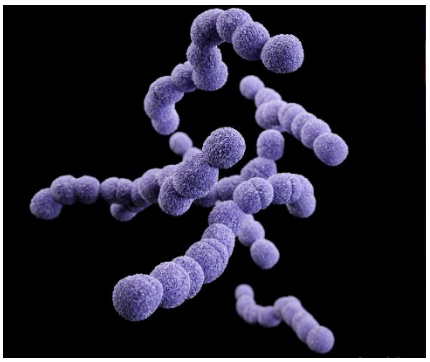
[127] CDC, "Antibiotic Resistance Threats in the United States, 2019," Revised December 2019.

Transferable Exclusivity Extension

Industry organizations, most notably The European Federation of Pharmaceutical Industries and Associations (EFPIA), have proposed several potential incentive mechanisms to national and international policymakers. Most recently the European Commission has been considering the concept of a "Transferable Exclusivity Extension (TEE)," an incentive scheme by which the development of a novel anti-infective can be used to extend the patent of another product within the company portfolio. Understandably, this has been met with significant criticism from both governments and consumers highlighting its potential to contribute to significant increases in healthcare expenditure.

The Development of Small Molecule Antibiotics

S. agalactiae

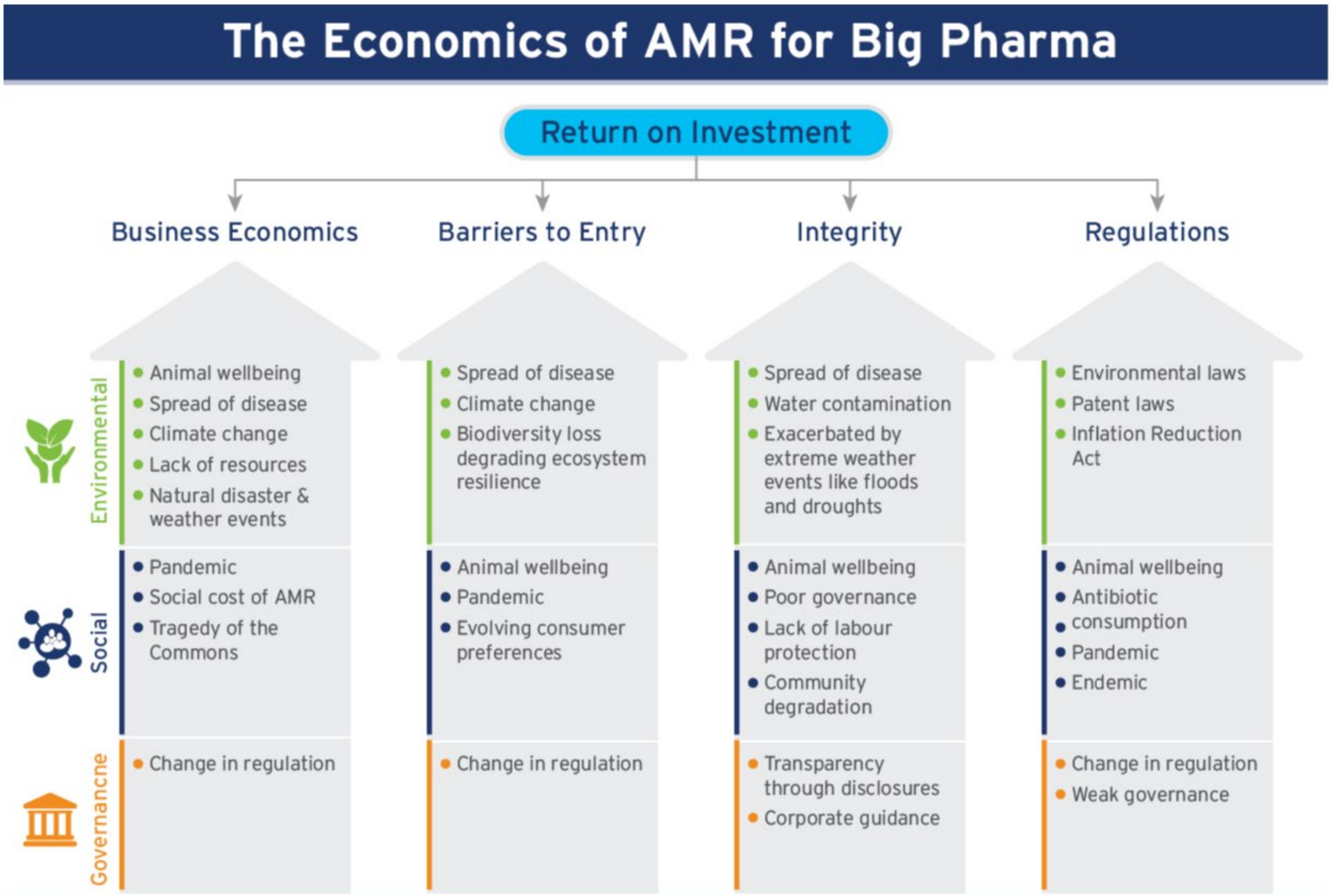


It appears that while AMR has global recognition as an issue of AMR, no solution currently exists that both governments and industry find mutually satisfactory when it comes to the development and innovation of small-molecule antibiotics. Instead, government and industry bias favors addressing AMR-related public health concerns through investment in novel vaccines, facilitated by a raft of advances in reverse vaccinology (which uses expressed genomic sequences to find new potential vaccines), novel antimicrobial adjuvants, and the application of mRNA vaccine technology. Despite the greater development costs, the likely certainty of positive returns for vaccines against infectious diseases is much more convincing than for antibiotics given a well-defined reimbursement model and increased surety on commercial returns.

Antimicrobial Innovation and ESG rankings

Sadly, much like COVID-19, it may take the emergence of an MDR, pathogenic, transmissible bacteria affecting the developed world to trigger enactment of the Netflix-type subscription model beyond a handful of countries or to push development incentives beyond current levels. Alternatively, the explicit inclusion of antimicrobial innovation to address MDR infections in ESG rankings could pressure pharma companies to rethink their levels of investment. However, it seems this level of granularity is unlikely.

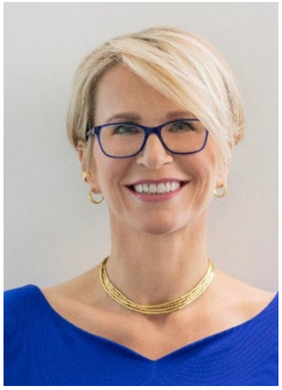
Figure 29. The Economics of AMR for Big Pharma



Source: Adapted from FAIRR Initiative, Factory Farming; Assessing Investment Risks (2016), Citi GPS

Expert Contribution: Emma Walmsley

Ambitious Innovation Needs Ambitious Policymakers



Emma Walmsley
CEO
GSK

Emma has been GSK CEO and Board Director since April 2017.

The global community is at an inflection point on antimicrobial resistance (AMR). As we all consider the lessons learned from the COVID-19 pandemic, and how to better protect ourselves against health security threats, the time to get ahead of AMR is now.

Rising resistance to antibiotics and the existential risk this poses to our health has been well understood for many years, as have the market challenges facing new antibiotics. Developing new antibiotics is uniquely challenging on two fronts — scientific and financial. Bacteria constantly evolve, which creates a need to develop antibiotics that are effective against antibiotic resistance. Clinical trials for new antibiotics are complex. They often require a large number of trial sites to enroll enough patients with multi-resistant infections. Even if a novel antibiotic is eventually brought to market, it is often kept in reserve so that it can be used to manage otherwise resistant infections. This appropriately limits use but can reduce returns on innovation, stifling sustainable future investment.

In the face of these challenges, GSK has persisted in AMR-relevant research. Getting ahead of infectious disease and impending threats like AMR will help protect lives and livelihoods. It will also help protect health systems from the strain and disruption caused by infectious disease emergencies, as we saw during COVID-19, meaning they are better placed to keep delivering essential care to patients.

So infectious disease is front and center of our strategy — one of four therapeutic focus areas for GSK. Harnessing our expertise in vaccines and medicines, we focus on both prevention and treatment, helping to stop infections in the first place and mitigate them when they do happen.

Our AMR-relevant research includes programs targeting pathogens deemed “critical” and “urgent” by the WHO and the U.S. Centers for Disease Control and Prevention. We have consistently ranked as industry leaders in the Access to Medicine Foundation’s AMR Benchmark. The most recent Benchmark highlighted the diversity of our R&D, recognizing us as having 31 relevant R&D projects, balanced across antibacterial medicines and vaccines.

Partnerships are crucial to making progress. We were pleased to be an initial contributor to the AMR Action Fund, which invests in companies that are developing therapeutics for priority pathogens.

Also, we seek out promising research that complements our strengths and builds our portfolio. Recently, we struck deals to bolster our antibiotic pipeline and bring in a vaccine technology that could help target bacterial pathogens.

Vaccination already helps to protect people against a range of infections. This makes vaccines an important tool against AMR as they can reduce the need for antibiotic treatment, limiting opportunities for resistance. Looking to the future, new scientific insights should help us target pathogens most likely to develop resistance, so we can look to develop effective vaccines more rapidly compared with traditional approaches. We are excited about new technologies — and sometimes combinations of them — that could transform the way we develop vaccines and help broaden the protection they offer.

Infectious disease research should have a bright future thanks to scientific and technological advances. An ambitious policy agenda is needed to ensure that this innovation can realize its full potential and make a difference to patients.

First and foremost, governments should introduce economic incentives and reimbursement approaches that stimulate investment and innovation in antibiotics — providing a return for innovators while maintaining ideally low prescription volumes.

We've already seen examples of this in action, with the U.K. government's pilot of a subscription payment model for antibiotics. This trial demonstrated that it is possible to design and implement "pull" incentives that pay for value, not volume. We look forward to seeing how this translates into a permanent sustainable U.K.-wide solution for evaluating and reimbursing antibiotics and recognizing the full value these treatments bring to patients, the health system, and society.

It's time now for other countries to lead progress. One example is in the U.S. where, if Congress approves, the PASTEUR Act would create a sustainable financial incentive for novel antimicrobials while also promoting appropriate use of antimicrobials. Never before have we seen bipartisan support for AMR policy across both chambers of Congress as we see with PASTEUR. We must act on this momentum.

Surveillance and stewardship — including responsible manufacturing — are critical pieces of the jigsaw too. It is important to prudently supply our existing antibiotics to help limit resistance and maximize their global health impact. COVID-19 reinforced the need for strong frameworks for collecting, using, and sharing data. Critical data gaps on AMR remain, including tracking the burden of community-acquired infections. We must address these data gaps if we are to truly understand the scale of AMR and take targeted action, ensuring interventions reach patients where they will make the biggest impact.

Finally, governments must fully recognize and value the role of vaccines in the fight against AMR. By increasing uptake of current vaccines and incentivizing development of future vaccines, policymakers have a win-win opportunity: improving public health through helping to prevent infection and potentially reducing the need for antibiotics.

Chapter 8: The Paradox — Precious Medicines and International Trade in Colistin

The rise and spread of antimicrobial resistance has meant that the antibiotic colistin has assumed great importance in human medicine over the last decade. Colistin, also known as polymyxin E, is an antibiotic medication used as a last-resort treatment for multidrug-resistant Gram-negative infections (e.g., bacteria resistant to multiple drugs and increasingly resistant to most available antibiotics) including pneumonia.

Colistin is usually reserved to treat bacteria, for example *E. coli*, which are resistant to all other antibiotics. Colistin is an active agent against aerobic Gram-negative pathogens that frequently represent the mainspring of life-threatening infections, such as carbapenem-resistant *P. aeruginosa*.

Colistin resistance is considered a serious problem due to a lack of alternative antibiotics. Colistin is an antibiotic meant for therapeutic purposes in veterinary care, but this drug has been highly misused in the poultry industry as a growth promoter for prophylactic purposes. One of the reasons for anti-microbial resistance in India is due to unwanted use of the drug in the poultry industry.

Resistance in Last-Resort Antibiotics: The Last Frontier of Human Pharmacopeia

In 2015, something globally significant happened in the world of AMR — a group of Chinese academics found that the globally ubiquitous *Escherichia coli* was starting to display modest but elevated levels of resistance to a last-resort antibiotic used to treat life-threatening infections in humans.[128] The World Health Organization listed colistin as one of the critically important antibiotics highlighting the seminal importance of negating resistance to this life-saving drug.[129]

The antibiotic in question, colistin, was thought to be impervious to resistant mechanisms carried on bacterial plasmids but the breach of the last frontier of human pharmacopeia had finally happened.

The World is a Small Place for Viruses and Antibiotic Resistance

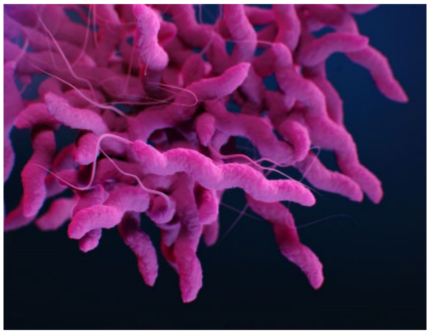
Since its discovery in 2015, this resistance mechanism known as Mobilized Colistin Resistance (MCR), has now been reported from over 70 countries and like COVID-19, typifies that the world is a small place when it comes to both viruses and antibiotic resistance.[130] The question is: Why did MCR first appear in China? While not definitively known, MCR was thought to have been driven by the use of colistin in Chinese farming as metaphylaxis, prophylaxis, and in animal feeds. It has been deployed in China in these ways since 2007-08.[131]

At the time, China was not using colistin clinically to treat extreme-drug resistant infections and the logic was therefore — why not use it on farms? However, knowing the ramifications of the discovery of MCR, Chinese academics and representatives from the Chinese ministries of both Health and Agriculture met in November 2015, and the decision to ban colistin from Chinese agriculture use was thus invoked.[132]

[128] Yi-Yun 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, No. 2, February 1, 2016.
[129] WHO, "World Health Organization Model List of Essential Medicines: 22nd List (2021)," PDF, September 30, 2021.
[130] Masego Mmati, Nontombi Marylucy Mbelle, and John Osei Sekyere, "Global Epidemiology, Genetic Environment, Risk Factors and Therapeutic Prospects of *mcr* Genes: A Current and Emerging Update," *Frontiers in Cellular and Infection Microbiology*, Vol 12, August 26, 2022.
[131] Zhangqi Shen et al., "Early Emergence of Mcr-1 in Escherichia Coli From Food-Producing Animals," *The Lancet Infectious Diseases,* Vol. 16, No. 3, March 1, 2016.
[132] Timothy R. Walsh and Yongning Wu, "China Bans Colistin as a Feed Additive for Animals," *The Lancet Infectious Diseases,* Vol. 16, No. 10, October 1, 2016.

MCR: A Global Phenomenon

Campylobacter



As MCR became a global phenomenon and since it affects both animals and humans, global policy discussions regarding the use of colistin ensued. In 2016, the European Medicines Agency updated the risk level of colistin resistance from low to high.[133] Many countries, including Brazil (2016), Thailand (February 2017), China (April 2017), Japan (July 2018), Malaysia (January 2019), Argentina (February 2019), and India (July 2019), have approved the withdrawal of colistin use as a feed additive in animals. [134]

Moreover, global colistin sulphate production decreased from 13,746 metric tons in 2016 to 4,292 metric tons in 2019 — mainly from the ban in China.[135] Further evidence of this cause-and-effect (i.e., evidence of the fact that use of colistin on Chinese farms fueled the dissemination of MCR) was affirmed when China formally banned the use of colistin in agriculture in April 2017, which subsequently resulted in a dramatic decrease in the prevalence of MCR and colistin-resistant *E. coli*.[136]

Halting the Use of Colistin in Farming

While measures to curb global colistin consumption in farming may seem admirable, global colistin sulphate production in 2019 was 4,292 metric tons with 96% of this total consumption in poultry and pig farming.[137]

In the beginning of 2019, the Europe Union through Regulation 2019/6, attempted to address the issue of veterinary medicines with respect to the health consequences in both humans and animals.[138] However, the text is non-committal and not enforced by EU Law. Consequently, companies operating in many European countries including Belgium, the Netherlands, Germany, France, Italy, and Spain import and export colistin knowing that it will be used in farms in low- and middle-income countries (LMICs) and drive colistin resistance in animal and humans.

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[133] European Medicines Agency, "Updated Advice on the Use of Colistin Products in Animals Within the European Union: Development of Resistance and Possible Impact on Human and Animal Health," PDF, July 27, 2016.

[134] Yingbo Shen et al., "Anthropogenic and Environmental Factors Associated with High Incidence of Mcr-1 Carriage in Humans Across China," *Nature Microbiology,* Vol. 3, No. 9, July 23, 2018; Masaru Usui et al., "Decreased Colistin Resistance and Mcr-1 Prevalence in Pig-Derived Escherichia Coli in Japan After Banning Colistin as a Feed Additive," *Journal of Global Antimicrobial Resistance*, Vol. 24, February 23, 2021; Zhandra Zuleta, "Argentina: No More Colistin in Veterinary Products," Pig Progress, February 14, 2019; Madlen Davies and Ben Stockton, "India Set to Ban Use of 'Last Hope' Antibiotic to Fatten Livestock After Bureau Story," Bureau of Investigative Journalism, December 5, 2018.

[135] Yi-Yun 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, No. 2, February 1, 2016.

[136] Yang Wang et al., "Changes in Colistin Resistance and Mcr-1 Abundance in Escherichia Coli of Animal and Human Origins Following the Ban of Colistin-Positive Additives in China: An Epidemiological Comparative Study," *The Lancet Infectious Diseases*, Vol. 20, No. 10, June 4, 2020.

[137] Ibid.

[138] See clauses 41-50 of European Union, "Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on Veterinary Medicinal Products and Repealing Directive 2001/82/EC (Text with EEA relevance)," July 1, 2019.

The Emergence of Intensive Livestock Farming in LMICs

Countries with emerging intensive livestock farming, such as Pakistan and Nigeria, are a significant consumer of antimicrobials in food animal production where colistin is widely used to treat and control colibacillosis.[139] Although there has been a demonstrable reduction in colistin resistance in other countries, manufacturing and export of colistin as either pharmaceutical raw material or feed additive still continues.

Data captured by the Ineos Oxford Institute on Pakistani and Nigerian farmers' understanding of colistin and its consequences for colistin resistance was, at best, very limited, highlighting the need for better public awareness on antibiotic consumption across all cultures and socioeconomic sectors.

Global meat consumption is projected to increase by 14% by 2030 and LMICs, in particular, will need to ensure farming practices meet the demands of a growing human population.[140] Farmers in LMICs will need support to make the necessary improvements in farm hygiene, management, and animal husbandry that enable restrictions on the use of antimicrobials while still protecting animal welfare and avoiding catastrophic losses of livestock from disease.

Developing Animal Feed Additives

One obvious solution would be to use animal feed additives containing antimicrobials that are not used in humans and more importantly, do not select for resistance against human antibiotics.[141] However, the recent European Medicines Agency update on veterinary medicinal products still advocates the use of many human antibiotics in veterinary practices, including colistin.[142] The support needed to deliver changes is lacking and will take considerable commitment from all global stakeholders including adequate financial support to ensure rigorous implementation and sustainability. In the current climate of One Health AMR awareness, it is counterintuitive that, in 2022, colistin, a WHO Reserve list antibiotic, is still sold and disseminated as a growth promoter.[143]

Global Action Points

1. International pressure needs to be applied on all financial stakeholders and investors to ensure an ethical code of conduct is in place and that the global community can fully cease the international trade in colistin.

2. Far more effort needs to be applied to online companies to understand the role of the internet in antibiotic sales — both for humans and animals.

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139 Yanhong Jessika Hu and Benjamin John Cowling, "Reducing Antibiotic Use in Livestock, China," *Bulletin of the World Health Organization*, Vol. 98, No. 5, February 28, 2020.

140 OECD/FAO, *OECD-FAO Agricultural Outlook 2021-2030,* July 5, 2021.

141 Mohamed E. Abd El-Hack et al., "Alternatives to Antibiotics for Organic Poultry Production: Types, Modes of Action and Impacts on Bird's Health and Production," *Poultry Science,* Vol. 101, No. 4, April 2022.

142 European Medicines Agency, "Advice on the Designation of Antimicrobials or Groups of Antimicrobials Reserved for Treatment of Certain Infections in Humans — in Relation to Implementing Measures Under Article 37(5) of Regulation (EU) 2019/6 on Veterinary Medicinal Products," PDF, May 25, 2022.

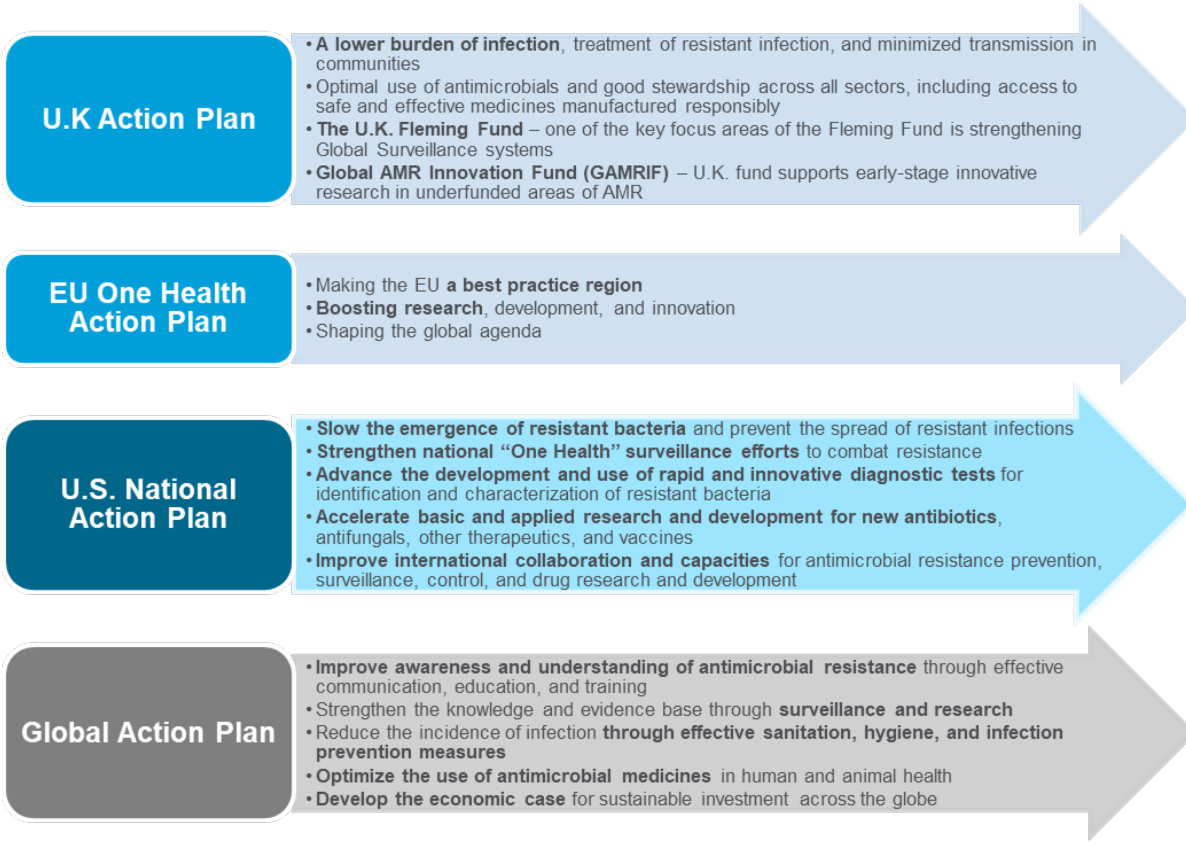
143 WHO, "WHO Model List of Essential Medicines – 21st List 2019," July 23, 2019.

Chapter 9: How Governments Are Rising to the AMR Challenge

The Global Action Plan, which governs the World Health Organization approach to AMR, identifies strategic objectives alongside surveillance efforts that propose a standardized approach to the collection, analysis, interpretation, and sharing of AMR data. The European Commission and U.S. National Action Plan adopt a One Health approach that brings together practitioners across human, animal, and environmental health. These government initiatives have clearly influenced the global agenda coalescing around reducing the spread of resistance, improving surveillance systems, increasing uptake of rapid diagnostic testing, and supporting research and innovation by recognizing the transboundary nature of AMR. This chapter expands on government initiatives that echo the calls from contributors to this report for an enabling and encouraging policy landscape.[144]

[144] Maria Larsson Ortino, Alexander Burr, and Emma Cameron, "AMR and the Water Sector: The Pandemic in the Shadows," Legal & General Investment Management, October 3, 2022.

Figure 30. National and International Antimicrobial Resistance Initiatives



Source: European Commission Public Health, Centers for Disease Control & Prevention, World Health Organization, Citi GPS

The Global Action Plan

In 2015, World Health Organization Member States approved a plan to tackle AMR. This had five strategic objectives, which the WHO summarize thus:[145]

1. "To improve awareness and understanding of antimicrobial resistance through effective communication, education, and training.

2. To strengthen the knowledge and evidence base through surveillance and research.

3. To reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures.

4. To optimize the use of antimicrobial medicines in human and animal health.

5. To develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investments in new medicines, diagnostic tools, vaccines, and other interventions."

145 WHO, "Global Action Plan on Antimicrobial Resistance," January 1, 2016

Building on the key objective of advancing surveillance efforts, the World Health Organization launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in October 2015.[146] The system was created to advance the second objective of the Global Action Plan by providing a standardized approach to the collection, analysis, interpretation and sharing of data by countries.

European Regulation

In the EU, AMR is estimated to be responsible for 25,000 deaths per year with an estimated annual cost of €1.5 billion.[147] It was in 2016 that the European Commission drafted an Action Plan to tackle AMR, including reducing the emergence and spread of resistance together with bringing novel antimicrobials to market both in the EU and beyond.[148]

The Plan adopted a One Health approach and brought together practitioners across the fields of human, animal, and environmental health — including the European Food Safety Authority, the European Medicines Agency, and the European Centre for Disease Prevention and Control.

Three Key Objectives of the EU Action Plan:[149]

1. To **make the EU a leader** in addressing AMR, including by strengthening the evidence base on the emergence and spread of AMR, boosting public awareness, improving coordination on regulation and implementation across the region, supporting infection control measures both in healthcare settings and the natural environment, and developing partnerships with other key stakeholders.

2. To **support research and innovation** relevant to tackling AMR, including novel antimicrobials and alternatives, improved treatment regimens using existing medicines, preventive vaccines, and diagnostic tools — and all of these across both human and animal populations — together with deepening our understanding of the environmental spread of AMR. The plan acknowledges the importance of altering economic incentives to encourage such innovation.

3. To contribute to **shaping the global agenda**, including elevating the presence of the EU in global institutions working to tackle the threat of AMR, strengthening co-operation with key strategic partners (including Brazil, China, and India), and supporting developing countries, including with the development of their health systems.

[146] WHO, "Global Antimicrobial Resistance and Use Surveillance System (GLASS)," accessed November 14, 2022.
[147] European Commission, "The New EU One Health Action Plan Against Antimicrobial Resistance," downloaded from Publications Office of the European Union," PDF, accessed November 14, 2022.
[148] UN Environment Programme, LEAP (Law and Environment Assistance Platform) Montevideo Environmental Law Programme, "European One Health Action Plan Against Antimicrobial Resistance (AMR)," provided by FAO/FAOLEX, accessed November 14, 2022.
[149] Ibid.

There have been a number of developments following the publication of this plan in 2018. In May 2021, the European Commission adopted a delegated regulation which requires the Commission to adopt criteria that will allow the Commission to determine which antimicrobials should be reserved for human use.[150]

In April 2022, the European Commission published a draft list of the criteria determining which antimicrobials would be restricted. This has been met with mixed views: Some non-governmental organizations (NGOs) pointed out the irrelevance of some of the antimicrobials listed, considering they are not currently used for veterinary food production. Others criticized the focus on replacing, rather than reducing, the reliance on antimicrobials all together.[151]

U.K. Action Plan

In 2019, the U.K. set out a five-year National Action Plan which builds on the previous action plan that ran until 2018. The plan focuses on three key areas:

1. The first element of the plan is to **reduce the need for antimicrobials**. Specific targets to advance this first element include reducing the infectious disease burden, especially the number of drug-resistant infections.

2. The second element of the plan is to **reduce and better target antimicrobial consumption** in both humans and animals. Here, specific aims center on reducing the level of antimicrobial consumption in humans and animals and to gather data to understand the proportion of antimicrobial prescriptions that are administered with the support of a diagnostic tool.

3. The final element of the U.K. plan is to **invest in innovation**, including building capacity for high-quality AMR-relevant research, committing to the replenishment of the antimicrobial pipeline, and supporting access to antimicrobials at the global level.

U.S. National Action Plan

In 2014, the U.S. published its first strategy for combatting antibiotic resistant bacteria. This plan adopts a One Health approach to bring together practitioners across all three of human, animal, and environmental health. Progress reports have followed since the publication of the plan. The latest report cited achievements including a 10% decline in antibiotic prescribing in outpatient settings from 2011 through 2018 and a 22% decline in antibiotics prescribed to children.[152]

Many of the goals in the U.S. National Action plan echo those set out both in the U.K. and in international plans to address AMR. These goals include (1) reducing the emergence and spread of resistance; (2) improving surveillance systems across human, animal, and environmental health at the national level; (3) increasing the uptake of rapid diagnostic testing; (4) supporting research and innovation; and (5) recognizing the global nature of the threat to support collaboration.

[150] European Public Health Alliance, "The European Commission Should Not Let the Guard Down Against AMR," May 17, 2022.
[151] Eur-Lex, "Commission Delegated Regulation (EU) 2021/1760 of 26 May 2021 Supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by Establishing the Criteria for the Designation of Antimicrobials to be Reserved for the Treatment of Certain Infections in Humans," PDF, 2021.
[152] CARB, "National Action Plan for Combatting Antibiotic Resistant Bacteria: Year 5 Report," 2022

The recent Inflation Reduction Act in the U.S. could have an impact on AMR-relevant innovation. The Act includes steps to reduce drug prices, which are scheduled to start in 2026 and will apply to 10 drugs that year. As a result, millions of people with Medicare will spend less on their prescriptions.

It is of course laudable to reduce the financial barriers to accessing vital healthcare. Yet, it is important to consider the potential impact of the Inflation Reduction Act on the development of novel drugs, including novel antimicrobials. A consequence of the lower drug prices and constrained ability of drug companies to dictate margins on supernormal profits may be a reduction in desire to pursue innovation and develop new drugs due to the restrictions on future price increases.

We note that if the PASTEUR Act were to make progress, this could counter the pricing limits of the Inflation Reduction Act. However, this cannot be relied upon as (as discussed above) the PASTEUR Act may not remain a legislative priority.

Chapter 10: Recommendations for Policymakers

Based on the expert contributions to this Citi GPS report on AMR, policymaking appears to be the single most effective starting point in tackling AMR. For example, both Aviva Investors and Legal & General Investment Management (LGIM) suggested that one of the most impactful and valuable things investors can do is bring their voices together to advocate for tighter regulation and sustainable reforms. Others have also highlighted the specific policy steps required to catalyze action on AMR.

We summarize here some of the key recommendations for policymakers, which have been proposed throughout this report:

- **Address Market Failure**
  - Alter economic incentives to delink investment in research and development from volume of sales and consumption of antimicrobials.
  - Give due consideration to antibiotic use in livestock, agriculture, and aquaculture when negotiating trade agreements.
- **Increase Awareness and Strengthen Regulation**
  - Improve awareness of manufacturers and water utility companies to the threat of AMR.
  - Set incentives and stronger requirements to monitor the release and disposal of antimicrobial waste, for example by making the standards developed by the AMR Industry Alliance requirements.
  - Strengthen regulation around animal husbandry practices to support raising animals in healthy conditions and to avoid exposing them to a high number of infections.
  - Increase public awareness of the threat of AMR and the key hygiene, sanitation, and stewardship steps that individuals can take to prevent the spread of resistance.
- **Improve Data Collection and Surveillance**
  - Improve surveillance systems, especially in low- and middle-income countries, to help target interventions where they are most needed.
  - Further support data collection to understand the scale of the challenge presented by antimicrobial resistance, for example making antibiotic resistance an official cause of death.
- **Support Global Governance and Cooperation**
  - Facilitate global coordination and collective learning, while recognizing that individual countries will have specific needs and face specific challenges.
  - For example, convening a COP-like summit could help to convene global policymakers and elevate both health policy and the threat of AMR further up the global agenda.

– Create an additional UN Sustainable Development Goal for AMR, or a target within SDG 3 — Good Health and Well-being, to elevate the profile of AMR in global health policymaking.

For policymakers, as for other stakeholders, the lessons of the pandemic are relevant to addressing the challenge of AMR. Indeed, some of these recommendations would leverage public investments in tackling infectious disease made during the pandemic.

For example, where significant surveillance infrastructure was deployed to track COVID-19, the same efforts could be advanced to track the emergence of AMR. Similarly, a public campaign on the importance of hygiene and sanitation could build on the efforts undertaken to improve hygiene and prevent infection during the COVID-19 pandemic.

Conclusion

Climate change, biodiversity loss, and antimicrobial resistance are inextricably linked and share several similarities: All are global problems, pose threats to human health, require government support, and sit firmly within the nexus of responsible investment.[153] Building resilience into the climate system, food system, health system, and ecosystems underpins the healthy functioning of a global economy. System resilience will be critical to delivering on human security directly linked to the attainment of the UN Sustainable Development Goals (SDGs). The science of climate change and antimicrobial resistance is complex and at times overwhelming; however, the solutions, which are informed by the latest knowledge, offer the promise of hope supported by scientific advances and technological innovation.

The solutions and interventions required to tackle AMR can be split into four categories:

- **Reducing the burden of infectious disease** is a critical first pillar. This requires improvements in sanitation to prevent the spread of infection. The most simple but effective intervention would be to improve handwashing as the most common way to transmit bacteria is by hand, with approximately two million to four million bacteria found between the fingertip and the elbow.[154] Additional interventions to reduce the burden of infectious disease include the development and use of vaccines and alternatives, such as the adoption of a biosecurity strategy.

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[153] *The Lancet Respiratory Medicine*, "Antimicrobial Resistance—What Can We Learn From Climate Change?," Vol. 4, No. 11, November 2016.
[154] Professor Dame Sally Davies, Jonathan Grant, and Mike Catchpole, *The Drugs Don't Work: A Global Threat* (U.K.: Penguin Books, 2013).

- **Reducing the injudicious use of antimicrobials** in both human and livestock bred for human consumption is the second pillar to tackle AMR. This includes raising awareness and educating both the public and medical professionals on AMR. In practice, reducing consumption will require the development of rapid, robust, and affordable diagnostics to accurately identify the pathogen being treated and whether an antimicrobial is required. Animal health is also relevant: As demand for meat continues to grow, the insidious prophylactic use of antibiotics for growth promotion in intensive factory farming of livestock bred for human consumption must be curtailed.

- **Innovating for novel antimicrobials** to replenish the clinical pipeline is the third pillar. One step here is to address the shortage of trained professionals, including microbiologists, infections disease specialists, and epidemiologists. Investment may be required to incentivize entry to these professions. In the report, we highlighted the work of the CARB-X team, which is are building a portfolio of therapeutics and diagnostic tools, including multiple innovative antimicrobials, to target pathogens identified as priorities by the WHO and CDC.

- **Curtailing the spread of AMR** where it has already emerged is the final pillar. This requires stronger surveillance monitoring in developed and developing economies. The WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) is one example. Improving the treatment of water and solid waste with specific attention to antimicrobials also plays a role.

While the solutions and interventions required to tackle AMR are clear, there will still likely be challenges implementing them. For example, developing international agreements to limit antibiotic use is challenging as countries vary widely in income, capacity, and objectives. The Paris Agreement for climate change highlights common but differentiated responsibilities based on countries' respective capabilities. It also has several design elements that are useful as a model for action, such as a collective global goal, regular reporting on actions and outcomes, and an annual conference of parties. A future international agreement on AMR can draw on existing elements for momentum to reinforce existing action.

When it comes to the UN SDGs, AMR is one of the missing topics and threatens to SDGs on health, food security, environmental well-being, and socioeconomic development. There is no silver bullet to tackling AMR and an adaptive, multi-pronged approach that operates across the SDGs will require a cross-sectoral response placing AMR within the SDG agenda.

Climate change is a social justice issue; its unmitigated progression will disproportionately affect and the health and well-being of individuals in low- and middle-income countries. At a time when action is taken at every level to reverse climate change to avert future climate-related events, we call for similar urgent and rapid action to be taken to tackle the rising tide of AMR to protect long-term planetary, ecosystem, and planetary health.

Appendix A: Initiatives

Figure 31. Initiatives

Access to Medicine Foundation **2021 Antimicrobial Resistance Benchmark Report**	The Access to Medicine Foundation has been working to stimulate and guide the pharmaceutical industry to do more for people living in low- and middle-income countries for more than ten years. The Foundation works to stimulate the pharmaceutical industry to do more for people living in low- and middle-income countries. This is done by defining the actions pharmaceutical companies can and should be taking to improve access to medicine in low- and middle-income countries, and to curb antimicrobial resistance and then analyze what they are actually doing. In practice, that means talking with the experts in global health, in access to medicine, AMR, and the industry to define ambitious but achievable actions pharma companies can take. Companies are then benchmarked against these expectations. The Foundation's research is publicly and freely available. To translate findings into action, the Foundation engages with the companies evaluated and with organizations from the private sector, donors, NGOs, governments, and the investor community. The Access to Medicine Foundation is an independent non-profit organization.
Biomedical Advanced Research and Development Authority (BARDA)	The Biomedical Advanced Research and Development Authority (BARDA) is a U.S. Department of Health and Human Services (HHS) office responsible for the procurement and development of medical countermeasures, principally against bioterrorism, including chemical, biological, radiological, and nuclear (CBRN) threats, as well as pandemic influenza and emerging diseases. BARDA was established in 2006 through the Pandemic and All-Hazards Preparedness Act (PAHPA) and reports to the Office of the Assistant Secretary for Preparedness and Response (ASPR). The office manages Project BioShield, which funds the research, development and stockpiling of vaccines and treatments that the government could use during public health emergencies such as chemical, biological, radiological, or nuclear (CBRN) attacks.
Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)	CARB-X is a global non-profit partnership accelerating antibacterial products to address drug-resistant bacteria — a leading cause of death around the world. The CARB-X portfolio is the world's most scientifically diverse, early development pipeline of new antibiotics, vaccines, rapid diagnostics, and other products. CARB-X is the only global partnership that integrates solutions for the prevention, diagnosis, and treatment of life-threatening bacterial infections, translating innovation from basic research to first-in-human clinical trials. CARB-X is funded by a global consortium of governments and foundations. CARB-X headquarters are located at Boston University.
FIND	FIND aims to ensure equitable access to reliable diagnostic tools around the world in primary care settings. This will involve reducing the testing gap in diseases like TB, hepatitis, pneumonia, and other both infectious and non-communicable diseases. To achieve this, the initiative aims to connect funders, decision-makers, and healthcare providers across communities and across countries to increase innovation in testing and diagnostics. Following co-leadership of the Diagnostics Pillar of the Access to COVID-19 Tools (ACT) Accelerator, their 2021 strategy aims to build on the momentum that diagnostic testing saw during the COVID-19 pandemic.
The FAIRR Initiative	The FAIRR Initiative is a collaborative investor network that raises awareness of the environmental, social, and governance (ESG) risks and opportunities in the global food sector. FAIRR's mission is to build a global network of investors who are aware of the issues linked to intensive animal production and seek to minimize the risks within the broader food system. 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 such resource is the Best Practice Policy on Antibiotic Stewardship for Food Companies. This is a publicly available resource on antibiotic stewardship which was 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 antibiotics for prophylactic and metaphylactic use, and to set time-bound targets.
The Fleming Fund	The Fleming Fund brings evidence and people together to encourage action against drug resistance for a healthier world. They support low- and middle-income countries to generate, share, and use data to improve antimicrobial use and encourage investment in AMR. The Fleming Fund is a U.K. aid program supporting up to 25 countries across Africa and Asia to tackle antimicrobial resistance. The Fund is managed by the Department of Health and Social Care and invests in strengthening surveillance systems through a portfolio of country and regional grants, global projects, and fellowship schemes. The U.K. government established the program in 2015 in response to the U.K. AMR Review and the WHO Global Action Plan on AMR, which called for funding to improve AMR surveillance, public awareness, and responsible drug use. The program focuses on low- and middle-income countries (LMICs) because they are expected to bear the heaviest consequences of the spread of AMR. The U.K. AMR Review estimated that by 2050, up to 90% of all deaths related to AMR will come from Africa and Asia. The Fleming Fund is named after Sir Alexander Fleming, the scientist who discovered penicillin and contributed to the development of the world's first antibiotic drug.

Global Antibiotic Research & Development Partnership (GARDP)	GARDP was created by the World Health Organization and Drugs for Neglected Diseases in 2016 to help deliver on the Global Action Plan on Antimicrobial Resistance. By bringing together governments, the private sector, academia, and civil society, GARDP develops new treatments for drug-resistant infections. This initiative has already collaborated on screening 65,000 compounds and evaluating >100 entities for antibacterial activity, leading to six additions to the GARDP pipeline of innovative anti-infectives. GARDP also works with partners to improve access to treatments, to promote responsible use, and to ensure affordability for those in need.
Ineos Oxford Institute (IOI)	The Ineos Oxford Institute for Antimicrobial Research was established to advance the search for solutions for one of the biggest public health challenges of our time. They work in the lab, in the field and with the public to discover new ways to prevent and treat drug resistant infections. In the lab: The Institute undertakes the basic science to produce novel molecules and compounds that will act as alternatives to the current limited “medicine cabinet” of antibiotics. In the field: The Institute surveys, models, and assesses the global AMR burden to discover new ways to prevent and treat drug-resistant infections.
Novo Holdings REPAIR Impact Fund	Novo Holdings established the REPAIR Impact Fund commissioned by the Novo Nordisk Foundation in February 2018 with a total budget of $165 million to invest in companies involved in discovering and the early-stage development of therapies targeting resistant microorganisms. The fund is expected to invest $20 million to $40 million per year over 3–5 years in about 20 projects, which is anticipated to yield at least one new therapy reaching the market. The REPAIR Impact Fund will invest in start-ups, early-stage companies, and corporate spin outs. The Fund's philosophy is to support ambitious programs addressing antimicrobial resistance through a broad range of therapeutic modalities. REPAIR is an acronym: Replenishing and Enabling the Pipeline for Anti-Infective Resistance.
The PASTEUR Act	The PASTEUR Act is legislation that has been introduced in the U.S. Senate and House of Representatives by a bipartisan group of lawmakers. The proposed legislation aims to spur innovation in the development of novel antibiotics, especially those that would address unmet clinical needs. It would do so by altering the payment structures for antibiotics to create financial incentives for the development of novel antimicrobials while at the same time incentivising their sustainable use. This has been described as a subscription model that delinks payments from how much medicine is consumed.
The Wellcome Trust	The Wellcome Trust is a charitable foundation focused on health research based in London, in the United Kingdom. It was established in 1936 with legacies from the pharmaceutical magnate Henry Wellcome (founder of one of the predecessors of GlaxoSmithKline) to fund research to improve human and animal health. The aim of the Trust is to "support science to solve the urgent health challenges facing everyone." It had a financial endowment of £29.1 billion in 2020, making it the fourth wealthiest charitable foundation in the world. In 2012, the Wellcome Trust was described by the Financial Times as the United Kingdom's largest provider of non-governmental funding for scientific research, and one of the largest providers in the world.

Source: Citi GPS

Appendix B: Investor Action on Antimicrobial Resistance

Founding Collaborators

The Investor Action on Antimicrobial Resistance (IAoAMR) initiative was founded by the Access to Medicine Foundation (ATMF), the FAIRR Initiative, Principles for Responsible Investment (PRI), and the U.K. government's Department of Health and Social Care. It was launched on January 23, 2020 at the World Economic Forum Annual Meeting in Davos. It is a collaborative initiative aiming to tackle the global threat of drug-resistant infections caused by antimicrobial resistance (AMR), — an urgent public health challenge associated with an estimated 4.95 million deaths globally in 2019 alone and estimated to cost the world $100 trillion in global economic losses by 2050. The initiative's current 16 Investor Partners have more than $10 trillion AUM combined.

Objectives

The initiative seeks to raise investor awareness and engagement on the material risks and opportunities of AMR, and to leverage investor influence to make change happen.

By joining, Investor Partners get the opportunity to:

- Join a pioneering network of investors seeking to better engage on the ESG risks related to AMR and opportunities to mitigate such risks.
- Receive expert research and analysis on the materiality of AMR, including the exclusive expertise and support of the Founding Collaborators (ATMF, FAIRR, PRI, U.K. DHSC).
- Gain access to knowledge-exchange, guidance tools including best practices and policies, and stakeholder convening events on AMR.
- Receive a quarterly newsletter highlighting relevant developments in AMR (publications, innovations, events, investor letters, shareholder resolutions, etc.).
- Join collaborative engagements with companies across a range of sectors (pharmaceuticals, food, water utilities).
- Publicly demonstrate your organization's commitment to preserving the efficacy of antibiotics for human and animal health.
- Be listed on the coalition's website, with the option to publish a public statement (written or video).

What does it mean to join?

Investors that wish to join the initiative are requested to: (1) work with ATMF and FAIRR to adopt an AMR lens when making investment decisions and engaging with investee companies, either bilaterally or as part of collaborative engagements, and (2) undertake at least one specific outcome (a "challenge") to help combat the growing threat of drug-resistant superbugs in humans, animals, and the environment. Investor Partners can take on a wide range of challenges, such as commissioning research into AMR-related risks and opportunities, developing guidance and tools related to AMR, raising awareness of AMR's materiality, and engaging policymakers on AMR funding and regulation.

Progress Report: The Investor Action of Antimicrobial Resistance Progress Report

In November 2022, ATMF, FAIRR and PRI will publish the IAoAMR Progress report. This report will provide a One Health overview of the drivers and implications of AMR as an environmental, social, and governance (ESG) risk for investors while exploring the role of investors in curbing this systemic risk. It will also outline the actions that Investor Partners have taken to date in relation to the challenges they took on. Lastly, it will introduce tools and collaborative mechanisms for investors to use in tackling this issue, as well as signposting areas where greater action from all stakeholders is required.

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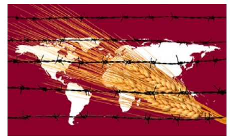

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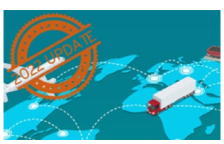

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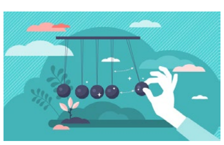

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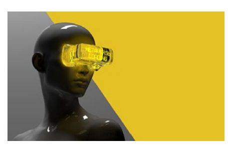

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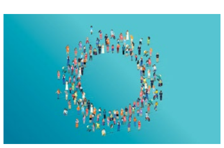

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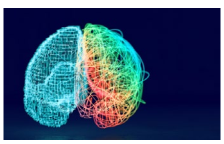

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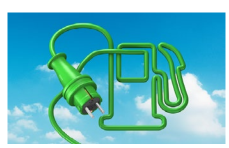

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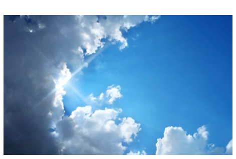

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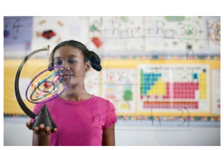

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IMPORTANT DISCLOSURES

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Key Insights regarding the future of Antimicrobial Resistance

INNOVATION

The misuse of antibiotics by patients, as well as shortcomings by governments and physicians over the past 30 years, have led to an increasing number of drug-resistant infections globally. / Innovation is also critical to replenish the clinical pipeline of new medicines and requires investment into early-stage research and drug discovery as well as building the pipeline of talent to ensure scientists are attracted into AMR relevant fields.

SUSTAINABILITY

More than 73% of global antimicrobial consumption is directed at food production. / Farmers in low- and middle-income countries will need to make necessary improvements in farm hygiene, management, and animal husbandry that enable restrictions on the use of antimicrobials while still protecting animal welfare and avoiding catastrophic losses of livestock from disease.

SOCIAL CONSTRUCTS

Populations that do not have access to infrastructure supporting good hygiene practices and sanitation are at higher risk of contracting infectious diseases. / A public campaign on the importance of hygiene and sanitation could build on the efforts undertaken to improve hygiene and prevent infection during the COVID-19 pandemic.