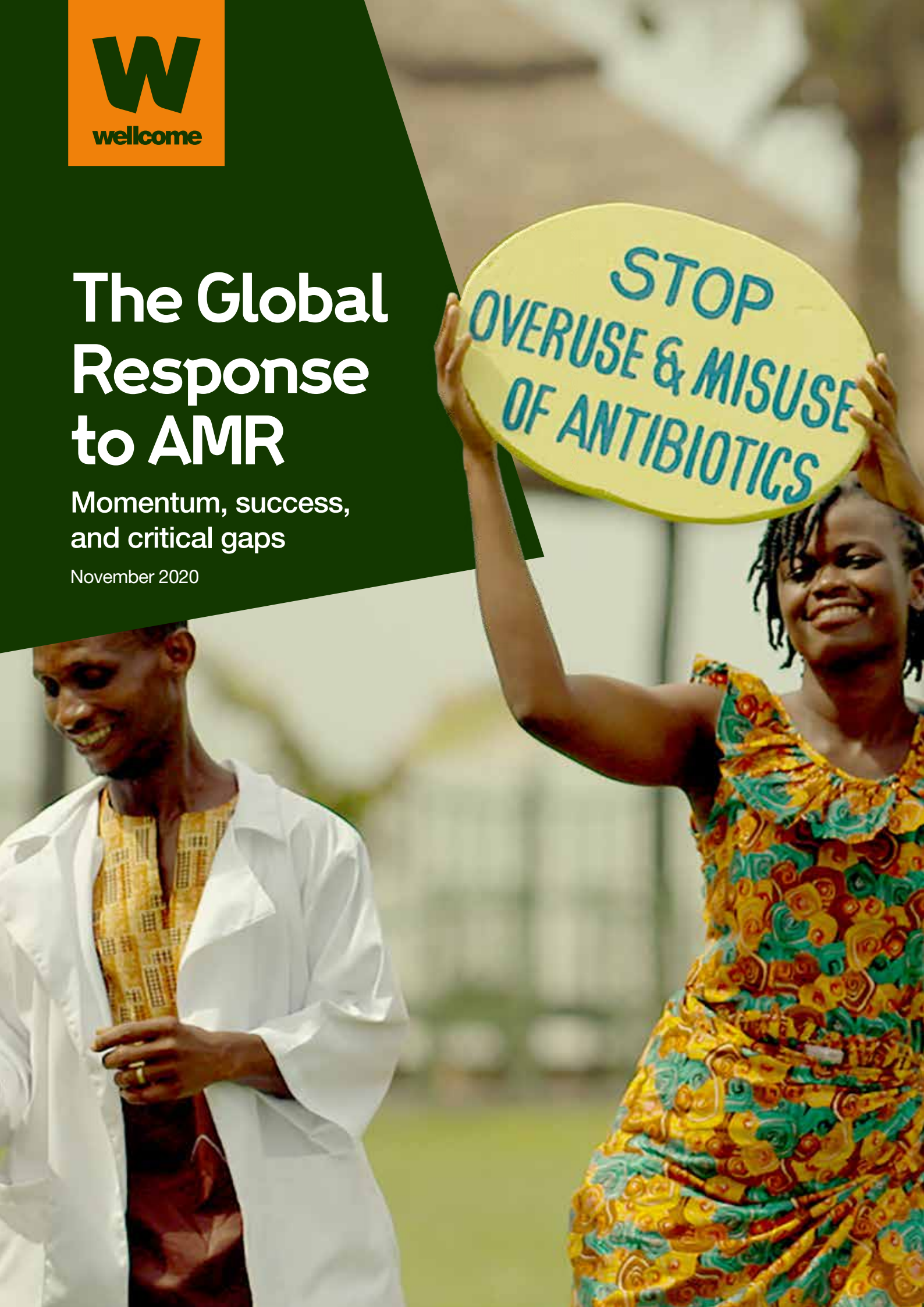
wellcome

The Global Response to AMR

Momentum, success, and critical gaps

November 2020



Contents

Acknowledgements

This report was produced by the Wellcome Trust. McKinsey & Company contributed analyses to this report.

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The McKinsey & Company team was led by Matthew Wilson, Senior Partner, and Lars Hartenstein. Major contributors include Konstantin Sietzy and Anthony Darcovich.

We would like to thank all external contributions to this report. These findings are based on the input of approximately 150 external contributors across each of the thematic areas discussed within this report.

Preface

Covid-19 is the most severe global health crisis we've faced in over a hundred years. Beyond the direct health impact of the virus, the pandemic's implications for wider public health, societies, and economies will be felt for a long time.

Wellcome recently announced our new vision and strategy. Wellcome supports science to solve the urgent health challenges facing everyone. We will be taking on three urgent health challenges – Mental Health, Global Heating and Infectious Disease – that threaten the health of humanity for decades to come.

Although the development of our vision and strategy started before the Covid-19 pandemic, this is a critical moment in shaping the future of our world and how we – as Wellcome and a wider global health community – solve the Infectious Disease challenge.

Antimicrobial resistance (AMR) is a major piece in the puzzle that we must solve to overcome the challenge of infectious diseases. The pathogens that cause infections can evolve and develop resistance to the treatments we use to control them. This could lead to common infections becoming untreatable and medical procedures such as surgeries or chemotherapy becoming too risky. For years, Wellcome has prioritised tackling drug-resistant infections. We've supported a dedicated and comprehensive AMR agenda and community because we believe that to stop life-threatening infections from escalating, the world must stay one step ahead by controlling the spread of drug resistance.

And right now, we're falling behind.

Drug-resistant infections already contribute to at least 700,000 deaths a year, and its impact is unequal across the world. In Brazil, Indonesia and Russia, 40 to 60% of infections are already caused by drug-resistant bacteria, compared to an average of 17% in OECD countries. Given the current trajectory, drug resistance could lead to 10 million deaths annually and plunge 24 million people into extreme poverty by 2050.

Recognising the severity of the threat, a UN High-Level Meeting on AMR was held in 2016 and provided a rallying moment for the global response.

This was only the fourth time in the history of the UN that a health topic was discussed at the General Assembly and it spurred global political momentum on the issue. In 2019, Wellcome analysed the AMR landscape since this critical meeting to identify where progress has been made, and what critical gaps remain. We sought input from leading experts within the public health, policy and scientific communities. Over the summer of 2020, we expanded this research to understand the impact that the Covid-19 pandemic was having on AMR.

Through this analysis, numerous, and at times diverging, viewpoints were raised on how best to position AMR in a post-Covid-19 world. As a landscape analysis, the report captures these different perspectives without selecting one over another.

As Wellcome, however, we have a strong view on the best path forward that is grounded in our role, our experience, and our commitment to the global response on Infectious Disease and drug-resistant infections.

To us, the analysis demonstrates that Covid-19 has changed the landscape around AMR and a fresh approach is needed.

- The global health community must build on the current momentum to shape a comprehensive infectious disease threats agenda, of which drug-resistant infections should be an integrated piece. While Covid-19 galvanises attention to the tremendous importance of infectious disease threats, airborne viral diseases are only one part of this broader category.
- Several AMR topics will benefit from this broader agenda. For example, the current focus on infection prevention and control and on water, sanitation and hygiene (WASH), such as by promoting hand washing and increasing laboratory capacity, will have significant benefits for the global response to drug-resistant infections.
- However, other AMR topics will likely continue to require discrete attention, such as antimicrobial consumption in humans or, for the immediate future, the development of new antibiotics.

Such a comprehensive infectious disease threats agenda will require an enormous increase in scale and ambition. We recognise this but are steadfast that such action is necessary. We also appreciate that such progress will require prioritisation and collaboration among the many facets of the response to antimicrobial drug resistance – something that has been challenging to do in the past. Action is necessary from actors across public/government sector, business sector and civil society, and needs to proceed in concert and be built on partnerships. To this end, the report delineates a critical path forward for the AMR community based on expert consultations.

Within this critical path, we at Wellcome have identified where we can best contribute to collective global action to protect people from drug-resistant infections:

1. Development of and access to therapeutics – the world needs new treatments to deal with drug-resistant infections, and additional funding to deliver innovative solutions to add to the arsenal of interventions.
2. Appropriate use of antibiotics - Antibiotic use must improve to reduce the drivers of drug-resistant infections, through evidence-based, optimised use and the development and uptake of diagnostic tools.
3. National action to achieve maximum impact – concrete, ambitious, evidence-based action led and owned by individual countries, as this is how to best deal with the particular local problems caused by drug-resistant infections.

Many predicted a global pandemic prior to Covid-19, but the world was still ill-prepared. We must not be caught out the same way by drug resistant infections, a slow-moving pandemic whose impact we are already seeing today. We can prevent it from developing into an irreparable crisis but the time to act is now. We must learn from the tragedy of this pandemic to ensure that we treat drug-resistant infections with the urgency and scale it requires.

Jeremy Farrar
Director

Tim Jinks
Head of Drug Resistant Infections (DRI)

Executive summary

Antimicrobial resistance (AMR) is a growing public health concern in every country in the world. It already causes at least 700,000 deaths due to drug-resistant infections per year globally, a number that may increase to 10 million per year by 2050 – unless significant action is taken. AMR is not only reversing recent gains made in controlling infectious diseases but also undermining improvements in healthcare provision in general. Its broader health effects include threatening the safety of many healthcare interventions that are today seen as routine, including chemotherapy, organ transplants and other major surgeries. As antimicrobial drugs lose their efficacy due to AMR, risks of prolonged hospital stays or additional surgical interventions increase substantially. The need to deal with AMR will burden health systems already struggling with cost inflation, and the damage to national economies resulting from increasing illness and death will further hit health budgets. These health and economic burdens will disproportionately fall on low- and middle-income countries (LMIC), preventing attainment of Sustainable Development Goals.

But this worrying scenario can be avoided, or at the very least mitigated. A large global community of actors spanning governments, multilateral agencies, civil society, and the private sector are working together on AMR. They have had some success already, but the scope for future progress hangs in the balance. The AMR community needs to agree on how the topic should be positioned relative to the broader pandemic preparedness and recovery agenda, and how to prioritise the most important areas for action.

This report provides a comprehensive **update on the status quo, recent developments, and remaining critical gaps in the AMR response globally.** It summarises these findings in two overarching chapters and underwrites these with profiles covering themed areas where work is needed, and factors that will enable that work across the global health landscape. It sketches what a critical path for the global response to AMR could look like, including how to define, prioritise, and implement actions in order to achieve greatest impact.

These findings are the result of interviews with over 100 experts and reviews of over 250 documents. Most of the interviews were conducted in 2019, when the world looked very different. **Covid-19 has radically changed the landscape for healthcare and infectious diseases.** It has put healthcare at the top of national and global agendas and elevated topics such as disease surveillance from technical to mainstream policy conversations (while perhaps impacting the resources and capacity to conduct them). The Covid-19 response has also seen a sea change in the global conversation on innovation and who pays for it, perhaps lastingly. To account for these effects, the views of more than 80 experts were captured during July and August 2020.

A core finding stands out: **the next few years will define the trajectory of the long-term AMR response** and how successful it can be.

The AMR community has achieved notable recent successes:

- **AMR has achieved prominence on the global political agenda:** It has moved from a largely technical topic to a political one – a precondition for building an enabling environment that secures funding, awareness, and leadership. The 2016 UN General Assembly Political Declaration raised AMR's international profile as a pressing concern. Some of the global momentum may have waned since then, especially given Covid-19, but political awareness of AMR remains – at least for now.
- **The AMR community is a broad, multi-sectoral coalition of actors aware of, and willing to tackle, AMR:** Among this community, there is an unprecedented commitment to an approach spanning sectors including human health, animals and agriculture, and the environment.
- **The discovery-stage and translational research environment is robustly funded:** Significant funds have been made available for early-stage research since 2016, especially on new therapeutics. Moreover, despite the Covid-19 pandemic, additional push funding has been launched in 2020, including the $1 billion AMR Action Fund.

This enabling environment for action on AMR **is at risk of irreparably weakening.** Three critical gaps drive this risk:

- **Ambitions have not always translated into meaningful action:** A substantial uptick in the prominence of global discussion on AMR over the past three to four years has not translated into broader implementation of initiatives. This is true especially in LMICs, where AMR typically competes for political attention and resources with other public health topics. Actors outside of policy-making circles frequently perceive the AMR community as a 'talking shop'.
- **Prioritisation is increasingly emerging as a gap:** The 'big tent' approach of the AMR response to date has increased awareness among a broad range of stakeholders. Yet experts across the AMR space are concerned that the multifaceted nature of the issue, the complexity of its narrative, and the multitude of possible interventions are paralysing the community, preventing impactful action. There are discrete problems for which known solutions exist; to prioritise effectively, the community must align on a critical path of sequenced steps towards implementation.
- **The AMR agenda was at risk of losing momentum even pre-Covid-19**: In late 2019, experts felt that the AMR agenda was at risk of losing significant momentum over the next 12 to 24 months unless it could demonstrate impact. Several mentioned the potential for short-term, small successes to demonstrate concrete impact and communicate the importance of AMR to an outside global audience. Covid-19 has made this concern more acute. AMR needs a new, focused narrative in a post-Covid-19 world that can rejuvenate attention, resources, and action towards impact.

Covid-19 has radically altered the world's conversation on public health. Experts universally agreed that **Covid-19 will affect the global response to AMR in at least two ways:**

- Covid-19 has exerted *both* upward and downward pressure on the development of drug resistance in infections through several mechanisms (for example, experts observed increased use of antibiotics in inpatient settings, but decreased use in outpatient settings) – the net effect remains to be seen.
- **The policy fallout from Covid-19 brings both risks and opportunities** for the attention AMR receives on a policy level, including funding, advocacy, and research. Opportunities may include increased understanding of infection prevention and control (IPC), increased surveillance and lab capacity (and awareness of its importance), or even a clearer pathway into finance ministries for preventive healthcare conversations. Risks may include suspended hospital surveillance programmes, young research talent too often diverted towards viral infections, resource constraints for implementation, ineffective stewardship, and a decrease in the availability of funding for the global health agenda.

Accordingly, there is a clear need to rethink AMR's position as part of the global health agenda. This raises the question of what that agenda may look like post-Covid-19. Broadly, experts perceived three (perhaps overlapping) possibilities:

- **The status quo of a limited, technical, and niche pandemic preparedness and recovery agenda.**
- **An expanded pandemic preparedness and recovery agenda,** prominent in political and social attention, and funded accordingly.
- **A much broader, revitalised infectious diseases agenda** that focuses on preparedness and response to novel pathogens in tandem with tackling existing endemic and pandemic diseases (e.g. Tuberculosis and HIV).

Crucially, experts were broadly confident that the first option was less likely than the other two; which of those two would be likelier is uncertain.

Assuming that one of these does develop, there is then the question of how the AMR agenda should be positioned. Broadly, experts identified three perspectives:

- **The AMR agenda should tie itself to an inclusive pandemic preparedness and response agenda.**
- **The AMR agenda should remain distinct because AMR is better served by distinctive narratives.**
- **The AMR agenda should remain distinct because linking AMR to a broad pandemic preparedness agenda is not feasible.**

In choosing between these perspectives and finding a common path forward, there are several open questions that should urgently be answered:

- **Which perspective is best supported by available evidence and information?**
- **Which perspective can established actors in the current AMR community align on?**
- **Which perspective resonates with external decision makers and potential funders?**
- **How, where, and to whom should a newly repositioned AMR agenda be communicated?**

In light of the perception that the AMR agenda was at risk of losing momentum even before Covid-19, it is imperative to start a broad exploratory dialogue on these questions sooner rather than later.

A first **sketch of a potential 'critical path' to impact** – focusing on implementing a narrower set of truly critical interventions – sets out two phases.

The first phase, 2020–30, focuses on mitigating the risk of resistance and its consequences, and on expanding the evidence base where gaps remain a barrier to action. **Beyond 2030,** the second phase will build on established infrastructure to control resistance and its consequences, moving into maintaining resistance control through prevention and through maintaining and scaling best practices.

The first phase prioritises **seven focus areas for action:**

- **Water, sanitation, and hygiene (WASH):** Access to clean water and sanitation reduces the transfer of resistant pathogens and prevents infection. Achieving this would depend on communicating a clear and actionable vision for the WASH community. This will require attention but only limited additional resource commitments from the AMR community.
- **Infection prevention and control:** IPC measures reduce the need for antibiotics and thus their consumption. Given the robust global agenda on IPC, there will be significant benefits from mainstreaming AMR awareness into existing IPC interventions. This will require attention but only limited additional resource commitments from the AMR community.
- **Therapeutic innovation:** As resistance to existing treatments continues to develop, new ones must be developed continuously and sustainably. There is widespread agreement that the current R&D ecosystem has not produced enough drug candidates for a sustained response, and large-scale, global pull incentives to spur innovation appear further away than in 2016.
- **Surveillance:** Effective surveillance systems are critical to understanding the problem, designing and implementing interventions, and assessing the effectiveness of the response. Key gaps in existing surveillance systems include capturing data that is actionable and utilising all existing data sources.
- **Human consumption of antimicrobials:** Optimising human consumption of antimicrobials requires guaranteed access for those who need treatment as well as adequate stewardship to limit overconsumption. This is a natural priority given rising consumption among humans and its role in resistance development. Yet behavioural change among both prescribers and patients has remained hard to achieve.

- **Vaccine development and access:** By preventing infection in humans and animals, vaccines play an important role in reducing antimicrobial consumption. While the case for vaccines to support the AMR response is clear in principle, more and better evidence is needed to mobilise investment, particularly for vaccines for pathogens that are of priority concern from an AMR standpoint.
- **Antimicrobial use in animals:** For a response that is preventive, not just focused on treatment, a holistic perspective that includes other topics across the One Health spectrum is essential. One such factor is that reducing drug-resistant infections in humans requires ensuring appropriate antimicrobial use in animals.

Other topics warrant attention and investment in the near term, but may not be the focus of urgent action. These include developing and ensuring access to (new) **diagnostics,** combatting **low-quality** or falsified antimicrobials, strengthening **health security** systems and cooperation, limiting AMR in **plants** and in the **environment,** ensuring f**ood safety and security,** improving **drug discovery and translational research,** and setting up **clinical trial networks.**

In the second phase, beyond 2030 moving into maintaining resistance control, some of these areas are likely to grow in importance. **New evidence** (e.g. on increased resistance transfer from animals to humans) could propel topics to higher priority much sooner. Each of these topics, including the priority topics, are discussed in **detailed profiles in Appendix 1.**

In the move from prioritisation to implementation, specific strategies will vary widely across countries. While a systematic or comparative assessment across countries was outside the scope of this effort, deep-dive interviews with multiple in-country experts on national action suggested **lessons for different country archetypes.** These findings on **National Action and Global Governance are also detailed in Appendix 1.**

In conclusion, prioritisation is increasingly emerging as a gap in the AMR response. The community must align on a more specific critical path to achieve impact. This will involve mapping a set of key issues to focus resources and attention on, and developing a perspective on the appropriate level and sequencing for implementation. Importantly, which actions to support, or which to prioritise, will differ for actors in different areas of the AMR agenda. There is not a one-size-fits-all plan. All of this becomes even more important in the context of Covid-19 and its impact on AMR. There are many outstanding questions, but regardless of how these are answered, the response to AMR should not attempt to be all-encompassing in one step. An effective strategy will require a focus on a critical path of priority activities.

Glossary

Acronym	Term
AMR	Antimicrobial resistance
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CDC	US Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics & Policy
CRE	Carbapenem-resistant Enterobacteriaceae
DALY	Disability-adjusted life year
ECRAID	European Clinical Research Alliance on Infectious Diseases
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organisation
FDA	Food and Drug Administration
FIND	The Foundation for Innovative New Diagnostics
GARDP	Global Antibiotic Research and Development Partnership
GLASS	Global Antimicrobial Resistance Surveillance System
HIC	High-income countries[1]
IACG	Interagency Coordination Group
IPC	Infection prevention and control
IPPC	International Plant Protection Convention
LIC	Low-income countries
LMC	Lower-middle-income countries
LMIC	Low- and middle-income countries[1]
MIC	Middle-income countries
NAP	National Action Plan
ODA	Official development assistance
OIE	World Organisation for Animal Health
OECD	Organisation for Economic Co-operation and Development
PCV	Pneumococcal conjugate vaccines
REDISSE	Regional Disease Surveillance Systems Enhancement Program
SDG	Sustainable Development Goal
UMC	Upper-middle-income countries[2]
USP	US Pharmacopeia
WASH	Water, sanitation, and hygiene
WHO	World Health Organisation

[1] Following the World Bank's 2019–20 definition; cf. World Bank Data Team. New country classifications by income level: 2019–2020. World Bank 2019 1 July. https://blogs.worldbank.org/opendata/new-country-classifications-income-level-2019- 2020.

[2] Ibid.

Introduction and context

AMR as an urgent public health concern.

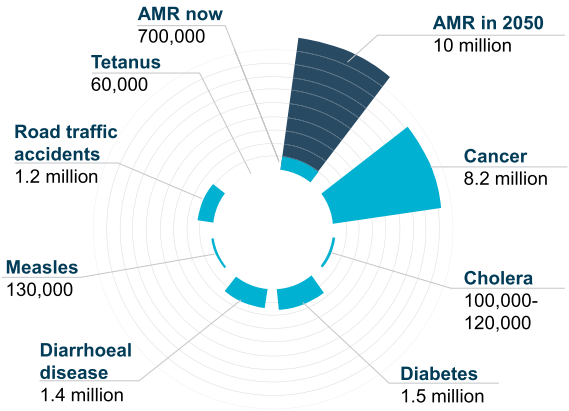
Antimicrobial resistance (AMR) is an essential public health concern and already the cause of at least 700,000 deaths per year globally. Left unchecked, AMR is likely to become one of the world's largest health threats, surpassing many other major conditions, such as diabetes and cancer, in scale.[3] have a severe effect on economies around the world. The economic costs of AMR will burden health systems already struggling with cost inflation. The World Bank estimates that AMR will reduce global GDP by 1.1 to 3.8 per cent by 2050, and cause an annual shortfall of $1.0 trillion to $3.4 trillion by 2030 versus the baseline.[4] This estimate only considers

Antibiotics are a cornerstone of modern medicine

Exhibit 1 – adapted from Review on AMR

Deaths attributable to AMR every year

compared to other major causes of death



Context

- Drug-resistant infections currently account for **~700,000** deaths each year
- Without continued efforts to develop effective antibiotics, this toll could rise to **10m** by 2050, with an economic cost of **~USD 100tn**
- The development of new, **innovative antibiotics is essential** to stay ahead of drug resistance

In addition to direct health effects from drug-resistant infections, AMR will have a detrimental impact on a range of other healthcare interventions, many of which are routine procedures that are taken for granted, such as surgery, chemotherapy, and organ transplants. If antimicrobials lose their efficacy due to AMR, it will significantly raise the chance of prolonged hospital stays and riskier surgical interventions for these patients, especially where immune systems are already weakened. This burden will disproportionately fall on low- and middle-income countries (LMIC). In addition to its impact upon human health, AMR will shocks to labour supply and livestock productivity and is likely to underestimate the total economic impact. Moreover, a 2019 study by the Council for Canadian Academies, supported by the Government of Canada, found that 5,400 lives were lost and Canada's GDP was reduced by Can$2 billion as a direct result of AMR in 2018.[5] Beyond this, the costs of AMR can be catastrophic for affected individuals as well. According to the World Bank, "in the high AMR-impact scenario, an additional 24 million people would be forced into extreme poverty by 2030."[6]

[3] Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. J O'Neill and Wellcome Trust (contributors). London: Review on AMR; 2014.

[4] Jonas O et al. Drug-Resistant Infections: A threat to our economic future (Vol. 2): final report (English). Washington: World Bank; 2017 1 March. The O'Neill Review estimated a total production shortfall by 2050 of $100 trillion.

[5] Council of Canadian Academies. When Antibiotics Fail: The expert panel on the potential socio-economic impacts of antimicrobial resistance in Canada. Ottawa: CCA; 2019. https://cca-reports.ca/wp-content/uploads/2018/10/When-Antibiotics-Fail-1.pdf.

[6] Jonas O et al. Drug-Resistant Infections: A threat to our economic future (Vol. 2): final report (English). Washington: World Bank; 2017 1 March.

Emergence of AMR

AMR affects all classes of microbes: bacteria, viruses, fungi, and protozoa. AMR is a naturally occurring phenomenon resulting from genetic mutation or gene transfer between microbes. The use of antimicrobials increases selective pressures on microbial populations, causing susceptible bacteria to die, while resistant bacteria are able to survive and proliferate.

While antimicrobials are an important part of preventing and controlling infection in humans, animals, and plants, their inappropriate use, overuse, and misuse significantly accelerate resistance development. This applies to overuse at the population level, increasing the total selective pressure on microbial populations. Similarly, underuse – such as from exposure to substandard medicines – can promote resistance, as microbes survive that would have otherwise been destroyed. In a similar way, using antibiotics for growth promotion in livestock is a concern when they are applied at a subtherapeutic dosage, where bacteria are exposed to the antibiotic but likely not fully eliminated, thus selecting for resistant strains that survive and may transfer to humans.

The global response to AMR

AMR is one of the most complex and multifaceted health challenges facing the global community today. It involves many types of pathogens and diseases. Resistance development, transfer, and transmission all occur in different pathways involving factors and stakeholders in human, animal, and plant health, as well as the environment. Interventions to reduce inappropriate use, overuse, and misuse of antibiotics must address regulatory gaps, introduce appropriate incentives, and drive behavioural change, while still ensuring appropriate access, especially in LMIC.

This response is usually viewed through a focus on two sets of interventions:

- **AMR-specific solutions** aimed directly at mitigating development or transmission of resistant pathogens.
- **AMR-sensitive solutions** focused on leveraging other global health (and other) agendas to generate positive externalities for decreasing the prevalence of AMR, such as improved hygiene, sanitation, and infection prevention and control (IPC) measures, which reduce the overall need for antimicrobials.

Given this complexity of stakeholders, incentives, and trade-offs, the global AMR community has taken a One Health approach to the crisis to bring a comprehensive set of agendas to the table. At the global level, the UN Food and Agriculture Organisation (FAO), the World Organisation for Animal Health (OIE) and the World Health Organisation (WHO) have taken leadership roles on informing, coordinating, and driving the response to AMR, formalised in 2010 as the Tripartite. This increased attention to AMR culminated in 2015's 'Global Action Plan on Antimicrobial Resistance', endorsed by all three agencies, which set out five strategic objectives to tackle AMR around the world.

In September 2016, the UN General Assembly adopted the Political Declaration on Antimicrobial Resistance. This represented a major step by the global community to formalise and strengthen the response to AMR, with the inclusion of a broader coalition of nations and actors.

One of the key outcomes of the Political Declaration was the creation of an Interagency Coordination Group (IACG) on Antimicrobial Resistance, tasked to draft a set of recommendations on future global action on AMR to the UN Secretary General. The IACG's final report was released and presented to the UN Secretary General in April 2019. It made recommendations in five areas:

- **Accelerate progress on a national level:** Ensure access, accelerate development and implementation of National Action Plans (NAPs), and phase out antimicrobials for livestock growth promotion.
- **Innovate to secure the future:** Increase investment into new antimicrobials, strengthen access initiatives, and strengthen research coordination and collaboration.
- **Collaborate for more effective action:** Systematically engage civil society groups and the private sector.
- **Invest for a sustainable response:** Include an AMR lens in investments across all public and private investor classes and increase domestic and donor funding dedicated directly to AMR.
- **Strengthen accountability and global governance:** Enhance capacity for the Tripartite and develop a Global Development and Stewardship Framework.

The IACG report recommended strengthening the global institutional framework for an AMR response through the creation of two new bodies, a One Health Global Leadership Group on Antimicrobial Resistance, and an Independent Panel on Evidence for Action against Antimicrobial Resistance.

Context and objectives for the landscape analysis

Four years after the Political Declaration, where does the global response to AMR stand? This is the core question that this report attempts to answer. To ensure the analysis represents an accurate and balanced view of the AMR landscape, it sought to capture the inputs and reflections of over 90 key stakeholders, whose expertise spans the full breadth of the AMR field.

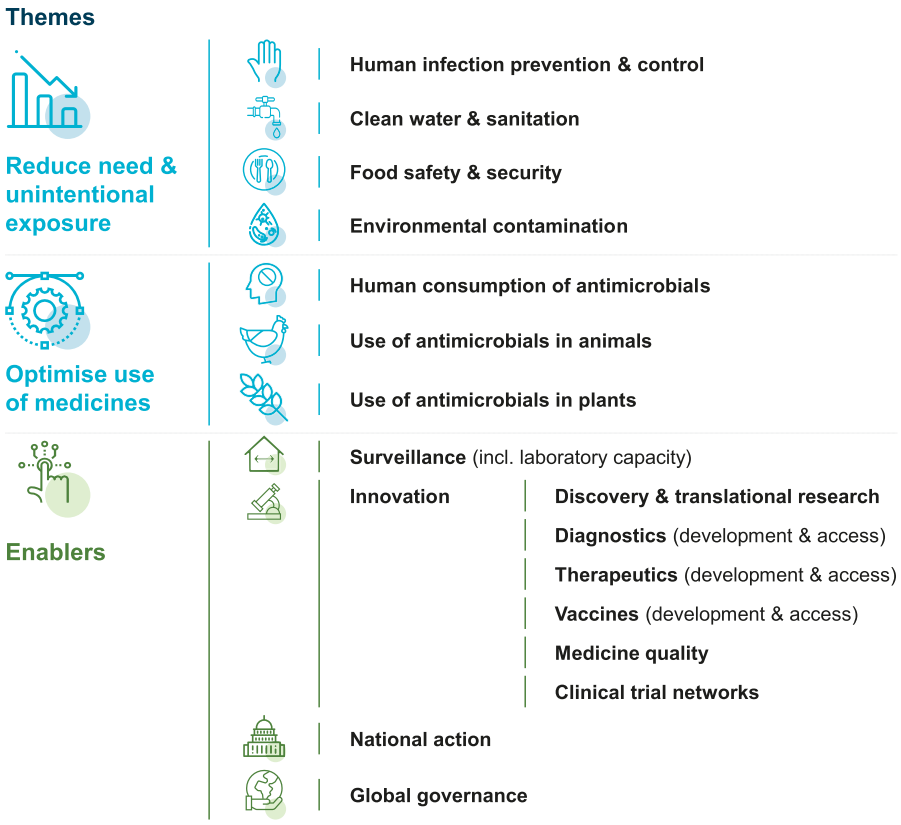
The analysis hopes to shed some light on three dimensions of today's AMR response:

- **Developments since 2016 and momentum:** What impact has the Political Declaration had on the response and what progress has been made since? Is the current momentum positive or flat (or even negative)?
- **Status quo:** How do experts assess the maturity of the response today, both in terms of the enabling environment and with respect to implementation?
- **Critical gaps:** Perhaps most importantly, where do experts see critical gaps in the response today and over the next 5 to 10 years?

Due to the complexity of AMR and the multitude of possible solutions, the answers to these questions will differ depending on which segment of the response one looks at. To this end, the analysis structures the AMR response into seven themes and nine enablers that underpin these themes (see Exhibit 2).

AMR landscape framework

Exhibit 2



Appendix 2 provides a detailed overview of the landscape's methodology, sources and sampling.

A note on Covid-19

When the bulk of the interview work for the landscape analysis was conducted (July to September 2019), the world – and especially the world of infectious diseases – looked very different than it does one year later. Covid-19 has radically shifted conversations on healthcare and infectious diseases into the centre of human life in many societies. It has touched upon all themes in the above framework: Increasing exposure to antimicrobials (through real and perceived risks of Covid-19 bacterial co-infection, but also broader effects on IPC) and challenging efforts to optimise the use of antimicrobials (at least in humans, by changing how and when antimicrobials are available and prescribed).

Yet Covid-19 has also affected several of the underlying enablers. It has put healthcare at the top of both national and global governance bodies' agendas, and elevated topics such as disease surveillance from technical to mainstream policy conversations (while perhaps impacting the resources and capacity to conduct it). The Covid-19 response has seen a sea change in speed and attention on the race for effective vaccines and therapeutics, supported by novel, rapidly assembled institutions such as the Covid-19 Therapeutics Accelerator or COVAX. This has driven changes to the global conversation on innovation and who pays for it, perhaps lastingly.

As a result, a fourth and fifth objective were added to the analysis:

- **The implications of Covid-19 on the present AMR agenda:** How might Covid-19 be impacting the emergence and spread of drug-resistant pathogens? Has Covid-19 affected the elements of a critical path to successfully tackling AMR?
- **The questions a future agenda must answer for a post-Covid-19 public health landscape:** How should the AMR agenda position itself vis-à-vis changed conversations on global public health, infectious disease, and preventive interventions to optimally pursue the goal of reducing morbidity and mortality from drug-resistant infections in humans?

To answer these questions, the viewpoints of more than 80 experts were captured in a series of workshops and interviews conducted throughout July and August 2020, augmenting the 2019 landscape analysis. The purpose of these interactions was to pressure test and reconfirm the validity of the 2019 findings in priority areas, partially (but not exclusively) in light of the ongoing Covid-19 pandemic. In addition, these workshops and interviews sought to capture the perspective of a broad set of senior national and global stakeholders across the global health architecture on how Covid-19 impacts the future direction of the AMR response. These responses are reflected in a separate chapter, 'The Implications of Covid-19', as well as in the perspective on a critical path forward and (where relevant) the sections on the individual themes and enablers in Appendix 1.

Key findings

Overview

Across the themes and enablers, several overarching successes and critical gaps in the global AMR response emerged through the conducted interviews. A summary of the themes and enablers can be found in Exhibit 2 (for detailed information on the success and gaps identified within each individual theme and enabler please see Appendix 1). This section begins by considering the historical momentum since the 2016 UN General Assembly Political Declaration and discussing the critical gaps found in the 2019 landscape analysis. A first perspective on the impact of Covid-19 is summarised at the end of the chapter.

Successes and positive momentum since 2016

AMR has achieved prominence on the global political agenda

AMR has moved from a largely technical topic to a political one – a key criterion for building an effective enabling environment that secures funding, awareness, and leadership. The Tripartite has been engaged on AMR since 2010 (and its constituent members, the FAO, OIE and WHO, earlier than that). Political attention has lagged behind this development, but it has significantly increased over the past 5 or so years. As a testament to this, AMR was first mentioned as a side note in the G20 Leaders' Brisbane Statement on Ebola in 2014, and has since become recurrent on the G20 agenda.

Experts agree that the 2016 Political Declaration served as an inflection point in the political attention AMR received. Awareness and ownership of AMR expanded beyond health policy stakeholders in a few high-income countries (HIC) to become a mainstream political issue of shared global concern.

At the global level, some of the momentum for taking action on AMR as a highest-priority political issue may in fact have waned since 2016 (see section on Global Governance). Nevertheless, political awareness of AMR as a high-impact threat to health remains. As one expert put it, "AMR is not simply a niche topic subsumed somewhere under 'public health'. Leaders recognise it as an important political issue in its own right."

The AMR community is a broad, multi-sectoral coalition of actors aware of, and willing to tackle, AMR

Among actors willing to tackle AMR, the commitment to a multi-sectoral approach is deeply engrained. This is evident in the breadth of participants and signatories of the major AMR conventions over recent years, including the 2016 Political Declaration and the 2017 and 2018 Calls to Action. It is also emphasised heavily in the IACG final report and in NAPs to address AMR.

Globally, the WHO, FAO, and OIE Tripartite has taken a joint leadership role on AMR governance. Interviewed experts were generally positive about the effectiveness of this interagency cooperation. The new AMR Multi-Partner Trust Fund was established in June 2019 to take an explicit One Health approach to disbursing funds to support countries in implementing their NAPs (as of September 2020, around $13 million has been committed[7]).

At the national level, NAPs emphasise a One Health approach, and frequently involve, at a minimum, human health and agricultural ministries to steer their development and implementation. The official logo of Switzerland's 2015 NAP (Strategie Antibiotikaresistenzen, or StAR) exemplifies this approach (Exhibit 3):

[7] Multi-Partner Trust Fund Office. Antimicrobial Resistance Multi-Partner Trust Fund Factsheet. UN Development Programme; 2020. http://mptf.undp.org/factsheet/fund/AMR00?fund_status_month_to=10&fund_status_year_to=2020.

Exhibit 3

At the research level, interest in AMR is dispersed across several fields as well. A substantial research agenda has sprung up around AMR in the environment, for example. Multiple research groups, including in the UK, Denmark, Sweden, and the US, attempt to demonstrate linkages between environmental contagion and human infection with resistant pathogens. Vectors include farm, factory, and hospital runoff.

Further, a wide range of actors representing all sectors, geographies, and industries are beginning to develop an awareness of AMR and respond to the challenge with a variety of interventions. Illustrative examples spanning various areas of the global response include:

- Over 350 organisations from across all sectors globally have signed up with a pledge or commitment to the US CDC's AMR Challenge.[8]
- Salmon farming corporations in Chile are working with the government to limit the need for antibiotics in fish feed.[9]
- The University of Southampton's Network on Antimicrobial Resistance and Infection Prevention has used poetry and drama to tackle AMR in Uganda[10]

Private sector engagement has been strong across multiple dimensions at the global level, and also at the national level in HIC; for example:

- The $1 billion AMR Action Fund was launched in July 2020 to invest in companies targeting novel AMR treatments as they enter later-stage development. Launched as a collaboration between private sector pharmaceutical companies and multilateral organisations, including the WHO and the European Investment Bank, the fund aims to bring two to four novel antibiotics to market by 2030.
- Pharmaceutical companies released a 2016 road map on AMR, later culminating in the AMR Industry Alliance, that included notable commitments on limiting antibiotic residue contaminating the water supply through manufacturing processes. On reducing environmental pollution, the Alliance has received mostly positive reviews from the Access to Medicine Foundation's detailed annual progress assessments of industry action (although they were more critical on progress against commitments to support access and responsible marketing practices). It points to broad participation and a transparent process for attempting to set self-imposed standards. Prior to Covid-19, few, if any, other global health topics received such broad attention among industry executives.
- In the UK, the Food Industry Initiative on Antimicrobials brings together food producers, processors, and retailers to transparently measure and reduce antibiotic consumption.
- In the US, new One Health Certified labels that promote the judicious use of antibiotics are being created thanks to voluntary industry coalitions.

[8] Centers for Disease Control and Prevention. The AMR Challenge. CDC; 2020 29 July. https://www.cdc.gov/drugresistance/intl-activities/amr-challenge.html.

[9] Based on expert interviews in 2019.

[10] Global Network for Anti-Microbial Resistance and Infection Prevention. University of Southampton; 2020. https://www.southampton.ac.uk/namrip/index.page.

How to sustainably increase private sector engagement across LMIC will be one of the key challenges for the AMR community going forward.

Some substantial differences persist, especially between human health and other areas. This is partially a result of targeting the prevention of drug-resistant infections in humans. Stakeholders across animal health and the environment point to stark differentials in funding for their respective sectors. The WHO's AMR budget of $41.7 million in 2018–19 was 35 per cent larger than the entire OIE budget of $30 million. Experts pointed out that the FAO's full-time human resource commitment to AMR was limited to two junior staff members.

Conversely, stakeholders across human health, animal health, and the environment describe difficulty in bringing environmental agencies and policymakers to the table. Nevertheless, engagement with AMR outside of its traditional human-focused global public health corner has been strong.

The translational research environment is robustly funded

Led by efforts in the US and the EU, significant additional funds have been made available for early research, especially on new therapeutics. Examples of actions since 2016 include:

- CARB-X, which has invested $240 million since its creation in July 2016, and aims to spend a total of over $500 million by 2021. Furthermore, 16 of the companies supported by CARB-X have raised additional investments totalling $850 million. Currently, there are 22 antibiotics, 4 vaccines, 6 diagnostic projects, and several other projects in its portfolio.
- The Novo REPAIR Impact Fund, established in early 2018, which has a total budget of $165 million and plans to invest $20 million to $40 million per year. It currently lists 9 candidates in its portfolio.
- Global Antibiotic Research and Development Partnership (GARDP), which has secured €66 million in funding for public–private partnerships to address gaps in antibiotic discovery and development across four key programmes.
- The Foundation for Innovative New Diagnostics (FIND), which has raised over $450 million since 2013 and spent $44 million in 2017 across its programmes in Tuberculosis, Malaria, HIV/HCV, AMR, and more. Most of the overall funding from FIND goes to AMR-sensitive efforts, with a smaller share going to AMR-specific efforts.[11]

Provided current funding levels persist, stakeholders involved in antimicrobial R&D increasingly note that a lack of capabilities and talent are the rate-limiting steps for the advancement of early-stage and discovery and translational research. This stands in contrast to later stages of development in which funding appears to be the primary constraint – see also below.

Overarching critical gaps

Activity has not always translated into impact

In recent years, and especially since the 2016 Political Declaration, there has been much global activity and discussion surrounding AMR, such as the 2017 push to increase the coverage of NAPs. This has led to substantial improvement in parts of the AMR response, such as awareness, funding, leadership, and coordination.

However, it has not translated into broader implementation of initiatives, especially in LMIC, where AMR competes for political attention and resources with other crucial public health topics that may constitute more immediate (and certainly more immediately visible) priorities. Most interviewees expressed concern that NAPs are in part a paper-filling exercise, especially when they follow the WHO template too closely without being adapted to

[11] Donations received per FIND annual reports up to the end of 2017, including commitments to be paid out between 2018 and 2022.

country specifics or provide limited data on costing and allocation of budgets.

In particular, actors outside of policy-making circles perceive that at its highest levels, the AMR community all too often represents a 'talking shop'. For example, the almost 3-year period between the establishment of the IACG and presentation of its recommendations is viewed by some as lost time, even if the consensus perspective on the results is positive (e.g. establishment of the Leadership Group and Independent Panel on evidence[12]).

As one specific recommendation for improvement, several experts mentioned the need for target setting. Importantly, target-setting exercises would go beyond *process* targets (such as tracking numbers of countries that have complete NAPs), and would advance to focus on *outcomes* (such as reductions in drug-resistant infections, or slowing trends of resistance development).

The AMR community must align on a focused, critical path to impact

One reason why implementation has lagged is a lack of prioritisation. While efforts over the past few years have comprehensively identified the important elements for addressing AMR, there is broad alignment that a strategic discussion about a critical path is urgently needed to better define the achievable steps that should be taken now. Otherwise, stakeholders across the AMR space are concerned that the multifaceted nature of the problem, the complexity of its narrative, and the multitude of possible interventions are holding back the community and preventing impactful action.

Aligning on a critical path involves prioritisation of resources and the sequencing of activities. Sequencing needs to be considered to maintain momentum and ensure political will over the long timeframe needed, but also because interdependencies exist across themes and enablers. For example, optimising human or animal use of antimicrobials relies on data on antimicrobial consumption, prevalence of infections, levels of resistance, etc to 'make the case' for AMR as a policy priority, identify areas for action, and measure the success of interventions. This in turn requires the setup of a comprehensive surveillance network producing detailed and actionable data, even though this system itself does not directly improve antimicrobial usage.

The AMR agenda was at risk of losing momentum pre-Covid-19 – making it important to capture the new momentum in global health with a clear post-Covid-19 AMR narrative

Experts expressed a collective feeling in late 2019 that the AMR agenda was at risk of losing significant momentum over the next 12 to 24 months unless it could demonstrate impact. Given the long-term nature of AMR and many of its interventions, concrete, tangible, and impactful successes need to be demonstrated to ensure that collective morale is upheld. With the overall lack of perceived impact mentioned above, stakeholders across the field were concerned about a fading sense of urgency and lower political will, which could be detrimental to the enabling environment for AMR responses. Declining priority of AMR on the political agenda may entail lower funding, and leadership and coordination of efforts may fragment.

It is important to recognise that this dynamic was felt strongly by several experts months before Covid-19 emerged. As such, it will be important for actors involved in the global response to AMR not to simply blame any waning of political interest on external upheaval, but to examine opportunities for demonstrating impact within the AMR agenda, and to maintain continued focus on a critical path. Several experts mentioned that there is potential for short-term, small successes, which should be

[12] Concerning the new AMR Multi-Partner Trust Fund, select experts were concerned how this fund would work in the context of UN reform and the Resident Coordinator approach (Resident Coordinators acting as a supposed single in-country representative of all UN country development activities in each respective country).

tactically considered in a broader strategic prioritisation along with the overall long-term impact. Such ‘quick wins’ must be able to demonstrate concrete impact and should address an issue of interest that is easily communicable to a wider audience outside of the global AMR community.

At the same time, Covid-19 has reshuffled the global conversation around public health and infectious diseases, and any future AMR agenda will have to contend with this new reality. Especially in light of a perceived risk of slowing momentum, this highlights the need for a focused new narrative for AMR in a post-Covid-19 world that can rejuvenate attention, resources, and action towards impact. The final section of this chapter highlights several questions that may collectively point to a first answer.

Critical gaps per theme and enabler

Critical gaps moving forward are summarised over the following three pages for each of the seven themes and nine enablers. Please see Appendix 1 for further detail.

Image:
Dave Sayer, Wellcome

Summary of priority gaps per theme

Themes		Priority gaps moving forward	
Reduce need & unintentional exposure	Human infection prevention and control	**Gathering data on IPC**	There is often insufficient data gathering around the adherence to IPC standards
		Implementation at the point of care	In-country public health experts voiced concern about guidelines at the national level that may not translate into clinical practice (e.g. in Pakistan) ▪ Additional experts criticise translating effective HIC IPC interventions to LMIC
		Strengthening community IPC interventions	Currently, IPC interventions are focused on healthcare workers and facilities, while surveillance experts point to an underappreciation of community health settings for AMR in general
		Strengthening the AMR-specific IPC response	AMR-sensitive IPC interventions may be the most effective way for the AMR community to benefit from existing attention to IPC and its global infrastructure
	Clean water and sanitation	**Funding for AMR-sensitive WASH interventions**	On AMR-sensitive WASH interventions ▪ WaterAid estimated in June 2019 that "at current rates of progress, everyone in [the] least developed countries won't have safely managed water until 2131 – more than 100 years behind schedule"
		Improved coordination and effective mainstreaming of AMR in the WASH agenda	Experts in the WASH community expressed frustration that while lip service is frequently paid to the effectiveness of AMR-sensitive interventions and their impact on promoting WASH, this is not followed up with implementation support or funding
	Food safety and security	**LMIC action**	There is a lack of regulation enforcement with respect to the use of antimicrobials in food-producing environments (agriculture, aquaculture, and horticulture)
		Data generation on food security	At present, there is no systematic data, or estimates of the scale of risks posed to food security by AMR, and accordingly an adequate risk scoping is needed
		Reductions in overall use levels in food-producing industries	The overall excessive level of antimicrobial use in crops, livestock, and aquaculture production remains a primary driver of resistance
	Environmental contamination	**Evidence on human health impact**	Conclusive evidence of the impact of environmental AMR on human health remains elusive creating impediments to policymaker buy-in
		Awareness of the environment as a reservoir of de novo resistance development	There is the additional challenge of investigating both the roles of *very high concentrations* of antimicrobials (e.g. pharma effluence) in *a few places* as well as *much lower concentrations* of antimicrobials (e.g. excreted antibiotics) *in many places*
		Awareness and implementation among private-sector actors	There is a general lack of awareness on the impact of various pollution sources (e.g. farms, hospitals, WWTP, and esp. Indian and Chinese Gx and API pharma manufacturers)
		Engagement of the broader environmental community	Multiple experts and policymakers express frustration with attempts to engage the UN Environment Programme in the global response to AMR
Optimize use of medicines	Human consumption of antimicrobials	**Low awareness and ease of procurement**	A lack of AMR awareness (including in HIC) is compounded by the fact that procurement is frequently possible without a prescription (due to or without the involvement of trained healthcare professionals) ▪ Additional, and better enforcement of existing, regulations on over-the-counter antimicrobial sales is needed
		Limited access to effective therapeutics	Global access to antibiotics is hampered by a lack of affordability, supply chain issues, and a complex regulatory environment ▪ Other issues include weak health systems and the reluctance of drug companies to register products in LIC where they do not see a market
		Behavioural changes supported by evidence	Experts also highlighted the need for behavioural changes at all levels of the antimicrobial stewardship landscape, across payors, physicians, and patients
	Use in animals	**Evidence base**	Although transmission pathways linking animal and human AMR have been clearly demonstrated, there are still gaps in the quantification of transmission rates and the impact of AMR-specific interventions ▪ Evidence on whether an 'x-point' reduction in antibiotic use in animals leads to anywhere near a similar magnitude reduction in human drug-resistant infections is absent
		Regulatory interventions	Regulatory interventions, or threats thereof, have proven the most effective intervention in HIC, often quickly followed by voluntary industry action ▪ Consumer expectations, as well as investor demands, can be complementary levers to encourage compliance with antimicrobial use best practices
		Increased attention to aquaculture	The use of antibiotics in aquaculture is mostly unregulated in countries that account for the vast majority of use
	Use in plants	**Data on scale of use and evidence on resistance development**	Systematic data on use, stakeholder mapping of supplies and purchasers, and estimates of the resistance burden is needed ▪ Additionally, data on resistance development and transmission, and the resulting impact on human health, are currently limited to mostly individual pathogens (such as *C. auris*)
		Awareness	There is limited to no awareness in the AMR and plant health communities, both at the international and domestic levels

Summary of priority gaps per enabler (1/2)

Enablers		Priority gaps moving forward	
 Innovation	Vaccines (development and access)	**Lack of funding for R&D**	As with novel therapeutics and diagnostics, expected returns are low and uncertain, while there are limited incentives to promote investment and R&D activity ▪ Public-private partnerships with market guarantees for high-quality vaccines are an important mechanism to spur action
		Barriers to access and uptake	Major factors include: ▪ LIC: poor overall health systems, insufficient supply chains, and inadequate data collection systems lead to stock-outs ▪ MIC: the transition away from international financial support (for example, from Gavi), poses a significant challenge as the country moves past income eligibility ▪ Vaccine hesitancy and low patient adherence to schedules can lead to low coverage, even in HIC such as the US
	Medicine quality	**Lack of relevant data**	There is very limited data available on the prevalence of substandard and falsified medicines, as well as on the quantitative impact of such medicines on infection and resistance rates ▪ There is also insufficient funding ▪ And there is almost no information on the quality of veterinary drugs
		Weak regulatory authorities	National regulatory agencies and relevant regulations need to be strengthened and enforced; this includes ensuring good manufacturing practices with monitoring and inspection of production sites
		Lack of a holistic view on quality impact in decision making	In purchasing decisions, price is often the dominant factor for both funders and MIC health systems ▪ To address this, a holistic assessment of the total societal and economic cost of low quality against low purchasing costs is required and needs to involve multidisciplinary input from health economists, epidemiologists, etc.
	Clinical trial networks		Overall, clinical trial capacity and capabilities are simply insufficient ▪ Recent activity in the US and Europe and, to a lesser degree, in South-east Asia and Africa, is on the right trajectory ▪ However, the set-up of clinical trial networks is likely to be a multi-year process with significant impact on overall R&D cost functions several years out; experts also mention the difficulty in finding new sites with sufficient quality standards and skilled personnel to meaningfully expand networks without diluting quality ▪ In addition, the existing network expansion plans are geographically limited
 National action		**Implementation in LMIC**	NAPs have not equated to national action in many, but not all, LMIC ▪ Concerns exist that even where NAPs are present, some countries are conducting 'copy-and-paste' exercises from global action plans ▪ Additionally, experts highlight that almost no LMIC have successfully implemented their NAPs at scale without an external injection of funds
		Coordination and inclusion of all relevant actors	Challenges exist across all country segments: ▪ The process of drafting NAPs in LMIC commonly fails to bring all relevant actors to the table ▪ In MIC, attention to AMR from the human health communities is usually present, however, this does not necessarily translate into funding or political will ▪ In LIC, this attention may be less apparent due to more immediate public health concerns, and, as a result, levels of national engagement diverge widely
		Upward feedback loops from national to global level	Most information on interventions and best practices cascades downward from the global to the national level ▪ In addition, LMIC experts reported a persistent perception that the global response to AMR is driven by a small group of mostly HIC countries, with little room for LMIC to shape the global agenda
		Redefining the NAP narrative: Data and story	There is a clear need for a compelling narrative to 'sell' the story on AMR ▪ Given that no convincing narrative has emerged since the 2016 Political Declaration, some experts noted that there is a potential opportunity to frame AMR in the 'language of pandemics'
 Global governance		**Focus and prioritisation**	The complexity of the AMR landscape, combined with a dearth of evidence allowing policymakers to quantify the relative contribution to resistance of different themes, has led to a state of paralysis – the metaphorical 'deer in the headlights' ▪ Consequently, some prioritisation of actions is now needed to prevent sleepwalking into a crisis where the collective level of belief in its urgency has not been matched by impactful action
		Losing momentum	The current global response to AMR appears firmly lodged on a plateau following the 2016 Political Declaration and the COVID-19 pandemic
		Achieving accountability	Experts disagreed to what extent an insufficient global governance response has been a failure of resourcing (which, they generally agreed, is insufficient) or, at a more fundamental level, of political will ▪ Political will can be conceptualised into three levels of hierarchy (championing, funding commitments, and accountability), with AMR not reaching the final stage of accountability in almost any setting

Summary of priority gaps per enabler (2/2)

Enablers		Priority gaps moving forward	
 **Surveillance (incl. laboratory capacity)**		**Transforming surveillance data from informational to analytical and predictive**	Experts highlighted the gap between how surveillance data is currently used and the potential for its use ▪ There is an opportunity to use data to proactively improve clinical decision making (i.e. empirical prescribing) and to help national/regional governments predict areas of emerging resistance
		HIC: Set of surveyed focus pathogens may miss critical burden of disease or resistance	Selection of focal pathogens frequently occurs opportunistically, based on global trends not local resistance patterns, and surveillance systems are heavily biased towards hospital settings ▪ Experts pointed to two critical consequences: first, a systemic problem with missing the true burden of resistance or disease; and second, HIC surveillance systems may fail to detect large-scale resistance developments early enough
		LMIC: Inability to make the case for AMR as a policy issue due to lack of data	The lack of resources, capacity and capabilities (such as lab capacity, technicians, surveillance sites, and healthcare professional education) entails a lack of surveillance data ▪ Consequently, national AMR priority levels are often decided by the presence or absence of individual 'champions' rather than systematic needs
		LMIC: Inability to monitor progress	A lack of data hinders progress monitoring, which in turn limits knowledge of which interventions are effective and which are less so
 **Innovation**	**Discovery and translational research**	**Capabilities and talent**	Shortage of experienced researchers with skills and knowledge in infectious diseases ▪ There is a lack of capabilities in translational science (i.e. the transition from academic research to drug development during pre-clinical development) ▪ Experts expect that such shortages will only intensify in the context of the COVID-19 pandemic and are especially worried about the 'lock-in' implications of junior researchers specialising in viral infectious diseases instead of AMR
		Leadership and coordination	There is no demand for centralised global coordination (especially given the broad and dispersed nature of research activities), yet loose coordination efforts are helpful with regard to steering the pipeline, promoting a broad coverage of pathogens, and aiming for more innovative approaches (such as new targets and modes of action)
	Diagnostics (development and access)	**Technological challenges**	While the science of in-vitro diagnostics has progressed significantly, there are still technological challenges to producing the holy grail of a rapid, affordable, and effective point-of-care diagnostic device
		Business case for developing new diagnostics	The field lacks a viable business model to sustain diagnostics innovation ▪ There is a lack of investment due to weak commercial returns ▪ There are significant development costs, but only limited push funding especially for late-stage development, and no large pull-incentive on the horizon ▪ Changes in reimbursement plans are needed to promote the use of diagnostics and incentivize their further development
		Unclear way to address barriers to uptake and effectiveness of new diagnostics	Even if new, rapid, affordable, and effective diagnostics are developed, there are behavioural barriers to their uptake ▪ Use of current diagnostics are more expensive and time-consuming than direct treatment with antibiotics, limiting both wide use and access ▪ Even if diagnostics are used, improved guidelines are needed to increase adherence and improve stewardship – Healthcare professionals may still inappropriately prescribe antibiotics (e.g. due to patient pressure)
	Therapeutics (development and access)		An R&D ecosystem capable of supporting the development and commercialisation of drugs against a variety of pathogens is required; such an ecosystem would need to include: ▪ A viable business model for sustainable antibiotics research ▪ A global pull incentive to incentivize R&D investment ▪ Increased funding for the clinical development stages of drug development (i.e. the most resource-intensive stages) ▪ Expanded coverage of LMIC priority pathogens, such as *A. baumannii* or shigella infections ▪ A regulatory framework for pathogen-specific label expansion rather than the current indication-based approval process

The impact of Covid-19

Overview of findings

Covid-19 has radically altered the global conversation on public health. At the time of writing, it has led to close to 1 million officially recorded deaths,[13] likely years-long suffering and heightened morbidity for millions more, and countless individuals experiencing severe disruption to their lives and livelihoods.

Experts universally agreed that such large-scale change naturally affects several aspects of the global response to AMR. Yet in speaking with experts throughout the summer of 2020 about the effects of Covid-19 on AMR, one thing quickly became clear: the jury is still out on the nature of this eventual impact on the AMR agenda.

As such, the broader picture of the effects of Covid-19 remain in flux, and few points of consensus emerged from expert conversations. The below paragraphs attempt to reflect upon the different views (and the detailed justifications) experts offered. They do not attempt a similar degree of synthesis or identification of priority actions as in the broader landscape. In large parts, this is the result of a different approach: while the original landscape attempted to interview a very broad cross-section of the AMR community following a clearly defined interview structuring and scoring methodology, our interviews on the implications of Covid-19 – while equally rigorous regarding representation across sectors, geographies, and genders – were necessarily more open-ended and exploratory conversations (please see the methodology section in Appendix 2 for additional detail). Hence, the findings should be taken with a note of caution, and not confused methodologically with the findings of the original landscape.

Covid-19 will affect the global response to AMR in at least two ways: the acceleration or mitigation of resistance development itself, and the broader attention it receives on a policy level, including funding, advocacy, and research. Regarding the former, Covid-19 has exerted *both* upward and downward pressure on resistant infections through several mechanisms (e.g. experts observed increased use of antibiotics in inpatient settings, but decreased use in outpatient settings) – but the net effect remains to be seen. Regarding the latter, experts broadly agreed that the policy fallout from Covid-19 brings both risks and opportunities for the goal of a world better protected from drug-resistant infections. Opportunities may include increased understanding of IPC, increased surveillance and lab capacity (and awareness of its importance), or even a clearer pathway into finance ministries for preventive healthcare conversations. Yet risks, including stopped hospital surveillance programmes, young research talent too often diverted towards viral infections, or a decrease in the availability in funding for the global health agenda, may harm the response.

Yet the AMR community is not simply a 'taker' on the latter set of effects – it has the opportunity (and perhaps necessity) to actively shape the narrative of AMR in a post-Covid-19 global public health conversation. On how a single, unified narrative most beneficial to reducing morbidity and mortality from drug-resistant infections in humans should look, experts noted that there is a spectrum of choices as to how to position AMR on the global health agenda, bookended by two diametrically opposed positions. Several proposed a 'big tent' agenda focused on pandemic preparedness or even infectious disease risks as a whole, into which AMR is fully integrated. A similar number of voices suggested the opposite, citing AMR may be poorly served by narratives focusing around rare, low-probability events such as pandemics, or concerns around the feasibility of attempting to integrate the two.

The impact of Covid-19 on pathogen resistance

Experts agreed that evidence on the impact of Covid-19 on pathogen resistance was in the early stages, with limited data and even less robust analysis of what data is available. In their early assessments, even the directional or net impact of Covid-19 on pathogen resistance remains unclear: several factors exert upward pressure while others exert downward pressure and may even balance each other out; moreover, clear evidence is not yet available.

[13] As of September 2020: Johns Hopkins Coronavirus Resource Center. Covid-19 Dashboard. Johns Hopkins University & Medicine; 2020. https://coronavirus.jhu.edu/map.html.

Experts identified several developments that likely exert increasing pressure on resistance development. First and foremost was the standard treatment protocol across countries – spanning low-income countries (LIC), middle-income countries (MIC), and HIC – to prescribe broad-spectrum antibiotics to any patient presenting with Covid-19 symptoms out of a concern for bacterial co-infection, naturally resulting in a large number of prescriptions for a set of patients that may not have needed them in a counterfactual non-Covid-19 world. This protocol is in place despite significant uncertainty around the incidence of bacterial co-infection (cited estimated ranging from 7% to 50%), and significant regional differences – accordingly, it is clear that more data and research is required. Additionally, the absence of policy attention and funding for other global health issues, as well as specific capacity-limiting steps – such as the repurposing of GeneXpert machines for diagnosing drug-resistant Tuberculosis – will lead to the further spread of already-resistant pathogens (Tuberculosis being a prime example).

At the same time, there may be some downward pressure on antibiotic use in humans, possibly leading to downward pressure on resistance development. Following fears of catching the virus (and overwhelming healthcare facilities), the reduction in primary care visits and postponement of routine medical procedures may result in fewer patients presenting overall. Experts pointed towards drops in patient visits in community settings especially, which by some estimates accounted for around 80 per cent of antibiotic prescription volumes pre-Covid-19 (although this effect is partially compensated by the increased use of telemedicine, which can result in more prophylactic antibiotic prescriptions due to the lack of opportunity to run diagnostics in remote environments). In addition, one expert mentioned the expectation that community transmission of resistant pathogens, especially where sexually transmitted infections are concerned, will have reduced in lockdown and socially distanced settings. Finally, increased awareness of hygiene and infection control practices will further limit pathogen transmission more broadly, including of resistant pathogens. Evidence of this has already been seen with decreased case reports of influenza during Australia's 2020 flu season.

Opportunities

- **Elevated status of healthcare funding and innovation financing:** The global attention to pandemic-potential health threats – and the quantifiable economic disruption – brought by Covid-19 has forged a closer link between health and financing. Several experts expressed hope that aggregate funding for preventive healthcare interventions may increase, but also that health security threats, defined broadly, will now achieve prominent positioning on generalist policy and treasury agendas rather than being regarded as technical or specialist topics. Simultaneously, Covid-19 has forced healthcare policy makers, such as ministries of health, to accept the role of financiers of *innovation* – previously not regarded as their core area of expertise or comfort (e.g. compared to delivery). Such a renewed mindset may support overcoming the challenges that AMR therapeutics and diagnostics have faced on market-based innovation.
- **Expanded laboratory capacity and surveillance:** The focus on Covid-19 diagnostics has rapidly expanded laboratory capacity in many countries. Repurposing this capacity towards AMR and other infectious diseases, rather than decommissioning it, may be one of the primary opportunities for the AMR community to leapfrog years of arduous progress onto one discrete enabler of the response. This is complemented by reinvigorated and more mainstream excitement about the promise of pathogen-agnostic detection systems, especially through metagenomic sequencing, which may be of substantial benefit for detecting emergent hotspots.
- **Improved infection prevention and hygiene:** Covid-19 has expedited several AMR-sensitive interventions, especially in the IPC and WASH fields. Public health messaging beneficial to broader infection prevention programmes has been elevated from technical guidance documents to government messaging and wide, free dissemination through Facebook and other technology platforms. It is possible that the lower incidence of seasonal influenza in Australia could be a result of this increased attention on hand washing and mask wearing for those showing cold symptoms.

Risks

- **Funding cuts due to aggregate fiscal constraints:** While pandemic preparedness and healthcare innovation funding may increase in prominence, Covid-19 is likely to have detrimental effects on aggregate government expenditure in many or most countries. The net effect on funding for the AMR agenda remains to be seen. Aggregate fiscal constraints may result from two economic elements. First, Covid-19 has already substantially impacted economic productivity, and this will affect the overall financial position of governments, limiting revenue and putting downward pressure on their spending. The Organisation for Economic Co-operation and Development (OECD) notes that regardless of whether there is a fall 2020 surge in infections, global GDP will take at least 2 years to recover to its Q4 2019 levels.[14] Second, given the massive financial outlays by national governments to date, and the decreasing economic productivity mentioned above, national deficits will continue to grow, further limiting fiscal room for manoeuvring. One estimate projects an aggregate global deficit of $9 trillion to $11 trillion in 2020, and a $30 trillion shortfall by 2023.[15] As a point of comparison, the current fiscal measures taken by the G20 nations to address Covid-19 amount to around 11 per cent of their aggregate GDP – a figure three times what it was during the 2008–09 financial crisis.[16]
- **Research priorities shifting disproportionately towards viral infections:** The focus that Covid-19 has placed on viral threats – supported by conversations of a Covid-19 vaccine as a panacea to reopening societies – leads several experts to predict an overcorrection of the infectious diseases agenda away from bacterial (and other, e.g. fungal) threats towards viruses. This may express itself in innovation funding diverted towards vaccine platforms in the short term, but also more subtly, like in junior research talent and PhD funding becoming overly virus-focused.
- **Resource constraints for implementation:** The intense strain of deploying people and systems to respond to Covid-19 poses a risk to past achievements on AMR, both at the healthcare facility and policymaking levels. AMR-specific activities that do not offer immediate benefit to Covid-19 patients are likely to fall by the wayside or be viewed as expendable in times of crisis. Several interviewees pointed out that hospital surveillance activities tracking volumes of antibiotic prescriptions, such as Global-PPS, have been "almost completely abandoned". Others noted the unfortunate temporal coincidence that many 5-year NAPs, drafted around 2016, should now be entering an evaluation and updating phase to produce a subsequent round, but are instead likely to be put on the back burner in resource-constrained health ministries.
- **Ineffective stewardship:** The broader impact that Covid-19 will have on prescription practices remains a significant uncertainty, but experts pointed to it as an area of potential risk. Specifically, the vast shift to telemedicine that HIC have experienced since the onset of the pandemic limits the effectiveness of stewardship measures, as physicians cannot conduct anything but empirical diagnosis for remotely evaluated patients.
- **Challenges to advocacy accessibility:** Covid-19 also raises practical challenges; multiple stakeholders from the private and social sectors mentioned that remote working increased the difficulty of making the case for AMR to policymakers, due to fewer opportunities to 'be in the room'.

Perspectives on positioning the future AMR agenda vis-à-vis a changed infectious disease and pandemic preparedness landscape

The framework in which actors working to mitigate AMR operate will change drastically; experts agree on this conclusion based on the expectation of a significantly altered global infectious diseases landscape and conversation post-Covid-19. There is a clear need to rethink how the AMR agenda positions itself in order to take an active role in

[14] Organisation for Economic Cooperation and Development. A collapse in output followed by a slow recovery. OECD Economic Outlook: Statistics and Projections (database) 2020;107(1). https://oecd.github.io/EO-Outlook_chart_2/.

[15] Assi R et al. The great balancing act: Managing the coming $30 trillion deficit while restoring economic growth. McKinsey & Company 2020 16 June.

[16] Ibid.

shaping this new global environment, and clearly communicate this to the broader audience of policymakers engaged in a more mainstream health security and pandemic preparedness dialogue.

This raises the question of what such a new global environment may look like. Broadly, experts perceived three (perhaps overlapping) possibilities:

- **The status quo of a limited, technical, and niche pandemic preparedness and recovery agenda**
- **An expanded pandemic preparedness and recovery agenda,** firmly in the mainstream of political and social attention, and funded accordingly
- **A much broader, revitalised infectious diseases agenda** that focuses on preparedness and response to novel pathogens in tandem with tackling existing endemic and pandemic diseases (e.g. Tuberculosis and HIV)

Crucially, experts were broadly confident that the first option was less likely than the other two – and **the below perspective on a new agenda accordingly assumes that such a paradigm shift will happen.** Whether this will focus more narrowly on pandemic preparedness and response or broadly on infectious diseases cannot be predicted at this stage, and this could affect the positioning of AMR.

Yet experts noted that while there is a spectrum of how this positioning should look, there are diametrically opposed views. Interestingly, the split, as expressed in conversations and workshops on the topic, proved to be roughly even throughout, with no group conversation resulting in one side clearly convincing the other. Broadly, three perspectives stand out, the latter two of which reach the same conclusion, albeit as a result of different reasoning:

- **The AMR agenda should tie itself to an inclusive pandemic preparedness and response agenda:** On one side is the option of a broad, inclusive health security and pandemic preparedness and response agenda, with AMR as a fully integrated subpart. In this scenario, the response to AMR would tie its fate (as measured in resourcing and policy attention) closely to an anticipated accelerating focus on emerging infectious disease threats post-Covid-19. This may entail losing some of the specificity of AMR interventions, but may allow access to much broader pools of healthcare financing.
- **The AMR agenda should remain distinct because AMR is better served by distinctive narratives:** On the other side stands the opposite suggestion – but, crucially, for two different reasons. This first camp believes the response to AMR is *better served by distinctive narratives*. For instance, the impact of AMR is far more certain and tangible than a hypothetical future pandemic, and requires immediate measures safeguarding patients at risk of catching resistant infections as opposed to reliance on an 'expected value' narrative on the benefits of taking action.
- **The AMR agenda should remain distinct because linking AMR to a broad pandemic preparedness agenda is not feasible:** Others believe that tying AMR to a post-Covid-19 infectious diseases or pandemic preparedness and response agenda is not *feasible:* differences between the two topics are too large for policymakers and the general public to make the link. At the most basic level, linking viral to bacterial (or e.g. fungal, which is even more abstractly related) threats may prove counterintuitive for non-specialist and non-scientific audiences. This is exemplified by the public focus on a vaccine as the panacea for Covid-19, compared to the much smaller role of vaccine-based solutions for AMR (see also the deep dive on vaccines in Appendix 1).

Questions to chart a path forward: Given this broad spread in perspectives, there are several open questions that should urgently be answered to enable a common path forward for those working to mitigate AMR:

- **Which perspective is best supported by available evidence and information?**
- **Which perspective can established actors in the current AMR community align on?**
- **Which perspective resonates with external decision makers and potential funders?**
- **How, where, and to whom should a newly repositioned AMR agenda be communicated?**

Given the perception that the AMR agenda was at risk of losing momentum even before Covid-19, and its subsequent disruptions, starting a broad exploratory dialogue sooner rather than later on which perspective best mobilises resources for the continued response to AMR may be imperative.

First perspective on a critical path forward

Overview

This section sketches a first perspective on what a critical path for the global response to AMR could look like and does not represent a comprehensive AMR strategy.

- **Making themes and enablers actionable:** In a first step, the themes and enablers are grouped into different types of actions that the AMR community can take to limit the impact of drug-resistant infections, ranging from decisive commitment of resources to advocacy.
- **Long-term considerations of actions:** Given the long-term nature of the AMR response, shifts in these types of actions as certain interventions are implemented over time are considered as well.
- **Possible prioritisation of themes and enablers:** Next, the themes and enablers are prioritised by impact and feasibility, to encourage focusing actions – as identified in the first two sections – on a critical path. Importantly, this path may look different for different actors pursuing different pieces of the AMR agenda.
- **Focusing on the appropriate implementation level:** Finally, this section reviews implementation through global, intergovernmental, and (sub-) national action.

This first perspective emerges from the interviews and document analysis conducted as part of the landscape. Necessarily, however, translating this into a sketch of a critical path involves additional interpretation of the results. This section attempts to evaluate and synthesise the available evidence in an unbiased way. Nevertheless, this section does not aspire to the same degree of external validity as the preceding one on key findings. It represents a conclusion to the landscape analysis, but simultaneously serves as a starting point for more in-depth discussion and assessment.

Making themes and enablers actionable

Across the full set of themes and enablers, the roles, resources, and capabilities of the AMR community vary widely. Keeping in mind the need for actionability, there are distinct types of actions, into which themes and enablers can be grouped, ranging from significant resource commitments for AMR-critical fields to advocacy and alignment with adjacent communities in AMR-sensitive areas.

The below grouping represents **no order of priority**[17] or significance. Some themes and enablers fit into more than one group, however. Naturally, which are the appropriate actions – especially as they interplay with other segments of the global public health landscape – will be heavily impacted by the answers the AMR community finds to the questions on a new narrative raised by Covid-19, as stated above. Exhibit 4 allocates the most appropriate action(s) to each theme and enabler under the assumption that a distinct AMR policy agenda of some format will remain post-Covid-19.

Advocate for and interface with respective communities

In AMR-sensitive fields like **clean water and sanitation, IPC** or **medicine quality,** the AMR community should map out critical interfaces to its respective communities and align on a set of clear messages together. In these areas, the AMR community is not a leading stakeholder, but can realise positive externalities by mainstreaming AMR issues into existing agendas. A practical intervention could be reasonably senior representation of the AMR community at key meetings of other thematic communities. In IPC, this is already occurring at the WHO level, with a focus on hand washing. In clean water and sanitation, WASH initiatives in healthcare facilities may prevent hospital-acquired infections, which represent a significant share of the AMR burden (over 60 per cent of the AMR disability adjusted life year burden in Europe in 2015[18]).

Lead the field

The most critical AMR-specific fields warrant significant attention and resource commitment to drive the implementation of known or new solutions. This includes the priority areas of **therapeutics,**

[17] Centers for Disease Control and Prevention. Global WASH Fast Facts. CDC; 2016 11 April. www.cdc.gov/healthywater/global/wash_statistics.html.

[18] Cassini A et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: A population-level modelling analysis. The Lancet Infectious Diseases 2019; 19(1):56–66.

surveillance and optimising human consumption of antimicrobials, which have the potential to significantly impact the reduction of human drug-resistant infections, with less uncertainty than other interventions. The AMR community is clearly considered the leader in these topics and best placed in terms of expertise and capabilities to drive improvements. Importantly, on the former two priority areas, the AMR community should actively engage the resources (e.g. laboratory capacity) and attention brought about by Covid-19. But unlike WASH or IPC intervention, for example, capturing their benefits for the AMR response requires AMR-specific action, such as ensuring the right surveillance indicators are tracked, or innovation funding considers antibiotics.

Support implementation of solutions

There are less critical AMR-specific areas, which warrant some attention and resources to support implementation. **Translational research and clinical trial networks** are important enablers. Yet given significant existing efforts and/or funding mechanisms, they may be of lower focus relative to priority areas.

Conversely, for **diagnostic** innovation, feasibility is a significant hurdle that is unlikely to be overcome in the near term. This is due to the complex challenge of creating affordable and rapid point-of-care diagnostics while simultaneously addressing market failures – with business model and reimbursement innovation a core part of reducing structural challenges – and barriers to uptake. Still, given the high potential impact of the field, some effort should be committed to ensure the ability to capitalise on any catalytic breakthroughs.

Finally, **use of antimicrobials in animals** could have significant impact on human drug-resistant infections and can be reasonably well addressed. However, it still requires a more solid fact and evidence base.

Generate evidence

For **quality, environmental contamination, food safety and security, and use of antimicrobials in plants** (and to some degree **vaccines**), a lack of quantitative evidence is the main hurdle to action – and this uncertainty complicates alignment on their priority for action. Therefore, the focus of investment should be around evidence generation, such as on prevalence of substandard drugs, transmission rates or pathways of resistance. As mentioned above, the prioritisation of these areas could change substantially if the definition of impact is expanded beyond reducing human drug-resistant infections.

Long-term considerations of actions

When identifying a critical path to action, appropriate sequencing of themes and enablers is necessary, given their interdependencies. In addition, as interventions play out and parts of the AMR ecosystem improve, the long-term priorities and required actions per theme or enabler will change, as depicted in Exhibit 4.

Rather than laying out a detailed road map, the present sketch distinguishes three broad groups along two time horizons. Until 2030, depending on the expected impact and feasibility (see Exhibit 5), appropriate actions may be to:

- **Boldly combat risks:** In those fields where expected impact is high *and* maturity of evidence to support the response is high, a priority during the next decade is likely to either directly lead the field, or, in activities with greater AMR-sensitive demand such as IPC or WASH, to advocate for the priority of AMR within them.
- **Learn and build:** For those fields with less of a directly established evidence base, or lower impact on resistant infections in humans specifically, generating further evidence and supporting implementation of existing initiatives may be the most promising path in the near term.

It is difficult to predict where the global response will stand by the start of the period from **2030 to 2050**. Nevertheless, the likely focus will be to **maintain systemic response and prevention.** After that initial timeframe, if surveillance, IPC, and WASH infrastructure are established, their focus will move towards maintenance, decreasing priority and resource requirements as a result. Depending on the outcome of research, themes previously in the 'generate evidence' category may shift into the 'advocate', 'lead the field' or 'implement support' categories.

Shift in actions depending on time frame

Exhibit 4

Possible prioritisation of themes and enablers

A high-level perspective on prioritisation is given by assessing themes and enablers based on their **impact** to reduce or avoid human drug-resistant infections, and the **feasibility** of such impact.[19]

Impact is defined as reducing or avoiding morbidity and mortality from human drug-resistant infections, instead of more expansive targets, such as improving human health or well-being overall. For example, food safety and security may score higher on impact from a broader human welfare perspective.

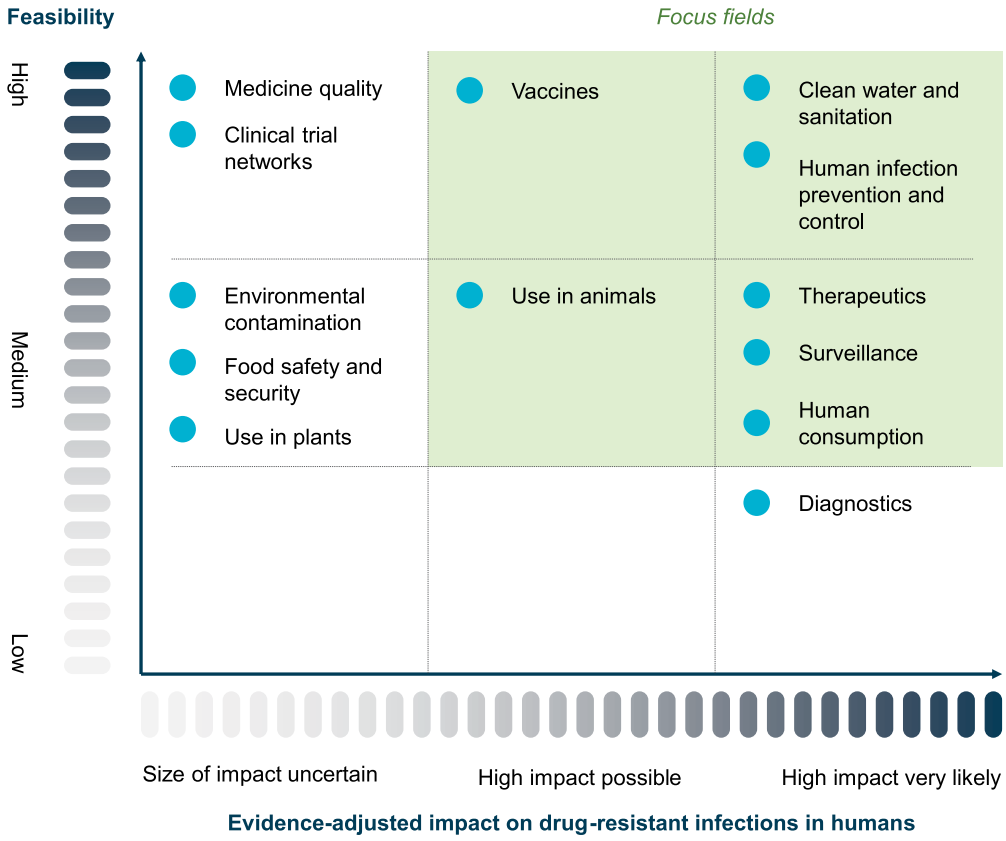
Feasibility refers only to the role the AMR community plays within the theme or enabler, including time, money, or effort required. It does not include any resources required from actors other than those focused on pursuing an AMR agenda (e.g. WASH resources to deliver on the overall WASH agenda). It estimates whether action to decisively advance the field would be feasible in the near term, not taking into consideration major shifts in the enabling environment (e.g. an influx of resources post-Covid-19, as it remains unclear in what form this would benefit the AMR agenda; see previous chapter).

[19] National action, global governance and discovery, and translational research are treated separately (see also the section 'Focus on the appropriate implementation level' below), given these enablers' special role as the lynchpin delivery mechanisms for all other themes and enablers.

Prioritisation of themes and enablers

Exhibit 5

Assessment matrix



Applying this framework to the findings from each theme and enabler yields several focus areas. Focus areas are selected following a **precautionary principle** approach: all fields where high impact is either very likely or very possible but yet to be confirmed, and where it is feasible (in the current environment) to achieve major steps towards impact in a timely fashion, are in focus.

- **WASH:** WASH improvements reduce human infection rates directly at both the healthcare and community levels and are expected to be highly cost-effective. The CDC cites estimates of "economic benefits ranging from $5 to $46 per $1 invested" across all regions.[20] In addition, water is increasingly studied as a significant transmission mechanism for resistant pathogens.
- **IPC:** IPC interventions highly impact human drug-resistant infections directly by preventing infection with resistant pathogens and indirectly through reducing the need for antimicrobials. In addition, they are generally cost-effective and simpler to implement than other themes or enablers. Compared to therapeutics, vaccines, or diagnostics, basic IPC interventions are less complex to introduce. Unlike those in animal or plant use, IPC interventions are also less controversial, as they do not inflict losses on the actors directly involved[21] (i.e. healthcare

[20] Centers for Disease Control and Prevention. Global WASH Fast Facts. CDC; 2016 11 April. www.cdc.gov/healthywater/global/wash_statistics.html.

professionals, patients, public health officials), which may significantly lead to behaviour change.

- **Therapeutic innovation:** Sustained therapeutic innovation is critical for keeping up with the continuing emergence of new resistance and to have treatment options going forward. It thus represents one of the highest impact opportunities. However, innovation is expensive and time-consuming, while facing fundamental economic challenges. Potential interventions should be perpetual where possible due to the constant evolution of microbes. At the same time, given the intense scrutiny therapeutics have received in the field of AMR, potential interventions are relatively clearly defined and sized (e.g. market entry awards). However, not all elements needed to enable sustained therapeutic innovation are currently in place.
- **Surveillance:** Adequate surveillance is the lynchpin of an effective policy response to AMR. Knowing the extent of the overall AMR burden, resistance levels of different pathogens to different antimicrobials, development over time and geographical differences are necessary preconditions for designing and targeting interventions. Especially in LMIC, national AMR champions consistently describe the difficulty of making the case for AMR as a political priority without adequate surveillance data. Generally, surveillance is feasible from a technical view, and clear processes and supporting tools exist, such as the WHO's guidance on country implementation of the Global Antimicrobial Resistance Surveillance System (GLASS). However, quality and coverage remain a challenge in LMIC due to a lack of infrastructure and expertise.
- **Human consumption:** Ensuring appropriate human use of antimicrobials is a high-impact priority, given the direct link between antimicrobials use and resistance development in humans. This includes ensuring both adequate access and comprehensive stewardship mechanisms. The feasibility of influencing human consumption of antimicrobials is more difficult to assess. While reducing inappropriate consumption may require fewer financial resources than therapeutic innovation, for example, the complexity of the underlying incentive structures and behavioural patterns present a challenge.
- **Vaccines** (especially in the longer term): Vaccines prevent infection and transmission and play an important role in reducing antibiotic consumption and preventing infection in both humans and animals. As such, they constitute a critical investment in the longer-term AMR response. While the case for vaccines to support the response is clear in principle, more and better evidence (e.g. on the reduction of antibiotic use and the transmission of drug-resistant pathogens) is needed to mobilise investment, particularly with regard to vaccines for pathogens that are of priority concern from an AMR standpoint. The AMR community tends to see vaccines as more of a long-term priority that is not necessarily critical in the short to medium term. The vaccine community is embracing how the impact of vaccines on AMR strengthens the case for vaccination (e.g. pneumococcal conjugate vaccines specifically, and also more generally); however, experts question to what extent resources should be diverted from existing innovation and access priorities to previously non-prioritised AMR-specific vaccines.
- **Use in animals:** Taking a holistic perspective on the response to AMR by including other topics across the One Health spectrum is essential to a response that is preventive, not just focused on treatment. Hence, even a target of reducing drug-resistant infections in humans requires considerations around ensuring that using antimicrobials in animals is appropriate, and reducing their aggregate amount. Use in animals significantly exceeds use in humans, with estimates reaching up to 80 per cent of total antibiotic volume administered. Furthermore, antimicrobial use in animals is expected to be one of the fastest-growing segments, as aquaculture grows and an increasing part of the global population demands affordable meat consumption. Finally, use in animals – in aquacultural and farm runoff – can have significant second-order impact on environmental contamination with antimicrobials.

Additional detail on the relative criticality of gaps in each of these themes and enablers can be found in their respective detailed profiles in Appendix 1.

[21] It may, however, limit drug companies' revenues if demand for drugs drops.

Focusing on the appropriate implementation level

At what level can the sketched actions – especially the focus fields – be effectively implemented? This point is contested within the AMR community. The below section synthesises expert views on the appropriate implementation level, **suggesting a focus** on n**ational action,** especially in **MIC**.

Generally, there are three different levels [22] of implementation for AMR activities:

- **Global AMR governance** is seen by a broad range of experts and public health leaders as having produced activity that has not yet translated into impact (see section on critical gaps above). As such, global AMR governance has seen a **relative loss in importance in the view of most interviewed experts** versus other possible levels of implementation. It remains to be seen if the implementation of the IACG recommendations can reverse that trend.
- **Multinational action** presents the second pillar next to the global agencies and has been the primary driver for international action to date. Importantly, multiple experts in national and global policy positions lament having been forced to realise simply how dependent the advancement of global AMR governance was on the leadership shown by the UK and US prior to 2016. The almost simultaneous shift in geopolitical priorities in both countries since 2016 was described as a 'double whammy',[23] dealing a significant blow to the potential for coordinated multinational action on AMR. This context has led experts to **question which coalition of countries and what multinational action is likely to drive the global response going forward.**
- **National action** is the locus for delivering change in the systems which can achieve the goals of the AMR agenda, and **is widely considered to be the most critical element of the global AMR response in the years to come.** Effective national action will include the policy level, but necessarily also non-governmental and civil society actors such as research institutions, healthcare and veterinary professionals, food producers and processors, etc. **While national-level action has been successful in many HIC, action in LMIC has not kept up,** especially not from a full One Health perspective.

From a critical path perspective, **the national level appears to be the most important of the three for driving the AMR response.** National action needs to consider both the overall priorities in the global response, as well as specific national challenges and gaps. Given that national action has been (or is in the process of being) successfully implemented in many HIC, LMIC national action is significantly behind. Specifically, among LMIC, experts tend to single out **MIC** as the most promising path to impact, at least **in the near to medium term**.

MIC perhaps present the most likely priority across the two dimensions of impact and feasibility:

- Considering i**mpact,** overall antibiotic use remains high in HIC. Yet MIC have rapidly caught up or overtaken HIC on consumption levels in recent years. In 2000, HIC consumption of broad-spectrum penicillins was 2.3 times that of upper-middle-income countries (UMC) and 3.3 times that of lower-middle-income countries (LMC), as measured in defined daily doses per 1,000 inhabitants per day. By 2010, this had narrowed to 1.3 times and 1.6 times, and by 2015 to 1.1 times and 1.2 times, respectively. The same holds true for fluoroquinolones and cephalosporins.[24]

A similar picture emerges for agricultural production. In terms of gross agricultural production value, HIC accounted for 54.7 per cent of all production in 1991, while UMC and LMC combined accounted for 43.8 per cent. LIC accounted for 1.5 per cent. By 2016, the HIC share had decreased to 25.8 per cent, while UMC and LMC accounted for 71.9 per cent. The LIC

[22] Based on expert interviews, AMR action on a local or community level is not a central priority for advancing the global response. This may in part be due to the fact that AMR is substantially more multi-layered and complex than other public health challenges. Naturally, local- and/or community-level action will have relevance for some subtopics (e.g. teaching appropriate use in humans or using paraveterinarians to improve use in animals in LIC). However, these activities don't need to be part of an AMR programme.

[23] For example, there is a perception that, in 2016, the global AMR community was substantially closer to agreeing on a large-scale pull incentive for therapeutic innovation than it is today.

[24] Center for Disease Dynamics, Economics & Policy. ResistanceMap. CDDEP; 2020. http://resistancemap.cddep.org: data available for 69 countries

share remained relatively low at 2.3 per cent. A similar trend emerges when one considers meat production alone, with UMC production values significantly overtaking HIC.[25] Combined with widespread awareness of low regulatory and/or practical barriers to antimicrobial use in agriculture, this indicates that agricultural use in MIC will significantly outpace that in HIC and LIC in the medium term.

- In terms of **feasibility,** stable underlying healthcare systems significantly improve the chances of successful implementation (overall, the impact of resilient healthcare systems on AMR is fully AMR sensitive, at least with respect to concerns around any aspects beyond those covered as standalone dimensions in the current themes and enablers).

LIC face a different set of problems that usually prioritise accessing medicines, with lower assumed human overconsumption, as well as limited presence of intensive farming systems (appropriate analysis of LMIC consumption patterns is more challenging due to a paucity of data). It is nevertheless important to put both surveillance and stewardship mechanisms in place early in LIC to avoid knowingly replicating problems present today in MIC and HIC in the future. From a public health perspective, experts agree that trade-offs between effective stewardship and access are not inevitable and can be overcome by ingraining effective stewardship and surveillance systems in parallel with increasing access.

Naturally, the implementation contexts in different countries vary widely. While a systematic or comparative assessment across countries was outside the scope of this effort, deep-dive interviews with multiple in-country experts on national action suggested lessons for different country archetypes.

Conclusion

Prioritisation is increasingly emerging as a gap in the AMR response. Aligning on a more specific critical path to impact will include defining a set of themes and enablers to focus resources and attention on and developing a perspective on the appropriate level and sequencing for implementation. Importantly, which actions on the critical path to support, and/or which of the discussed actions to prioritise, will differ for different actors pursuing different aspects of the AMR agenda.

This becomes even more important in any Covid-19-induced scenario: if AMR can benefit from strengthened attention on infectious diseases, it must communicate clear priorities and funding needs. If Covid-19 instead crowds out other healthcare priorities from global conversations, AMR needs to double-down on the most critical priorities over the next 10 years.

Until 2030, the focus should be on mitigating the risk of resistance and its consequences, and on expanding the evidence base where gaps remain a barrier to action. Beyond this, focus may shift to moderating levels of resistance development through prevention and maintaining and scaling best practices.

How a critical path should look will require challenging trade-off decisions among various stakeholders in the AMR community. Several areas stand out as critical infrastructure-building priorities over the first phase until 2030, including surveillance, IPC, and WASH. Therapeutic innovation, human consumption of antimicrobials, and vaccine development and access require urgent investment. For several other areas, including use in animals, the environment and plants, or topics around quality, the appropriate actions in this period may focus on evidence gathering.

It should also be noted that there is an element of behavioural psychology which overarches all themes and enablers. Experts raised this point in a number of contexts (e.g. around why doctors and patients don't follow stewardship guidelines with respect to human use, and the disconnect between what we believe is important or should prioritise and what we actually devote resources towards). This view, while outside the scope of this effort, is nevertheless important to keep in mind.

An appropriate response to AMR should not attempt to be all-encompassing. An effective strategy will require a focus on a critical path of priority activities.

[25] Food and Agriculture Organization of the United Nations. Food and agriculture data. FAO; 2020. www.fao.org/faostat/en/: data available for 176 countries.

Appendix 1: Findings per theme

Overview

The next section presents brief profiles of the findings per theme or enabler. These focus on an overview of each topic and its critical gaps, and contextualise the theme or enabler within the broader findings of the landscape. Each profile is intended to be read in conjunction with the more detailed accompanying PowerPoint profiles.

Each profile briefly reviews the problem statement and context for the respective theme and enabler. It gives an overview of the status quo, highlighting the most relevant points from among the eight questions (e.g. funding, awareness and implementation level). In the third section, it emphasises the critical gaps identified across expert interviews. The final section of each profile sets these critical gaps and the priority of the overall profile into context for the entire landscape.

These profiles significantly rely on interviews with experts; some of the represented perspectives therefore contradict each other at times.

Human infection prevention and control

Image:
WaterAid/Tom Greenwood

Human infection prevention and control

Problem statement and context

IPC efforts limit antimicrobial use by reducing the need for antimicrobial treatment in the first place. As a result, AMR reduction efforts can profit from both AMR-sensitive and AMR-specific IPC interventions. Measures generally focus on the healthcare facility or community level. In both regards, IPC has significant similarities (and overlaps) with clean water, sanitation, and hygiene (WASH), which is discussed separately in the following section.

Status quo

AMR has achieved prominence on the global political agenda

The global AMR response benefits substantially from AMR-sensitive IPC interventions and leadership. Since 2016, global IPC work has received significantly more attention and funding, in part because of the 2014–16 Ebola outbreak (e.g. Sierra Leone's $3 million USAID programme in partnership with International Organization for Migration to fund IPC courses for healthcare workers). IPC infrastructure has been measurably strengthened as a result: according to the 2018–19 WHO AMR self-assessment survey, of 158 countries surveyed, 98 have national IPC programmes that are implemented. At a global level, this national infrastructure has been supported by the rollout of the new WHO IPC global unit since 2015–16. In addition, 2019 marked the launch of WHO's global survey on IPC programmes in healthcare facilities.

Awareness of the interlinkage between IPC and AMR is high among both agendas. In terms of the AMR community, IPC is strongly emphasised in global and national AMR action plans (e.g. the UK AMR strategy includes concrete targets: reducing incidence of selected drug-resistant infections in humans by 10 per cent by 2025 and healthcare-associated Gram-negative bloodstream infections by 50 per cent by 2023–24). Simultaneously, WHO heavily references AMR throughout its IPC work, such as in its 'It's in your hands' campaign. In 2017, WHO released separate guidelines for prevention and control of carbapenem-resistant *Enterobacteriaceae, A. baumannii,* and *P. aeruginosa.* This is beginning to be replicated in some national IPC governance bodies, such as the inclusion of AMR in Germany's hospital hygiene commission guidelines.

At the same time, interventions are undermined by a lack of conclusive evidence of the effectiveness of different interventions. WHO's 2017 'Guidelines on Core Components of IPC' admit that their evidence base is "very low to low quality" regarding almost all recommendations. In addition, beyond individual studies, no systematic evidence exists concerning the impact of IPC interventions on drug-resistant infections specifically.

WHO has taken a leadership role on IPC work globally, and supported coordination efforts (e.g. through its Global Infection Prevention and Control Network, which includes WHO and 24 participating organisations, such as ministries of health, public health organisations, non-profits and research institutions). However, no coordinated leadership body on the AMR-IPC interface exists within the AMR community, and no coordination mechanisms specific to AMR-IPC were observed. Furthermore, while AMR experts consistently point to IPC as central to the AMR agenda, few AMR-specific interventions were observed.

For both AMR-sensitive and AMR-specific interventions, funding needs are insufficiently specified, although room for more funding likely remains.

Critical gaps in IPC

Gathering data on IPC

While there are efforts to gather data on AMR more broadly, there is often insufficient data gathering on adherence to IPC standards. Experts noted that data on compliance could help track the effectiveness of various IPC interventions (both AMR-specific and AMR-sensitive) and lead to better implementation moving forward.

[26] BA June 2020 paper substantiates this concern: Ashley EA et al. Setting priorities for patient-centered surveillance of drug-resistant infections. International Journal of Infectious Diseases 2020 2 June;97:60–5. https://www.ijidonline.com/article/S1201-9712(20)30428-8/fulltext.

Implementation at the point of care

In-country public health experts voiced concern about IPC guidelines at national level that may not translate into clinical practice (e.g. in Pakistan). Separately, experts criticise the practice of translating effective HIC IPC interventions to LMIC, or selecting what are presumed to be the most suitable interventions based on HIC effectiveness.[26] Such translation is regarded as challenging and often insufficiently granular. Experts noted there has been some progress with adherence to IPC standards as a result of Covid-19 (e.g. hand washing); however, these same experts expressed concern as to whether this will be a lasting change, both for HIC and LMIC.

Strengthening community IPC interventions

Currently, IPC interventions are focused on healthcare workers and facilities, while surveillance experts point to an underappreciation of community health settings for AMR in general. Given that gaps in evidence persist, and that they may be even larger than those for healthcare facilities, implementation research is required.

Strengthening the AMR-specific IPC response

AMR-sensitive IPC interventions may be the most effective way for the AMR community to benefit from existing attention to IPC and its global infrastructure (see below). Nevertheless, implementation research on the AMR-specific benefits of sensitive IPC interventions would reveal priorities to ensure the AMR community can reap maximum positive externalities from IPC funding and attention.

Priority of critical gaps for the overall AMR response

IPC is likely a priority for the AMR community given its potential impact on preventing infections. Two arguments support this hypothesis. Firstly, given the more straightforward and linear relationship between the reduction in the use of antimicrobials and the reduction in the overall burden of drug-resistant infections, IPC is likely to have significant impact on the objective of reducing human drug-resistant infections. However, this is contingent on strengthening the evidence for individual IPC interventions – which is especially dependant on geographic context (see above). Secondly, several experts share the view that IPC interventions are expected to be highly cost-effective compared to other themes and enablers.

At the same time, considering the existing environment, it is likely that prioritising AMR-sensitive over AMR-specific interventions may be the more appropriate path to impact. This is especially true given the current focus, with hospital-acquired infections making up a major share of the drug-resistant infection disease burden. AMR-specific interventions focused on reducing human drug-resistant infections may emerge in the future, but the existing landscape of evidence regarding effectiveness has not clearly revealed any such interventions to date.

Clean water and sanitation

Image:
Dave Sayer Wellcome

Clean water and sanitation

Problem statement and context

Access to clean water, sanitation, and hygiene limits AMR both directly, by preventing drug-resistant infections, and indirectly, by decreasing the need for antimicrobials in the first place. Clean water reduces transmission of pathogens through the water supply; adequate sanitation is important, especially in preventing bacterial transmission through surfaces (or food) contaminated with faecal matter; good hygiene reduces the spread of pathogens that are present in the environment. WASH measures generally focus on the healthcare facility or community levels. Although WASH may conceptually be regarded as a subset of IPC, it is frequently treated as a distinct topic, especially given the wider importance of secure access to clean water.

Status quo

Widespread awareness of the importance of WASH to the AMR response was observed, and experts across all sectors of the AMR response frequently voiced the expectation that WASH (and broader IPC) interventions were among the most cost-effective interventions to reduce AMR. However, AMR is not always a priority for WASH experts when considering specific WASH interventions. Accordingly, several AMR experts described mainstreaming AMR into WASH intervention planning as low-hanging fruit.

The evidence of (waste)water as a vector for AMR transmission is widely accepted within the AMR community, although evidence supporting the impact of different WASH interventions on mitigation is less well-documented. The WHO conducted the Lisbon workshop in 2015 as a first attempt to launch a dedicated research agenda on AMR and WASH. The workshop identified an urgent need to quantify exposure to resistant pathogens via water, and to define effective interventions.

Consequently, little to no implementation of AMR-specific interventions was observed. In terms of AMR-sensitive interventions, differences persist between HIC and LMIC. Clean water is generally prevalent in HIC; the number of people without access to an improved source of drinking water in Europe, North America, and Central Asia made up 2.4 per cent of the global total of people without access in 2015.[27] Significant numbers of hospital-acquired infections, e.g. in Southern Europe (Italy in particular), indicate that some hygiene gaps remain at the healthcare facility level. This is similarly true at the community level; as an indication, the global WHO Clean Your Hands campaign was not explicitly targeted at LMIC.

Concerning LMIC, the WHO 2020 progress report on UN Sustainable Development Goal (SDG) 6: 'Ensure Access to Water and Sanitation for All', is pessimistic. Most targeted countries are not on track to fully implement the SDGs' indicators by 2030. Taking a broader historical view, positive momentum is visible: across LMIC, and especially LIC, access to clean water is improving. According to World Bank data, in the period from 1990 to 2015, the number of people without access to an improved water source halved from 1.26 billion to 666 million.[28]

Critical gaps in clean water and sanitation

Funding for AMR-sensitive WASH interventions

No AMR-specific funding, or even estimates of funding requirements, were observed. While AMR stands to benefit from AMR-sensitive WASH interventions, funding remains a critical gap.

The CDC estimates WASH interventions to be highly impact- and cost-effective. It cites studies stating WASH interventions:

- Have the "potential to prevent at least 9.1 per cent of the global disease burden and 6.3 per cent of all deaths"
- Resulted in a "rate of return of 23 to 1 for investments in water filtration and chlorination" between the period from 1900 to 1950
- "Produce[d] economic benefits ranging from $5 to $46 per $1 invested" across all regions.[29]

[27] Ritchie H, Roser M. Clean water. Our World in Data 2019. https://ourworldindata.org/water-access.

[28] Ritchie H, Roser M. Water use and sanitation. Our World in Data 2019. https://ourworldindata.org/water-access.

[29] Centers for Disease Control and Prevention. Global WASH Fast Facts. CDC; 2016 11 April. https://www.cdc.gov/healthywater/global/wash_statistics.html.

While the UN estimated that there was a 38 per cent increase in official development assistance (ODA) commitments to the water sector between 2016 and 2017, a 9 per cent decline was observed in 2018. On the other hand, ODA disbursements to the water sector reached $9.4 billion in 2018 (an increase of 6 per cent compared to the previous year), indicating some positive momentum.[30]

Yet, the OECD estimates that annual global WASH funding only makes up 15 per cent of the required total – $16 billion at present versus a need of $112 billion.[31]

Consequently, implementation lags behind schedule: WaterAid estimated in June 2019 that "at current rates of progress, everyone in [the] least developed countries won't have safely managed water until 2131 – more than 100 years behind schedule."[32]

Improved coordination and effective mainstreaming of AMR in the WASH agenda

In several interviews, experts in the WASH community expressed frustration that while lip service is frequently paid to the effectiveness of AMR-sensitive interventions and their impact on promoting WASH, this is not followed up with implementation support or funding. Multiple WASH experts expressed a perception of being underfunded and underappreciated versus AMR.

However, funding data indicates WASH may be substantially more well-funded than AMR efforts; and in contrast to AMR, WASH allows some political accountability at global level through the adoption of SDG 6 that includes concrete targets and a resulting set of indicators. The gap is consequently likely to be at least as much one of coordination as of relative funding levels.

Experts within the WASH community emphasise the difficulty of getting a seat at the table in broader public health dialogues. Multiple interviewees from the WASH community describe AMR optimistically as an 'entryway' into broader public health conversations. Additionally, experts highlighted that when WASH and AMR are given attention, it is generally only from a human health point of view. There is a strong desire for the discussion to be framed in the context of the One Health perspective.

One positive development is the WHO report, 'Technical Brief on WASH and Wastewater Management to Prevent Infections and Reduce the Spread of AMR' in June 2020. This is similar to guidelines for more effective WASH interventions to address AMR that exist for WASH-NTD, such as the WHO's 2015 WASH-NTD strategy and the 2019 'WASH and Health Working Together: A how-to guide for NTD programmes.'

Priority of critical gaps for the overall AMR response

WASH is likely to provide substantial and cost-effective contributions with the target of reducing drug-resistant infections, through both AMR-sensitive and perhaps future AMR-specific interventions. Nevertheless, stronger engagement of the AMR community with WASH will be crucial to capture the full potential from WASH interventions for positive externalities in reducing drug-resistant infections. This includes ensuring that WASH funding levels increase above 15 per cent of need, and that implementation ambitions go beyond achieving targets with an over 100-year delay. Even if these figures were found to be overly pessimistic, significant funding gaps clearly persist in the best-case scenario. In the words of one WASH expert, "[an] assumption that WASH will take care of [AMR] misunderstands the scope of WASH globally".

[30] United Nations. Goal 6: Clean water and sanitation. In The Sustainable Development Goals Report 2020. New York: UN; 2020 https://unstats.un.org/sdgs/report/2020/goal-06/.

[31] Goksu A et al. Easing the Transition to Commercial Finance for Sustainable Water and Sanitation. World Bank – Water Global Practice; 2017 August.

[32] Twigg B. Without access to WASH, the UK jeopardises the SDGs. WaterAid 2019 25 June. www.washmatters.wateraid.org/blog/without-access-to-wash-the-uk-jeopardises-the-sdgs.

Food safety and security

Image:
Hanson Lu, Unsplash

Food safety and security

Problem statement and context

Given the selection for and prevalence of antimicrobial resistant genes in natural and farmed environments, food presents an important vector for the transmission of antimicrobial resistant pathogens to humans.

In addition, multiple experts raised concerns about food security (i.e. the uninterrupted and sufficient, safe, and nutritious supply of food), which has generally been less well-recognised within the AMR agenda. Increasing levels of resistance in microbes that infect farm animals and plants, along with the development of resistance in soil microbiota, can lead to disease-related mass slaughters or harvest failures threatening food security.

Status quo

In addition to the overuse of antimicrobials, food contamination with resistant pathogens occurs through environmental vectors, especially manure and wastewater. Estimates that up to 80 per cent of human- and animal-ingested antibiotics are excreted in active form imply that fertilising crop fields with manure or watering them with wastewater may leave antibiotic and pathogenic residues on food plants. Wastewater contamination can persist beyond crops. A recent study[33] of fish sold at Zimbabwean informal markets found high levels of contamination, with all but one bacterial species being 100 per cent resistant to at least three drugs (multiple antibiotic resistance indices from 0.2 to 0.7) and identified raw sewage and human waste in rivers and lakes as the driver.

Considerations around food remain low on the AMR community's global agenda. Most food safety work is coordinated through regulatory work outside the AMR community, e.g. FDA refusing multiple shrimp entry lines from China and Vietnam in 2019 due to antibiotic residue contamination. Consequently, the only observed global coordination body on food safety and AMR is Codex Alimentarius's Task Force on Antimicrobial Resistance (TFAMR) with the Tripartite, working on food safety AMR issues as one of its many areas of focus. Consequently, little AMR-specific funding for food safety work was observed (other than in-kind contributions through the time of TFAMR members, the UK Fleming Fund's contributions to the Tripartite and some private donations to the FAO). One partial exception to this is the Innovative Veterinary Solutions for Antimicrobial Resistance (InnoVet-AMR) initiative launched in 2018 by the UK's Global AMR Innovation Fund in partnership with Canada's International Development Research Centre. This initiative seeks to reduce antimicrobial use in LMIC livestock and aquaculture through research into vaccines and alternative treatments. In doing so, it references its aim to "[reduce] the emerging risk to global health and food security posed by antimicrobial resistance in animals".[34]

Beyond AMR-sensitive interventions on buttressing general food safety, effective AMR-specific interventions are mostly limited to reducing use in plant and animal farming and food-production environments. Some actors among the food-producing, food-processing, and food-retailing industries, in both the EU and the US, have taken significant action to ensure judicious use of antimicrobials in their production and supply chain (e.g. ShakeShack, McDonald's and Tesco as part of the UK Food Industry Initiative on Antimicrobials).

Food safety concerns play a role in these actions, as evidenced by multiple examples of US retailers going over and above FDA Import Alerts to reduce or eliminate imports of foods exposed to high levels of antimicrobials (e.g. Costco switching its salmon procurement from Chile to Norway). These concerns on the industry side are in part driven by increased consumer and investor (e.g. Farm Animal Investment Risk & Return initiative) attention to the issue (see also sections on use in animals and use in plants). Yet experts agree that consumer understanding of the specifics of AMR risks remains low; at best, consumers are worried about antimicrobial residue in their food, with no appreciation for the larger risks of ingesting resistant pathogens.

No evidence was observed that such industry action is replicated in LMIC, or at scale in HIC outside the US and Europe. In addition, such measures appear limited to the animal protein supply chain. For instance, resistant pathogens in plant-based foods can have severe, direct consequences to human health since many fruit and vegetables are consumed raw or following minimal processing.

[33] Gufe C et al. Antimicrobial profiling of bacteria isolated from fish sold at informal market in Mufakose, Zimbabwe. International Journal of Microbiology 2019 May 2

[34] UK Department of Health and Social Care. DHSC joins global fight to tackle antimicrobial resistance in animals. DHSC 2018 12 April. http://healthmedia.blog.gov.uk/2018/04/12/dhsc-joins-global-fight-to-tackle-antimicrobial-resistance-in-animals/.

Critical gaps in food safety and security

LMIC action

Persistent challenges to effective regulatory actions that protect citizens from foodborne illnesses reduce the AMR-sensitive benefits of food safety regulation in LMIC. Limitations with regard to hygiene and biosafety lead to a higher potential for contamination along the farm-to-fork pathway (e.g. the persistence of wet markets and live-animal markets, which are significant contributors to cross-contamination and animal-to-human transmission, such as that of *E. coli* at US state fairs). In addition, a lack of enforcement of regulations that surround antimicrobial procurement in farming ensure high rates of use (see also section on use in animals).

Effective LMIC action is also undermined by a lack of funding of food-specific AMR surveillance from within the AMR community (although the priority of such versus patient-based surveillance systems is questionable).

Finally, antimicrobial use in food-producing environments (both animal and plant) is an important guarantor of food security in the short term. Eliminating the resulting incentive problem requires investment and capacity building around biosafety and its alternatives (especially in plant use).

Data generation on food security

At present, there is no systematic data, or estimates of the scale of risks posed to food security by AMR. Given the potential for very large disruptions to human well-being, an adequate risk scoping is needed to raise awareness around this concern and inform any response (see also below).

Reductions in overall use levels in food-producing industries

The overall excessive level of antimicrobial use in crops, livestock, and aquaculture production remains a primary driver of resistance (see the sections on use in animals and plants for details on reductions).

Priority of critical gaps for the overall AMR response

Food safety is not likely to be a critical gap for the overall AMR response. Implementing effective food safety is mostly an AMR-sensitive regulatory question, underwritten by national food safety agencies and international bodies to guide and harmonise their policies (mainly Codex Alimentarius). In LMIC, there are persistent concerns regarding the ability of governments to protect their citizens from foodborne illnesses; but solutions to this will again mostly be AMR-sensitive and not driven by the AMR community. While no wide-scale estimates of the burden of disease from foodborne resistant pathogens exists, foodborne illnesses overall are estimated to cause between 9 and 18 million disability-adjusted life years (DALYs) p.a. in LMIC[35], compared to an estimated 874,541 DALYs from AMR overall in the European Economic Area (EEA)[36]. With respect to the AMR-specific response, effective interventions for food safety and security do not differ significantly from those required to reduce antimicrobial use in plants, animals, and the environment.

Food *security* concerns, on the other hand, may be among the highest-priority topics for the overall AMR response, contingent on two factors. Firstly, a more limited definition of the overall AMR response as solving for a minimisation of human infections with resistant pathogens eliminates, or at least severely decreases, the direct concern of food security. Secondly, concerns about the scale of the problem so far are mostly anecdotal. A meta-review of the existing research feeding into a preliminary model of the scale of the potential impact of AMR on food security could help to motivate increased research funding in the area (depending on the findings of such a review).

Raising awareness about food security concerns could be a significant factor in promoting an improved One Health approach to AMR by bringing in non-human-health stakeholders who are concerned about the stability of the food supply and, perhaps, the wider implications for economic and political stability that food security may entail.

[35] Grace D. Food Safety in Developing Countries: An Overview. Hemel Hempstead, UK: Evidence on Demand; 2015.

[36] Cassini A et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: A population-level modelling analysis. The Lancet Infectious Diseases 2019 1 January;19(1):56–66.

Environmental contamination

Environmental contamination

Problem statement and context

Environmental systems (especially water and soil systems) may contribute to AMR in three central ways: as a transmission vector for human/animal-associated resistant microbes; as selective pressure for the development of resistance through complex mixtures of pollutants (e.g. antimicrobial concentrations in soil on crop farms or effluence from pharmaceutical factories); and, as a reservoir of novel genes. Central questions for the AMR community focus on the incidence, likelihood, and scale of environmental system transmission to humans, and innovations that reduce the impact when transmission does inevitably occur, such as through filtration technologies and behavioural change interventions

Status quo

The environment as a theme within the AMR community has received significantly increased attention and momentum over recent years. This manifests itself with research attention especially from large research groups in the UK, Denmark and Sweden. Yet funding remains limited: the Joint Programming Initiative on Antimicrobial Resistance's research funding dashboard lists environmental funding as the lowest among six tracked categories.[37]

Evidence around the environment as a transmission pathway, while only circumstantial, is widely accepted among scientific experts; and several environmental experts noted a shared perception that this is increasing within the AMR policymaker community as well (as it relates to transmission, not resistance development; see below). Additionally, there is widespread acceptance among experts that the environment as a theme is not distinct, and has a significant impact on all other AMR themes and enablers (i.e. the condition of the local environment is a key driver of human infections, which in turn affects human health, therapeutics, etc). Nevertheless, uncertainty remains regarding the ecological factors that may encourage the development of resistance in various environmental systems as well as around evidence of what concentrations are required (and in which systems) to drive such resistance.

Experts noted improved coordination among the research community, but commonly point to the Joint Programming Initiative on Antimicrobial Resistance's Environmental Dimensions of AMR workshop as the single example.

Multiple European countries have taken leadership roles on improving research and evidence generation (e.g. increased integration into calls for funding proposals in Sweden, including international grants from the Swedish International Development Cooperation Agency). This is supported by attention to environmental AMR concerns from social-sector institutions, such as the Centre for Science and Environment and the Center for Disease Dynamics, Economics & Policy (CDDEP).

Additionally, increased awareness of the importance of the environment has been reflected in HIC NAPs, e.g. in the UK's latest 5-year-strategy, which strongly emphasises natural and farmed environments as sources of resistance. In addition, recent WHO self-assessment surveys found a small but growing number of countries with meaningful policy limits on environmental contamination.

While a broad research community around AMR and the environment is now entrenched, challenges persist with regard to conclusively demonstrating and thus communicating the importance of the environment as a source of resistance development. Multiple researchers emphasise their frustration with the policy and the clinical/human-health-focused AMR community only viewing the environment as a transmission vector. At the same time, they acknowledge that it may be impossible to conclusively demonstrate resistance development events due to their rarity and the complexity of the involved systems.

Moreover, while awareness and acceptance of the underlying importance has improved significantly, this has only translated into limited implementation.

[37] Joint Programming Initiative on Antimicrobial Resistance. AMR Research Funding Dashboard. JPIAMR; 2017. www.jpiamr.eu/amr-research-funding-dashboard/: other categories are therapeutics, diagnostics, interventions, transmission and surveillance.

Concentrations of antimicrobials in run-off from farms and hospitals remain high enough to encourage the development of resistance. In LMIC, contamination through pathogenic wastewater and/or manure is difficult to limit and presents a direct transmission risk to the food supply. One notable exception to this has been voluntary action by parts of the pharmaceutical industry to limit the impact of antibiotic manufacturing effluence (see below). As a specific example, India proposed draft legislation in January 2020 to limit the amount of antibiotic effluent from antibiotic manufacturing facilities. However, implementation is currently stalled as a result of lobbying from the Indian pharmaceutical industry and the general policy distractions of Covid-19.[38]

Finally, the environmental AMR research agenda has been strongly driven by European countries, the US, Canada, and China, gaining only limited traction in other regions.

Critical gaps in environmental contamination

Evidence of human health impact

Despite increased resources and a significant research agenda, conclusive evidence of the impact of environmental AMR on human health remains elusive. This is partially rooted in the scientific difficulty in demonstrating this (e.g. showing clear cause-and-effect relationships in complex interconnected systems), and also in quantifying the scale of the transmission issue. These factors create impediments to achieving policymaker buy-in with many experts highlighting the precautionary principle as a key factor.

Awareness of the environment as a reservoir of de novo resistance development

A critical gap remains a lack of awareness of the environment as a source of resistance in the wider AMR community. There is the additional challenge of investigating both the roles of *very high concentrations of antimicrobials* (e.g. from pharmaceutical factory effluence) in a few places as well as *much lower concentrations of antimicrobials* (e.g. as a result of excreted antibiotics) i*n many places.* All interviewed environmental researchers expressed frustration that resistance development, rather than just transmission, was underappreciated among human-health-focused AMR policymakers.

Awareness and implementation among private-sector actors

Systematic interventions to limit antibiotic residue from hospitals, especially through sewage, present a challenge in both HIC and LMIC. The same applies to municipal sewage, which accounts for lower concentrations but higher total volumes of wastewater antibiotic residue (a potentially concerning issue considering the emergent, but unconfirmed, research that resistance may develop at low concentrations). While filtration techniques exist, a 2016 study[39] examining the effect of wastewater treatment on antibiotic concentrations from rural and urban hospitals found only a partial reduction following treatment.

No effective interventions to limit farm run-off were observed, other than bans on the 'inputs' (i.e. limits on the purchase and use of antimicrobials in farm settings). Potential contamination from run-off is mainly driven by antibiotic group treatment of animals (estimates that around 80 per cent of ingested antibiotic volume are excreted in active form) and plants (crop-spraying ensures that antibiotics are directly applied to the soil and water supply at treatment concentration, and thus far higher concentrations than are found in most other systems) as well as fish feed (with uneaten feed contaminating river and sea beds). In addition, antibiotic excretion from animal use is reapplied to fields in the form of manure, which is frequently left untreated.

A partial exception to the above has been the voluntary leadership taken by the pharmaceutical industry. The AMR Industry Alliance's 2016 road map on AMR lists the environment as the first of four

[38] Wasley A. Indian drug companies try to gut antibiotic pollution controls. The Bureau of Investigative Journalism 2020 31 March. https://www.thebureauinvestigates.com/stories/2020-03-31/indian-drug-companies-try-to-gut-antibiotic-pollution-controls.

[39] Lien LTQ et al. Antibiotics in wastewater of a rural and an urban hospital before and after wastewater treatment, and the relationship with antibiotic use: A one year study from Vietnam. International Journal of Environmental Research and Public Health 2016;13(6):588.

priorities to address. The Access to Medicine Foundation, which releases detailed annual progress assessments of the industry's actions on this topic, is broadly positive on the action taken so far, pointing to widespread participation and a transparent process for attempting to set self-imposed standards. However, the 2020 benchmark report showed manufacturing progress has somewhat stalled since 2018.[40] Criticism of the process includes a lack of transparency with regard to production sites for active ingredients, the levels of antibiotics in effluent, and the results of third-party audits. There is also limited participation of Gx players (who make up the largest share of antibiotic volumes);, lack of participation by Indian and Chinese manufacturers as well as questions of how deeply a commitment to action is reflected in Western pharmaceutical companies' supply chains, given high levels of outsourced active pharmaceutical ingredient production.

Engagement of the broader environmental community

Multiple experts and policymakers expressed frustration with attempts to engage the UN Environment Programme in the global response to AMR. This replicates the experience of some national officials overseeing the AMR response in human health, or agricultural ministries who describe the challenges of engaging environmental ministries. Momentum on this front appears mostly flat, with the 2016 Political Declaration effecting no significant change.

A partial cause for this lack of engagement is likely to be the shift in resources and attention, and the commensurate sense of urgency of climate change. Political focus on climate change as well as its immediacy bind the focus and resources of environmental policymakers. Given the multi-decade challenge to raise climate change action to political consciousness, it will be a challenge to see a second diffuse, precautionary topic with distributed costs and a tragedy-of-the-commons element take a significant place next to it on their agenda.

Priority of critical gaps for the overall AMR response

The environment as a vector for resistance, especially through water (and, perhaps, soil) systems, is widely accepted, and likely to have a significant enabling effect on other topics of the AMR response (e.g. food safety). It is unclear, however, how many effective interventions exist that are specific to the environmental dimension, rather than affecting earlier stages of the chain of transmission (e.g. bans on inputs). Furthermore, for specific existing interventions, there is a question of investment proportionality as well as collateral benefits (e.g. advanced wastewater treatment plant systems can be deployed, at significant expense, and in addition to treating wastewater for antimicrobial residues also reduce thousands of other known and unknown chemicals contributing to safer water resources for humans, animals, and the environment). Moreover, there is the cost consideration of treating high concentrations at few locations (e.g. pharmaceutical effluence run-off) versus low concentrations at many locations (e.g. all municipal wastewater facilities).

Resistance development in the environment itself may contribute substantially to the total burden of resistance, but evidence of this is inconclusive (although researchers point out that simply because no evidence of a hard-to-prove process exists, this should, of course, not be taken as evidence to the contrary).

[37] The Access to Medicine Foundation. Antimicrobial Resistance Benchmark 2020. The Access to Medicine Foundation; 2020 21 January. https://accesstomedicinefoundation.org/publications/2020-antimicrobial-resistance-benchmark.

Human consumption of antimicrobials

Image:

Luuk Rombouts, Ideo: Maurice, a pharmacist in Kenya, advised that many patients nearby cannot afford the doctor so they ask him to prescribe medications.

Human consumption of antimicrobials

Problem statement and context

Antimicrobial treatments are frequently misused for the wrong indication, in an improper dosage, or for the wrong treatment duration. This behaviour increases the potential for the development of resistant pathogenic microbes and eventually exhausts the efficacy of existing therapeutics.

Status quo

Antimicrobials are often administered to patients without a confirmed diagnosis from a quality-assured diagnostic, and even in cases of viral infections, for which they are not effective. While most countries require prescriptions for antibiotics, such regulations are often weakly enforced. However, since the 2016 Political Declaration, significant effort has gone into improving stewardship and increasing awareness.

According to the latest WHO survey on AMR progress[41], most countries do conduct some awareness campaigns – often linked to the annual AMR Awareness Week organised by the WHO itself – typically targeting the public as well as healthcare workers. In addition, over two-thirds of respondents include AMR-specific topics when educating and training human health workers. A similar share of countries has at least partially implemented national stewardship practices and instilled medical guidelines for professionals. Improvements have also been made in surveillance to establish a reliable baseline of usage and resistance data. Despite these efforts, only 50 per cent of countries monitor human consumption nationally. Encouragingly, all these metrics have improved over the past 2 years, indicating significant progress across nations.

At the same time, while antimicrobials are often overused, many countries still suffer from a lack of availability. Overall, lack of and/or delays in access to antibiotics lead to significantly more deaths than AMR. For example, a recent study[42] estimated that almost 300,000 deaths from pneumococcal infections in children could be prevented with higher vaccine coverage and access to treatment options.

Critical gaps in human use of antimicrobials

Low awareness and ease of procurement

Low awareness and ease of procurement are the main drivers of the misuse of antimicrobials in humans. A lack of AMR awareness is compounded by the fact that procurement is frequently possible without a prescription or without the involvement of trained healthcare professionals. There are also still significant knowledge gaps among the general public on the appropriate use of antimicrobials across all geographies. A 2018 European survey revealed that 57 per cent of participants were unaware that antibiotics are ineffective against viral infections.[43] Even when used for the correct indication, treatment compliance is low and patients often stop their regimen once they feel better instead of completing the course. Policies on whether treatment courses *should* be completed differ between countries, creating additional uncertainty for patients.

Although most countries have implemented bans on over-the-counter sales of most antibiotics, many can still be easily purchased due to a lax enforcement of regulations. A growing number of publications also highlight the prescription of antibiotics despite diagnostic results pointing to viral infections, often due to patient pressure.[44, 45, 46] Patients also consume drugs left over from previous treatments or shared by relatives and friends without proper consultations. Additionally, some experts noted that antibiotic use in hospitals may be an as large, or an ever larger, driver of AMR than over-the-counter sales. While evidence to support this assertion is still being gathered, it nevertheless highlights that stewardship efforts must focus on both over-the-counter sales and the in-hospital dispensation of antibiotics.

On the regulatory side, improving and enforcing legislations on the prescription and dispensation of antibiotics is a priority action. In addition, the reimbursement of treatments (consultation, diagnosis and therapy) should reflect the value of, and be tied

[41] World Health Organization. Global Database for Antimicrobial Resistance: Country Self Assessment. WHO; 2018. www.amrcountryprogress.org.

[42] Wahl B et al. Burden of *Streptococcus pneumoniae and Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: Global, regional, and national estimates for 2000–15. The Lancet Global Health 2018 July;6:744–57.

[43] European Commission, Special Eurobarometer 478: Antimicrobial Resistance. Brussels: EC; 2018 November.

[44] Fleming-Dutra KE et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. JAMA 2016;315(17):1864–73.

[45] Chua KP et al. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. BMJ 2019;364:k5092.

[46] Cole A. GPs feel pressurised to prescribe unnecessary antibiotics, survey finds. BMJ 2014;349:g5238.

to, stewardship activities. This includes reflecting the value of securing a confirmed diagnosis via a diagnostic – even if this entails cost increases over simply trying multiple inexpensive antibiotics. However, changes in human behaviours need to be addressed as well, while ensuring interventions aimed at curbing misuse do not restrict access to antimicrobials for appropriate reasons.

Most countries now conduct awareness activities on appropriate AMR use, both targeting the general population and providing guidelines to healthcare workers. However, more effort should go into tailoring messages to specific misconceptions or misbehaviours prevalent in respective countries. For example, a call to 'only buy antibiotics with a prescription' should only be used where over-the-counter sales are a major issue. Additional strategies could include public health awareness and behaviour change campaigns similar to those employed in many countries to curb tobacco use.

In addition, factors like poverty or lack of access to healthcare typically play a key role in the misuse of antimicrobials and must be reflected in messaging. Consequently, there should be more rigorous follow-up assessments of the impact and effectiveness of awareness campaigns to inform their design moving forward.[47]

Limited access to effective therapeutics

Global access to antibiotics is hampered by a lack of affordability, supply chain issues, and a complex regulatory environment. Other issues include weak health systems and the reluctance of drug companies to register products in LIC where they do not see a market. Where health systems are weak, poor patients often cannot afford the out-of-pocket expense of treatments. And even when they can afford treatments, the prohibitive (relative) cost of diagnostic testing makes empiric antibiotic treatment the most attractive option for patients and providers, if they are even consulted at all. At the same time, effective antimicrobials might not even be available due to inadequate stocks and unreliable supply chains. Even in HIC, newer antibiotics may not be available in hospitals due to price reasons.[48] Finally, the fragmented regulatory landscape and poor commercial environment hinder the worldwide registration of new drugs, especially for small and medium-sized pharma companies without a global presence.

Behavioural changes supported by evidence

Experts also highlighted the need for behavioural changes at all levels of the antimicrobial stewardship landscape, across payors, physicians, and patients. Top-down guidance on the behaviour psychology that underpins non-compliance, adapted for local contexts (for example, focused on the belief that antibiotics are good for your health in some countries or work against viral infections in other countries) could help guide national action and create a global incentive structure. However, any effort to understand the psychology behind antibiotic misuse must be paired with evidence linked to concrete outcomes. Far too often much of the data collected is not actionable, leading to an over-reliance on individual judgement at the point of care in antibiotic selection. Two areas of outcome research that warrant further exploration include definitively investigating treatment duration on outcomes and exploring antibiotic selection – both for individual medications and in combination – on outcomes.

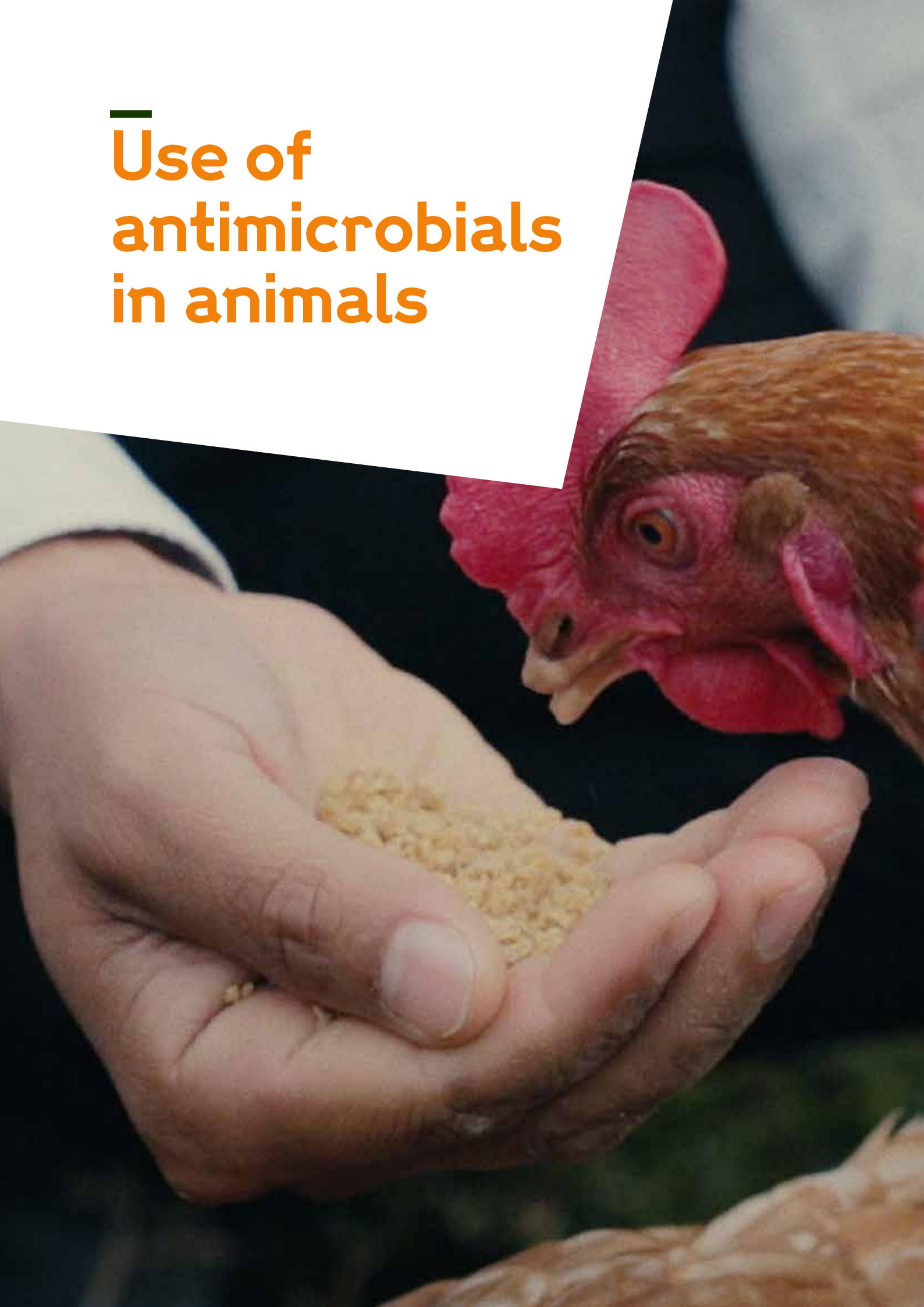
Priority of critical gaps for the overall AMR response

Optimising the use of antimicrobials in humans is crucial to maximising the effectiveness of current and future antimicrobials. Compared to the development of new therapeutics, it can also be cost-effective to slow down the development of AMR. Since changing human behaviour can be a slow process, it is essential to sustain a long-term approach with interventions tailored to target audiences and adapted to local circumstances. Nevertheless, it is also necessary to consider the practical constraints (economic, time, and resources) that underpin non-compliance and contribute to the development of AMR. A shift towards broad universal health coverage, especially in LMIC, could help transform the current incentive structure that leads to the increase of AMR.

[47] Huttner B et al. How to improve antibiotic awareness campaigns: Findings of a WHO global survey. BMJ Global Health 2019;4:e001239.

[48] Frost I et al. Access Barriers to Antibiotics. CDDEP; 2019 11 April; Rex J. New antibiotics are not being registered or sold in Europe in a timely manner. AMR Solutions 2020 7 September. https://amr.solutions/2020/09/07/new-antibiotics-are-not-being-registered-or-sold-in-europe-in-a-timely-manner/.

Use of antimicrobials in animals



Use of antimicrobials in animals

Problem statement and context

By volume, more antimicrobials are used in animals than in humans, especially for rearing livestock and – where permitted – for growth promotion or prophylactic group treatment. Clear transmission pathways have linked excessive use in animals to the development of AMR in humans, both through the transfer of AMR genes and via zoonoses, infectious animal diseases that can be transmitted to humans. With increasing food demands driving more intensive farming, the use of antimicrobials is expected to rise even further, especially in food-exporting MIC. Therefore, a major challenge will be to optimise antimicrobial use to support animal health without negatively impacting productivity and unduly limiting access to the food supply, especially in LMIC.

Status quo

Although antimicrobial use data is patchy in some geographies, there is a consensus that livestock accounts for the majority of global antibiotic consumption, with estimates indicating that approx. 70 to 80 per cent of consumption is from animals. Antibiotics are not only dispensed to treat individually infected animals, but often used in large volumes as a preventative measure. In addition, some countries also use antimicrobials as growth promoters, although this practice has been banned in the EU and the US. One success has been the effort undertaken by the OIE, in collaboration with the FAO and WHO, to build a global database of antimicrobials used in animal populations.

Recently LMIC, such as India and Pakistan, have also made moves towards banning or phasing out critically important antimicrobials for human use, such as colistin, from animal use. However, their use is still permitted in many LMIC, and feed antibiotics are readily available in large quantities without veterinary interventions. Programmes, such as a joint pilot in Bangladeshi poultry farms led by USAID and FAO, have shown that pointing to the economic case for better biosafety practice may be one of the most effective interventions to reduce antibiotic use in LMIC. It may be more effective than regulatory interventions due to the challenges of enforcement: a separate USAID-FAO landscape study showed that regulatory frameworks on limiting antimicrobial use were prevalent to a meaningful extent in Bangladesh, Cambodia, Thailand, Laos, Vietnam, and Indonesia, but were severely limited by a lack of enforceability.

In the US and EU, the industry has taken significant voluntary action – yet such action may have been motivated by the anticipation of regulatory intervention. For example, experts point to the fact that the planned 2022 ban on all preventative group treatments in the EU has already led to significant anticipatory reductions in antimicrobial use.

To facilitate a transition away from antimicrobial usage, experts point to the criticality of improvements to animal husbandry systems and biosafety. This requires significant capability and awareness building with stakeholders, especially in LIC. Basic veterinary services need to be established to enable the behavioural change required. In geographies lacking basic services, training paraveterinary professionals and expanding their use can be an effective intervention, but this requires concurrent improvements in infrastructure and policy (especially where veterinarians are financially incentivised to prescribe higher volumes of antibiotics).

Given the increasing food demands and the resulting pressure on agricultural productivity, there is a growing interest in the use of antimicrobial alternatives, including vaccines, prebiotics, and probiotics. However, there is only limited market data available on the efficacy of such differential interventions. In addition, policy makers and potential purchasers point to the absence of clearly regulated markets with common quality, safety, and efficacy standards for such products. This lack of transparency discourages use.

Beyond livestock, aquaculture is recognised as a significant possible contributor to antimicrobial overuse in animals. Guidelines on antibiotic use in aquaculture differ substantially between geographies (see also section on Vaccines for details).

Companion animals present the third segment of animal use. While the overall volume of antibiotic use is much lower, zoonotic or gene transmission events to humans may be higher due to closer physical contact. Yet it is unlikely that the transmission likelihood is high enough relative to that from livestock (or aquaculture) to make companion animals a significant target for AMR control interventions. In addition, resistance is less likely to spread from animal to animal among pets due to less contact with other animals, as is the case in intensive farming systems. The FDA has recently announced new research on scoping the size of the companion animal sector contribution to AMR, which may improve the evidence base on its relative importance within animal use more broadly. However, the final results of this research are not expected until FY2025.

Critical gaps in antimicrobial use in animals

Evidence base

Although transmission pathways linking animal and human AMR have been clearly demonstrated (for a detailed discussion on the impact of AMR on food, see the Food Safety and Security section), there are still gaps in the quantification of transmission rates and the impact of AMR-specific interventions. Improving the scientific case will require better surveillance and data gathering on antimicrobial usage and outcomes.

Additionally, evidence on whether an 'x-point' reduction in antibiotic use in animals leads to anywhere near a similar magnitude reduction in human drug-resistant infections is absent. The animal health community stresses that using antibiotic use as a proxy rather than effective surveillance of resistance unduly shifts responsibility and costs for generating difficult evidence away from human health bodies (although there is no indication this has decreased the willingness to engage or comply with usage-reduction efforts). The Wellcome-funded California Senate Bill 27 study on demonstrating the impact on human health in California may be an important first step to establishing such a relationship.

This data can also be used to support pragmatic guidance for farmers on how to farm sustainably without the use of antimicrobials. For smallholder farmers in LMIC whose livelihood is directly linked to production volumes, there needs to be a clear evidence base to support action. However, even in HIC, such as the UK, similar guidance on the use of antimicrobials in the poultry and pig sectors, has decreased use by around 40 to 70 per cent within a few years in the absence of direct regulation.

Regulatory interventions

Regulatory interventions, or threats thereof, have proven the most effective intervention in HIC, often quickly followed by voluntary industry action. The same may not be true for LMIC, where regulatory interventions have been burdened by implementation problems (see above). Yet in HIC, the specifics of regulatory interventions matter: experts reported that the 2006 EU ban on growth promotion may have seen no net reduction to animal antibiotic use at all, as use simply shifted to prophylactic group treatment (a situation that the planned 2022 ban seeks to remedy). Additionally, it is unclear how widespread the implementation of California's 2018 Senate Bill 27 has been over the past two years.

In addition to direct regulatory action, consumer expectations, as well as investor demands, can be complementary levers to encourage compliance with antimicrobial use best practices. If consumers demand that their livestock be raised with appropriate antimicrobial use, this can be as large of an incentive as regulations that control use (see specific example below regarding aquaculture).

Increased attention to aquaculture

The use of antibiotics in aquaculture is mostly unregulated in countries that account for the vast majority of use. For example, China, Indonesia, India, Vietnam, Bangladesh, and the Philippines accounted for 93 per cent of global aquaculture production in 2016. It should be noted, however,

that India has taken measures to limit the use of antimicrobials in aquaculture, with the Government of India's Marine Products Export Development Authority publishing 20 antimicrobial or pharmacologically active substances banned from use.[49] While the development of resistance is a concern for fish in general, there is also the risk associated with the direct injection of high concentrations of antimicrobials into water systems via uneaten fish feed.

As discussed in the previous section, one potentially effective avenue to decrease antimicrobial use in aquaculture has been pressure on exporters from importing nations, either through consumer awareness or import limitations (for example, years of negative press about antibiotic contamination and the resultant action by retailers like Costco have driven large-scale structural changes in the Chilean salmon fishing industry).

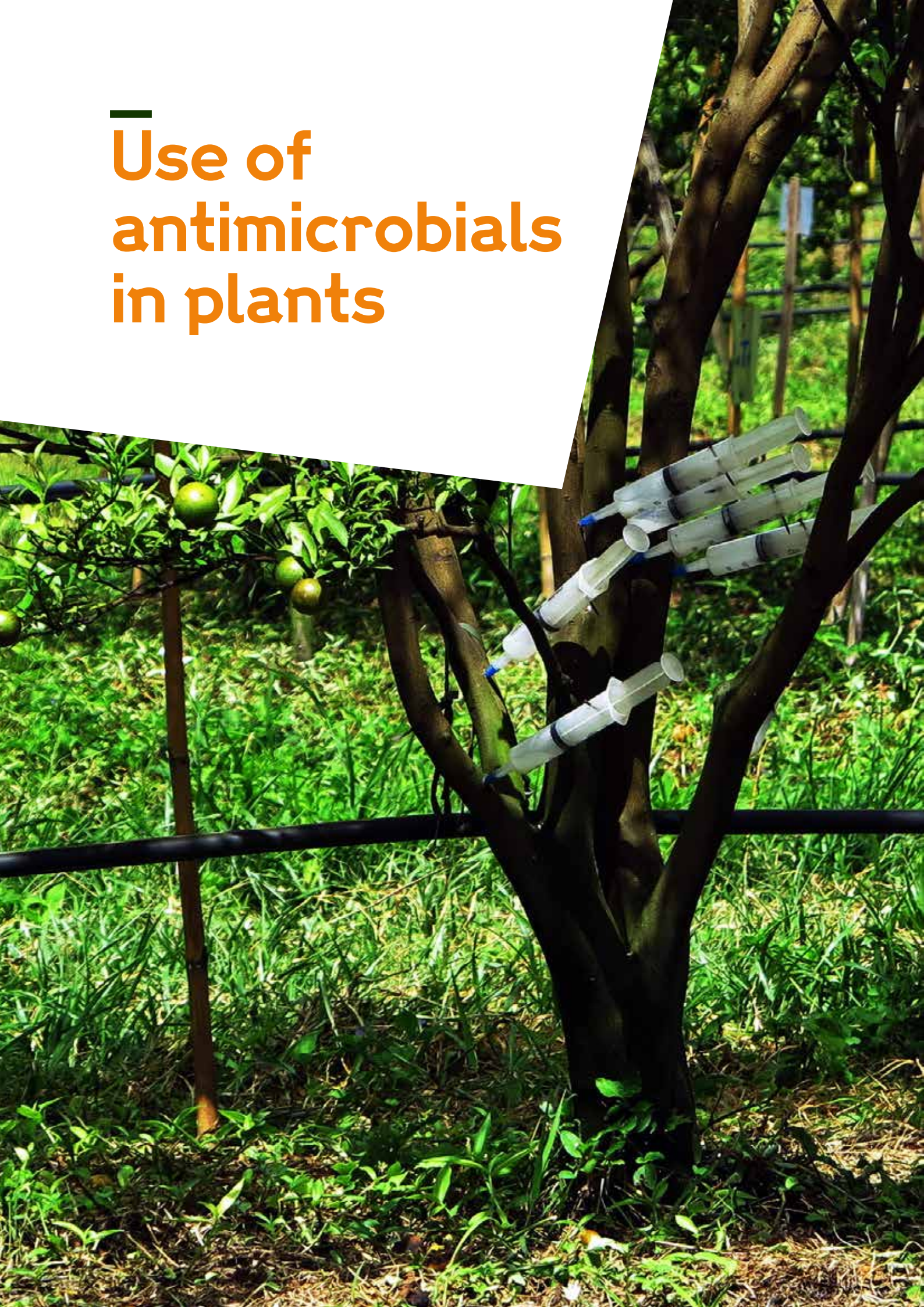
Priority of critical gaps for the overall AMR response

Given the high volume of antimicrobials used in the animal health sector, successful interventions can have a significant impact on global misuse and consumption. Unlike with human consumption, curbing usage in animals is often framed in purely economic/transactional terms, especially when targeting preventative and growth-promoting use. In this respect, it is also important to define alternative business models that disincentivise antimicrobial use in animals. However, the impact of veterinary antibiotic use on human health needs to be quantified in more detail before the relative contribution of animal use can be compared to other paths adding to the development of human drug-resistant infections.

https://www.reactgroup.org/wp-content/uploads/2018/11/Antibiotic_Use_in_Food_Animals_India_LIGHT_2018_web.pdf.

[49] ReAct. Antibiotic Use in Food Animals: India Overview. ReAct: Action on Antibiotic Resistance; 2018. https://www.reactgroup.org/wp-content/uploads/2018/11/Antibiotic_Use_in_Food_Animals_India_LIGHT_2018_web.pdf.

Use of antimicrobials in plants



Use of antimicrobials in plants

Problem statement and context

While the use of antimicrobials in animals receives the overwhelming majority of AMR community attention regarding agriculture, multiple stakeholders point to the use in plants as an additional field that receives insufficient attention. Antimicrobial use in plants is a potential concern due to (mostly food) plant infection with resistant pathogens, and due to the fact that high concentrations of antimicrobials are directly applied to the environment in many forms of plant application, such as mass crop spraying.

The main challenge of AMR in plants is the fact that there is almost no data to support even an initial scoping of the scale of the problem. This is true both for evidence regarding transmission risks (with a strong overlap with parts of the AMR, environment, and food safety agendas), as well as with regard to data on the overall use of antimicrobials in plants.

Status quo

Concerns around the use of antimicrobials in plants rest on the fact that their application in crop and other horticultural production systems applies selective pressure on pathogens that exist in soil and water systems. These pathogens can then be transferred to humans or share their resistant genes with pathogens that can infect humans through the food supply and, potentially, via water systems. Antimicrobials used in both crop production systems and human medicine include streptomycin and other aminoglycosides, tetracyclines, quinolones, and antifungals. Researchers, including at the CDC, have repeatedly suggested that *C. auris* ¬– a significant pathogenic concern to human health associated with a high mortality given its multidrug-resistant profile – may have developed resistance to azole antifungals as a result of mass azole use on crops.[50]

Selective pressures on pathogens may be especially high in soil and water systems of crop production environments because antimicrobials are applied directly to the environment at treatment concentrations, in “mg/L as opposed to the normal µg/L or ng/L” in the words of one academic expert.

This is amplified by the fact that the volume of critical antibiotics used in agricultural production may far exceed the volumes used for humans. For example, in May 2015, the US Environmental Protection Agency (EPA) approved the use of up to 650,000 pounds of streptomycin annually in US citrus groves – 46 times the estimated 14,000 pounds of total annual aminoglycoside use in humans[51] (see also below).

Moreover, a body of recent research has suggested that the exposure to a variety of antibiotics in combination with herbicides can substantially increase the rate of resistance development compared to the exposure to antibiotics alone (in some cases up to 100,000 times) [52,53,54].

Resistant genes persist into the food supply: the June 2018 ‘FAO-WHO expert meeting on foodborne AMR: role of crops, environment and biocides’ scoping review of literature, found antimicrobial-resistant pathogens on approx. 25 per cent of plant origin foods. This is exacerbated by the fact that, compared to meat and aquaculture products, fruit and vegetables (as well as other horticultural products, such as roses, which are heavily exposed to antimicrobials in India) are usually handled and consumed raw or following minimal processing.

Evidence on the extent and type of antimicrobial use in horticulture around the world is scarce. The International Plant Protection Convention (IPPC)

[50] In addition, there may be concerns around food security that are not limited to antibiotics and antifungals also used in humans; see also the section on food safety and security.

[51] Jacobs A. Citrus farmers facing deadly bacteria turn to antibiotics, alarming health officials. New York Times 2019 17 May. www.nytimes.com/2019/05/17/health/antibiotics-oranges-florida.html.

[52] Kurenbach B et al. Agrichemicals and antibiotics in combination increase antibiotic resistance evolution. PeerJ 2018;6:e5801.

[53] Kurenbach B et al. Herbicide ingredients change *Salmonella enterica* sv. Typhimurium and *Escherichia coli* antibiotic responses. Microbiology (Reading) 2017;163(12):1791–801.

[54] Kurenbach B et al. Sublethal Exposure to Commercial Formulations of the Herbicides Dicamba, 2,4-Dichlorophenoxyacetic Acid, and Glyphosate Cause Changes in Antibiotic Susceptibility in *Escherichia coli* and *Salmonella enterica* serovar Typhimurium. mBIO 2015;6(2):e00009–15.

admits that "there is currently no robust data on the volume of antimicrobial use by the plant sector worldwide". This is reflected in conversations with senior policy makers in the plant health space, who admit that they have limited to no insight into even a simple list of the major plant antimicrobial suppliers. One recent success is an analysis that explored the extent and volumes of antibiotics used on crops in LMIC based on data from the Plantwise Online Management System.[55]

Interviewed experts conclude that since the use of antimicrobials in horticulture is completely banned or restricted to plant health emergencies in most HICs, the highest volumes of use are likely in LMIC, where their sale is frequently unregulated or the enforcement of any existing regulation is lacking.

Plant health has not made the AMR agenda in any meaningful sense, with no dedicated funding or inclusion in NAPs identified. When plant health receives any consideration at all, it is as an indirect reference as part of the AMR in agriculture and AMR in the environment agendas.

Additionally, there is no indication that AMR has taken any meaningful role in the international plant health agenda. The IPPC and its governing body, the Commission on Phytosanitary Measures (CPM), have not taken major actions to investigate or suggest guidelines on AMR. The CPM's most recent 14th Session in April 2019 (the 15th Session, originally scheduled for spring 2020, has been postponed to 2021 due to the Covid-19 pandemic) listed AMR as a brief agenda item and released a five-page summary document, but this consisted mostly of a description of the problem of AMR at a general level. It contained no concrete recommendations for action. Participants describe the difficulty in achieving traction for AMR on the IPPC agenda.

As one of few actors, the UK government (via the Department for Environment, Food and Rural Affairs) has attempted to promote AMR within the international plant health community, raising the issue with the IPPC among others. This has not achieved any observable traction so far, partly due to the scarcity of resources dedicated to the topic of plant health globally. No known initiatives on plant health and AMR were observed across LMIC.

Coordination in the plant use AMR field is hampered by the competing priorities of reducing resistance on one hand, and food security and the livelihoods of farmers on the other. This is illustrated in the recent discussion around the application of streptomycin and oxytetracycline to citrus groves to combat citrus greening in the US, which the EPA allowed over vocal objections from the CDC and FDA. In the private sector, no industry-coordinating mechanisms among either producers or purchasers of plant antimicrobials to contain AMR have evolved (as they have in the field of animal use).

Critical gaps in antimicrobial use in plants

Data on scale of use and evidence on resistance development

Given the absence of consolidated use data (and in many cases even the transparency on who the stakeholders in the plant antimicrobial value chain are) the initial critical gap to raising this item on domestic and international agendas is systematic data on use, stakeholder mapping of supplies and purchasers, and estimates of the resistance burden. The Plantwise Online Management System is a good first step in this regard, and could be implemented more broadly to ensure more representative global coverage.

Additionally, data on resistance development and transmission, and the resulting impact on human health, are currently limited to mostly individual pathogens (such as *C. auris*). Ultimately, better evidence should generate better awareness and potentially better funding that is more commensurate with the identified scale of the problem; but also launch a conversation on what would constitute responsible levels of use that balance the trade-off between plant health and AMR risk.

[55] Taylor P, Reeder R. Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors. CABI Agric Biosci 2020;1:1. https://doi.org/10.1186/s43170-020-00001-y.

Awareness

There is limited to no awareness in the AMR and plant health communities, both at the international and domestic levels. This results in a lack of appropriate risk assessment with the evaluation of antimicrobial use in plants (like in the case of the EPA decision referenced above, which appears to have been taken over the objections of human health agencies in the same government, rather than as a result of careful risk-benefit trade-offs between plant and human health).

Priority of critical gaps for the overall AMR response

Based on a precautionary approach, the risks of AMR from use in plants may be high, given the application of antimicrobials in higher volumes and the environmental uptake at higher concentrations than that which is present for human and animal uses. The relative contribution of this on the overall scale of AMR largely depends on evidence on the overall capacity for resistance development in horticultural environments; as well as evidence on the rate of transmission from soil and water systems to humans through food or other environmental exposures.

In HIC, general bans on the use of antimicrobials in plants may significantly limit problems. On the other hand, antifungals are likely less of a problem given they are believed to have a lower impact on human health (*C. auris* being one notable exception). EPA permission for mass streptomycin and oxytetracycline application so far appears to be an isolated incident and, as such, does not warrant a systematic response from the AMR community; rather, it is important that bodies responsible for human health are included in risk-benefit decision making in such cases.

Given the limited use in HIC, the majority of the resistance burden is likely to be concentrated in LMIC, which may complicate both use-data generation and compliance with regulatory interventions, when compared to analogous experiences in human and animal uses. While a focus on AMR in plants may have a significant impact in this context, feasibility is more questionable.

Finally, considering overall human well-being, beyond the immediate risk of infection with drug-resistant pathogens, the food security element of AMR in plants presents a substantial additional cause to take action (see the section on Food Safety and Security for a more detailed discussion of this topic).

Surveillance (including laboratory capacity)

Image:
Dave Sayer, Wellcome

Surveillance (including laboratory capacity)

Problem statement and context

Surveillance measures the emergence and spread of drug resistance in humans, and possibly also in animals, plants, and the environment (the focus of this section is human surveillance). Effective surveillance systems are a chief enabler of an effective AMR response, both at the aggregate global level and within countries. It underpins action on AMR in at least three ways: allowing estimates of the scale of the AMR problem relative to other public health challenges, which can inform policy interventions and treatment guidelines; providing a basis for prioritising and allocating scarce resources within the AMR response (that is to different regions, different infections, different interventions); and creating visibility on progress that is being made, allowing for monitoring and course corrections where required.

Laboratory capacity is a key element of functioning surveillance systems. At least one national reference laboratory is a key requirement for countries to fully participate in WHO's GLASS (although countries can temporarily collaborate with a qualified institution in another country).

Status quo

Awareness of the importance of AMR surveillance is widespread and has increased further as a result of the 2016 Political Declaration (according to one expert, "the Political Declaration process really showed us what we don't know"). Surveillance is consequently a central pillar of the global action plan and NAPs, and at least 64 countries now have a national reference laboratory.[56]

In LMIC, awareness of the importance for surveillance is especially high among AMR leaders from clinical and health communities, who emphasise the need to be able to present accurate, country-specific data to policy makers outside the AMR community in order to generate stronger (budgetary) attention to AMR.

At the global level, WHO's GLASS is the leading institution on global AMR surveillance coordination. Launched in October 2015, the network covers 91 countries[57] enrolled in the AMR surveillance module, however adequate coverage of Latin America, Central Asia, Central and West Africa, and Australasia is still lacking. It provides aggregated data publicly as part of individual country profiles, showing resistance levels for selected pathogens and data on surveillance infrastructure. GLASS finished its 'early implementation' phase at the end of 2019, which focused on assessing the status of countries' existing systems and surveillance of selected human priority bacterial pathogens. Following this initial implementation, GLASS is now positioned "towards [developing] a representative database that will reveal the burden of AMR, trends in resistance, determinants and ultimately, the cost of inaction."[58]

Some experts voiced a range of criticisms of GLASS, including the restrictive policy for accepted sources, largely excluding independent academic institutions, as well as data held by pharmaceutical companies. There are additional concerns around the quality of some data submissions.

At the national level, this has translated into varying degrees of implementation. Relative enrolment in GLASS of LIC (42 per cent) and LMC (47 per cent) is actually higher than HIC (38 per cent) and UMC (27 per cent). Yet experts point to high variations in data quality levels, including the number of pathogens screened for and number of submitted isolates. In HIC, experts worry about the selection of priority pathogens as well as potential hospital bias in sampling (see below). In LMIC, funding remains a key gap (see below).

Outside of GLASS, a small number of projects attempt to create transparency with publicly available data on resistance per pathogen per antibiotic. CDDEP's ResistanceMap aggregates data from other national and regional surveillance

[56] As of January 2019.

[57] As of April 2020.

[57] World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: Early implementation 2020. Geneva: WHO; 2020. p. iv. https://www.who.int/glass/resources/publications/early-implementation-report-2020/en/.

networks to provide a time-series of resistance development. The Swiss INFECT programme provides an app-based traffic light solution to show susceptibility levels of 40 pathogens to a range of antibiotics (with data limited to Switzerland but offered as an open software solution). The Global Research on Antimicrobial Resistance Project, led by the Oxford Big Data Institute and Institute for Health Metrics and Evaluation, may in the future provide an additional valuable resource of globally comparable analysis as it places AMR in the context of the Global Burden of Disease. The Global Research on Antimicrobial Resistance Project draws upon a wider range of data sources than GLASS and includes a focus on outcomes-data that CDDEP and INFECT cannot reflect. Additionally, the Open Data Institute and Wellcome AMR Register compile and provide public access to raw surveillance data from the pharmaceutical industry. Experts expressed frustration with data that is frequently siloed between the public and private sectors. While the projects discussed above are a good first step, disaggregating the currently available data remains a challenge.

Three major sources of LMIC surveillance funding exist. The Fleming Fund aims to support 24 countries to establish effective surveillance systems by 2022, constituting the largest grant area of its £265 million funding. While generally well-received, individual experts offered scepticism on the effectiveness of implementation to date. No public systematic reviews of its effectiveness were identified.

The World Bank's Regional Disease Surveillance Systems Enhancement Program (REDISSE) commits almost $400 million to West African countries. While REDISSE is not specific to AMR, the latest $120 million Phase III funding round is explicitly AMR-sensitive. As of 2018, REDISSE funding dispersal had been significantly (around 50 per cent) slower than initially projected. No further information to verify the extent or effectiveness of its contribution to AMR laboratory capacity was obtained.

In addition, in June 2020, Wellcome and Pfizer partnered to launch the Surveillance Partnership to Improve Data for Action on Antimicrobial Resistance (SPIDAAR) targeting four sub-Saharan African countries: Ghana, Kenya, Malawi, and Uganda. This partnership brings together the combined resources of governments and the private and non-profit sectors to support better AMR surveillance and enhance the availability of actionable data.

Despite these initiatives, experts point to LMIC AMR surveillance as significantly underfunded. A persistent challenge in getting LMIC to supplement or match donor funding to strengthen domestic surveillance is the difficulty in deciding to limit resources that could actually be used for the treatment of patients for the less direct and less immediate benefits of strengthening surveillance. In this point, surveillance is somewhat analogous to challenges faced with increasing the use of diagnostics.

In HIC, no significant funding gaps exist. Experts explicitly emphasise behaviour change over resource commitment.

WHO leads and owns surveillance at the global level through its creation and support of GLASS. Additionally, several regional, disease-specific surveillance networks, integrated with and/or supported by WHO, have been in existence for decades (such as gonococcal surveillance networks). In HIC, domestic leadership is generally held by national governments in collaboration with academic centres and dedicated research groups, such as those in the UK, Denmark, Norway, or Germany.

In LMIC, leadership and ownership frequently hinge on eminent individuals and/or public health leaders tied into global dialogues, who champion the importance of surveillance. Among policy makers more broadly, ownership is limited; as it is at the point of care and among private sector consumers of antimicrobials. International donors, but also domestic 'champions', express this lack of ownership reflected in the almost complete reliance on donor funding for any budget lines on surveillance. Additionally, this is exacerbated by the aforementioned trade-offs between short-term treatments and long-term public health benefits.

Since the start of the Covid-19 pandemic, many experts have noted that hospital surveillance

programmes established over the past few years have been almost completely abandoned. Most expressed that this was to be expected given the massive shift in resources towards Covid-19 treatments and research, as well as the significant burden placed on frontline staff. At the same time, Covid-19 (and renewed attention to diagnostics) has led to substantially increased laboratory capacity in many areas, which could potentially prove beneficial for AMR surveillance in the future.

Experts noted that the final impact of Covid-19 on AMR surveillance is still to be determined and strongly contingent on how the pandemic changes medicine and prescribing overall. There is a view that if the increase in telemedicine, that has developed during the pandemic, persists afterwards, there will be an increase in empirical diagnosis and prescribing. This could have a tremendous impact on the development of AMR and pose a challenge for AMR surveillance (both with respect to the ability to track its development given the anticipated decline in laboratory confirmed diagnoses and the challenges associated with tracking data that is available in a remote-first medical landscape).

Critical gaps in surveillance

Transforming surveillance data from informational to analytical and predictive

Experts highlighted the gap between how surveillance data is currently used and the potential for its use. In most countries – both HIC and LMIC – surveillance data is used primarily for informational purposes, not analytically or predictively. Accordingly, there is an opportunity to use data to proactively improve clinical decision making (i.e. good data on local levels of resistance could improve empirical prescribing) and to help national/regional governments predict areas of emerging resistance and react accordingly.

HIC: Set of surveyed focus pathogens may miss critical burden of disease or resistance

Multiple surveillance experts voiced concern over the selection process for which predefined pathogens make up the focus of HIC surveillance. Selection frequently occurs opportunistically, with focal pathogens shifting based on global trends, despite very different levels of resistance between countries. Additionally, surveillance systems are heavily biased towards hospital settings. This may be partially justified, concerning the intense burden hospital-acquired infections imply for healthcare systems (63.5 per cent of drug-resistant infections in the EU and EEA in 2015).[59] However, this must be contrasted with the large volumes of antibiotics prescribed in outpatient settings (up to an estimated 90 per cent in Denmark, for example).

Experts pointed to two critical consequences: first, a systemic problem with missing the true burden of resistance or disease. In one Nordic country, approx. 1 per cent of *S. aureus* qualifies as methicillin-resistant Staphylococcus aureus, having approx. two times the mortality of non-multi-resistant *S. aureus.* Yet methicillin-resistant Staphylococcus aureus receives most of the attention of healthcare practitioners and policy makers, despite representing under 2 per cent of the mortality burden. Second, HIC surveillance systems may fail to detect large-scale resistance developments early enough.

LMIC: Inability to make the case for AMR as a policy issue due to lack of data

In LMIC, the lack of resources, capacity and capabilities (such as lab capacity, technicians, surveillance sites, and healthcare professional education) entails a lack of surveillance data. This is especially true for identifying resistance to large sets of antibiotics for large sets of pathogens in specific countries, or for variations at subnational levels. This, in-country AMR champions point out, is the biggest barrier to 'making the case' for the

[59] ACassini A et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: A population-level modelling analysis. The Lancet Infectious Diseases 2019; 19(1):56–66.

importance of AMR to policy makers, versus competing health (and non-health) budgetary priorities. Consequently, national AMR priority levels are often decided by the presence or absence of individual 'champions' who happen to be clued into global dialogues or expert networks, rather than objective trade-offs on the impact of AMR on public health and other outcomes. Better data will not only help frame the impact of AMR on the budgeting process, but could also help LMIC move from aid dependence to more sustainable financing models.

LMIC: Inability to monitor progress

Finally, where the need for an effective response to AMR has been accepted, a lack of data nevertheless hinders progress monitoring. This in turn limits knowledge of which interventions are effective and which are less so; and contributes to fatigue resulting from a lack of measurable progress (see also the section on Global Governance).

Priority of critical gaps for the overall AMR response

Adequate surveillance is the lynchpin of an effective policy response to AMR. Accordingly, surveillance and laboratory capacity have received significant attention from the global AMR community over recent years. With GLASS, a global coordination body with significant backing from WHO exists and is accepted by all involved parties. Additionally, with the Fleming Fund, a (mostly) dedicated funding mechanism exists that covers at least a subsection of countries and guides their implementation with a comprehensive programme that goes beyond the simple provision of templates and guidelines and addresses many of the criticisms of the broader AMR NAP process. Nevertheless, two critical gaps persist.

In LMIC, significant room for surveillance funding remains – many countries remain uncovered by the Fleming Fund; and where it is active, healthcare experts voiced questions about how local health systems would maintain the infrastructure after funding runs out. Not being able to adequately measure progress or have a sustainable database to inform global prioritisation is a substantial hindrance to AMR progress.

In HIC, the questions around the process for the selection of priority pathogens should also be a concern for policy makers who frequently regard their job as mostly complete, at least as compared to many LMIC. Multiple experts voiced genuine concerns about the possibility of missing the spread of a critical resistant pathogen for substantial amounts of time.

Innovation: Discovery and translational research

Image:
Thoko Chikondi, Wellcome Collection

Innovation: Discovery and translational research

Problem statement and context

The development of new antimicrobial therapeutics is essential to combatting infections and requires a healthy early-stage research environment and pipeline from lead identification through clinical validation and early clinical trials. However, the fundamental economic challenges of many therapeutics also complicate sustainable research activities at those early stages.

Beyond discovery and translation, there are also other basic research topics (for example, on routes of transmission, mechanisms of gene transfer, or reversibility of resistance) that are relevant to AMR. While they provide essential insights into the microbiology of AMR, they are not covered in this segment, which focuses on the innovation of new therapeutic products.

Status quo

Most research into new antimicrobials is conducted by smaller players, such as academia and small start-ups. While most of the focus remains on traditional small molecule therapeutics, novel approaches, such as biologics, bacteriophages and microbiome projects, have gained attention. Research into novel small molecules is likely the clearest path forward, given the decades of experience in this area and the relatively straightforward evidence requirements for approval. While there are also various biologics in the antibiotics pipeline, they are typically developed for pre-emptive or adjunctive therapy, and do not yet represent a full-fledged alternative to traditional antibiotics. Newer approaches targeting the microbiome are still in early stages of research, with the understanding of the complexity around the interplay between microbes in the gut, oral, and skin not yet fully understood.

Since 2016, various efforts have led to a significant improvement in the funding environment. With many reports unanimously calling for more push (and pull) funding to incentivise research, CARB-X, GARDP, and the Novo REPAIR Fund were established and endowed with significant resources, in addition to further support from national governments. At the same time, venture capital funding has become difficult to obtain due to the high-profile financial challenges and even bankruptcies of biotechs, such as Melinta and Achaogen. Investors have lost substantial investments and are adjusting to the current reality of the investment opportunity, especially since global pull incentives have not materialised yet. Most recently, the approx. $1 billion AMR Action Fund was formed, partially in response to this dampened venture capital environment, to invest in companies targeting novel AMR treatments and support them through late-stage development and onto market, supported by a coalition of private and public organisations.

Overall, funding for early stages of research has improved to the point that the critical challenge now seems to lie with the later and more resource-intensive clinical development stages and with ensuring sufficient funding pre- and post-approval to prevent approved products from collapsing into bankruptcy.

Critical gaps in discovery and translational research

Capabilities and talent

Antimicrobial research faces a shortage of experienced researchers with skills and knowledge in infectious diseases. In particular, there is a lack of capabilities in translational science (i.e. the transition from academic research to drug development during pre-clinical development). Experts expect that such shortages will only intensify in the context of the Covid-19 pandemic and are especially worried about the 'lock-in' implications of junior researchers specialising in viral infectious diseases instead of AMR. Such specialisation decisions now will have long-term implications on the availability of non-viral infectious diseases talent. Regular scientific congresses organised by national and international institutions and research associations, such as the American Society for Microbiology, the Infectious Diseases Society of America, or the European Society for Clinical Microbiology and Infectious Diseases, are helping to mitigate this gap; as well as training events, such as the International Course on Antibiotics and Resistance, offered by the Pasteur Institute, and the REVIVE webinar by GARDP.

Leadership and coordination

With leading institutions and well-known researchers throughout the field, there is no demand for centralised global coordination, especially given the broad and dispersed nature of research activities. At the same time, loose coordination efforts are helpful with regard to steering the pipeline, promoting a broad coverage of pathogens, and aiming for more innovative approaches, such as new targets and modes of action. One challenge here is the lack of a global overview, as pre-clinical pipeline assets are typically not made fully public by the industry. This is in contrast to the clinical pipeline where Pew, WHO, and others have mapped and analysed the current assets in development. Currently, CARB-X likely has the best pre-clinical overview as a result of their project applications. The AMR R&D Hub serves as an additional institution with potential to plug this gap but has yet to fully deliver on its potential.

Priority of critical gaps for the overall AMR response

The development of new therapeutics is widely considered to be a short and mid-term priority for the AMR response. Creating a sustainable environment for research is therefore crucial to ensure a healthy clinical pipeline in the coming years. Significant progress has been made on improving the funding situation, a major gap at the time of the 2016 Political Declaration, and it is essential to maintain the current level of support. At the same time, the fundamental business challenges faced by therapeutics needs to be fixed in order to create a viable market and to ensure the resources spent during early research stages are not undone by problems in the late development or post-marketing phases. In this way, it is essential that global, regional, and national pull incentives be developed.

Image:
Thoko Chikondi, Wellcome Collection

Innovation: Diagnostics (development and access)

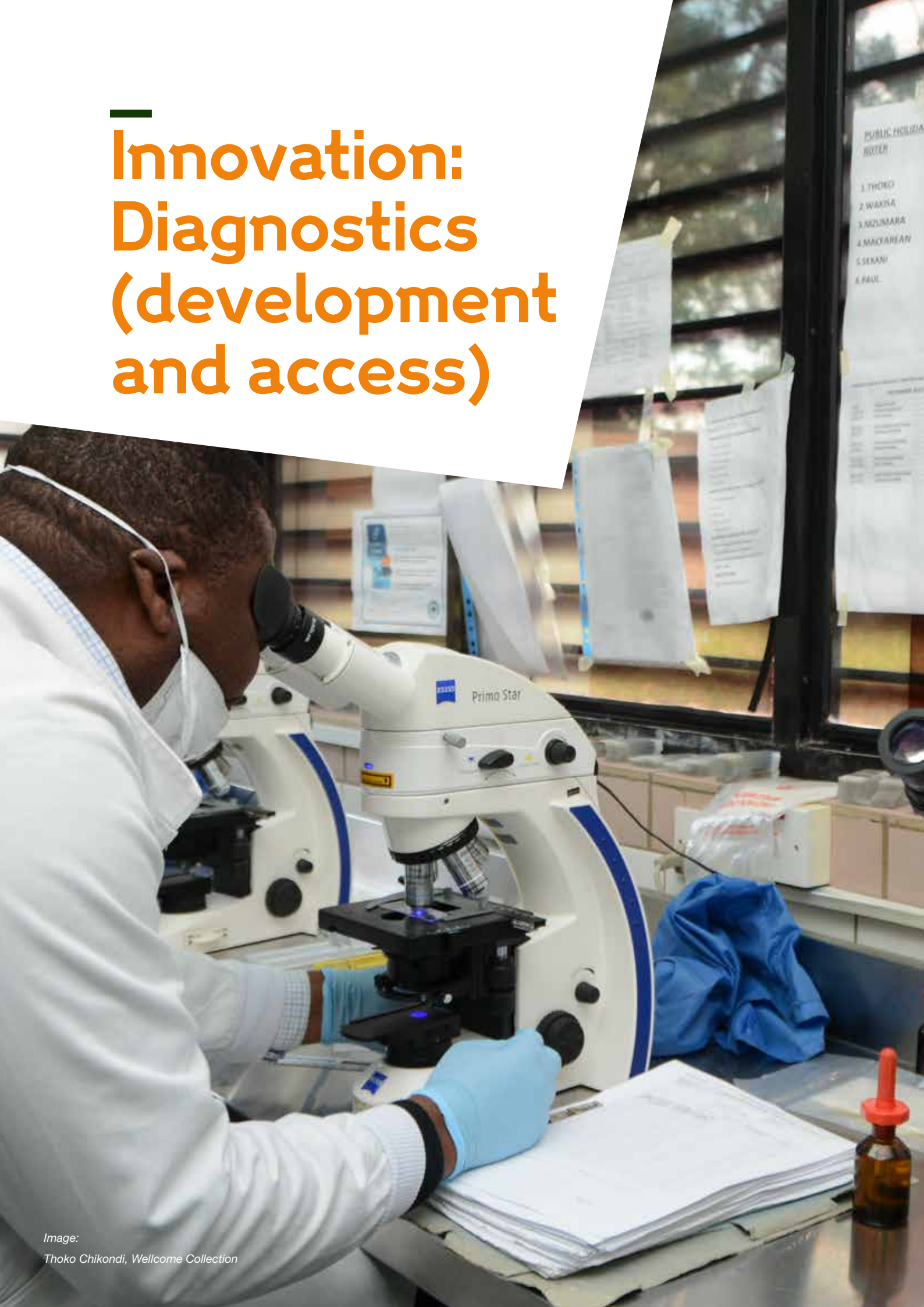


Image:
Thoko Chikondi, Wellcome Collection

Innovation: Diagnostics (development and access)

Problem statement and context

Diagnostics are a key component in the AMR response, with the potential to guide the appropriate use of antibiotics and thus improve patient outcomes, facilitate the development of new drugs, and enhance the surveillance of AMR. Rapid, affordable, and effective point-of-care diagnostics are urgently needed in both community and hospital settings to distinguish between viral and bacterial infections, identify pathogens, and test for AMR and susceptibility to antibiotics. However, there is insufficient development of new products due to market failures and various barriers to uptake.

Status quo

The main diagnostics players include major device companies, such as Abbott, Becton Dickinson, bioMérieux, Bio-Rad, Janssen, or Roche. In addition, small and specialised biotechs as well as academia are also driving innovation. Companies are organised in industry associations, such as the Global Diagnostics Association which includes AdvaMed, EDMA (European Diagnostic Manufacturers' Association), ALADDIV (the Latin America Alliance for the Development of IVDs) and the Japanese Diagnostics Manufacturers' Association, as well as AMR-specific groups (such as the AMR Industry Alliance, the Antimicrobials Working Group).

There are several non-profit entities supporting the development of new diagnostics. One such example, FIND, was established in 2003 and has since raised over $450 million for the development and delivery of diagnostics across various infectious disease areas, including AMR, HIV, malaria, and tuberculosis. Additionally, MSF itself is developing mini-labs to do blood cultures and antimicrobial susceptibility testing in field settings. Moreover, CARB-X was established in 2016 to accelerate antibacterial research and, while its main focus lies in developing new treatments, it currently supports six diagnostics projects. Moreover, it launched a new funding round in August 2019 specifically aimed at diagnostics.

There are also several prizes that were established to spur the development of new diagnostic tests. The Longitude Prize of £10 million was initiated in 2014 and is still ongoing. The EU Commission's €1 million Horizon Prize was awarded in 2017 and the Antimicrobial Resistance Diagnostic Challenge was launched by NIH/BARDA in 2016 with $20 million in prize money.

There has been a limited global coordination of efforts, mainly due to the fragmented landscape of specialised product developers and a wide variety of stakeholders, ranging from manufacturers, researchers, and healthcare workers to regulators, multilateral organisations, and funders. The WHO has introduced a list of essential *in-vitro* diagnostics (including but not limited to AMR) and is working on aligned target product profiles (focused on AMR) to guide development, supported by Wellcome. To improve coordination for respiratory infections, the University of Antwerp, bioMérieux, Becton Dickinson, and the Wellcome Trust launched VALUE-Dx in 2019, bringing together diagnostic companies, academia, and other stakeholders.

Critical gaps in diagnostics

Technological challenges

While the science of *in-vitro* diagnostics has progressed significantly, there are still technological challenges to producing the holy grail of a rapid, affordable, and effective point-of-care diagnostic device. Especially in LMIC community settings, it needs to be sufficiently robust for use in different, challenging environments and simple enough to be administered by untrained staff without specialised equipment. However, stakeholders point out that while these challenges exist, the overall market failure and barriers to uptake represent the larger problem.

Business case for developing new diagnostics

Like therapeutics (see section on Therapeutics), the field lacks a viable business model to sustain diagnostics innovation. Sales expectations are low, because in most cases it is cheaper, faster, and more convenient for healthcare workers to simply treat with antibiotics based on an empirical assessment of symptoms instead of waiting for the outcome of a diagnostic test. Sales would also be limited because there is no global purchaser for low-income countries, like Gavi for vaccines, further decreasing volumes and returns.

At the same time, R&D of diagnostics is associated with significant costs. As with therapeutics, the testing of new devices via large clinical trials is expensive and time-consuming. Patients with

drug-resistant infections can be difficult to find and recruit for trials due to timing and ethical considerations. Additionally, the regulatory landscape is fragmented and the approval of diagnostics is largely unique to a specific country, requiring developers to undergo a lengthy and costly submission process. Harmonisation of registration regulations could accelerate the commercialisation of new products.

While there is push funding available from FIND and CARB-X, for example, it is insufficient to achieve an overall positive business case, unless the return-side is fixed as well. Furthermore, there is only limited push funding to support the large late-stage clinical trials and commercialisation.

A significant pull incentive rewarding innovative solutions has been proposed, for example, in the Review on AMR, and could provide a return closer to the true value of an effective diagnostic test to the patient and the overall health system. The prizes established in various R&D competitions are a step in this direction, but their relatively low volume is unlikely to spur catalytic research activity. The Longitude Prize, for example, has had to extend its original deadline because none of the 250 registered participants met all winning criteria. At the same time, new pricing or reimbursement models that could create a market are still in early stages of discussion.

Unclear way to address barriers to uptake and effectiveness of new diagnostics

Even if new, rapid, affordable, and effective diagnostics are developed, there are behavioural barriers to their uptake. Given the low price of antibiotics, healthcare workers may decide against using them because they are unaware of their importance and positive impact. In LMIC, where patients often cover their own healthcare costs, it would also be difficult to pay for an additional diagnostic test, even if relatively cheap.

Reimbursement plans would need to be reformed to incentivise the use of diagnostics, for example by mandating their use in certain cases or expanding coverage to compensate for their costs. This would require a fundamental shift in the way diagnostics are valued in health technology assessments, for example, by quantifying not only the short-term impact on individual patients but also the long-term health and economic effects on the overall system.

Even so, access to new devices can remain an issue, especially in LMIC. Aside from the fragmented regulatory landscape, barriers to widespread use can include poor supply chains, lack of lab capacity, insufficient storage infrastructure, and untrained staff.

However, even when diagnostics are used, healthcare professionals may still inappropriately prescribe antibiotics, for example, due to patient pressure. In one recent study, 21 per cent of patients were prescribed antibiotics despite a confirmed viral diagnosis, and there is a growing body of literature describing this issue, especially in outpatient situations.[60,61] In some settings, doctors can even feel slighted if forced to use a diagnostic test instead of being allowed to rely on their own abilities.

Priority of critical gaps for the overall AMR response

Due to the current insufficient pipeline and spread of extensively resistant microbes, more attention is given to developing therapeutics rather than diagnostics. Most stakeholders agree that the need for new therapeutics is more substantial and more critical than that for new diagnostics. At the same time, both the therapeutics and the diagnostics ecosystems face similar market failures and lack of investment due to low expectations on returns. However, diagnostics suffer from additional behavioural and structural barriers to uptake, making it more difficult to resolve compared to the already complex therapeutics environment.

Nonetheless, diagnostics are and will remain an important part of the AMR response. Efforts to support diagnostics developments should be supported since better diagnostics could accelerate the clinical research of new drugs, simplify and speed-up patient recruitment for clinical trials, and even enable new approval paradigms.

[60] Li J et al. Role of rapid diagnostics for viral respiratory infections in antibiotic prescribing decision in the emergency department. Infection Control & Hospital Epidemiology 2019;40(9): 974–8.

[61] Chua KP et al. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study. BMJ 2019;364:k5092.

Innovation: Therapeutics (development and access)

Innovation: Therapeutics (development and access)

Problem statement and context

The development of new therapeutics is the most crucial component to offset the effects of AMR. However, many therapeutics, such as antibiotics, face fundamental economic challenges. The costs to develop new drugs can reach over $1 billion per successful launch, including the costs of failed drug candidates. At the same time, prices are comparatively low and novel therapeutics are often kept in reserve, leading to low sales volumes.

Status quo

Regarding the antimicrobial pipeline, since 2016 the FDA has approved 9 antibiotics, of which 7 target priority pathogens, 10 HIV drugs, and 2 antimalarial drugs. However, especially on the antibiotic side, there has been little innovation towards new classes of medication or novel mechanisms of action despite several launches. This is also evident in the current industry-wide clinical pipeline, which contains approx. 30 antibiotics targeting priority pathogens, of which only approx. 25 per cent can be considered innovative to some degree. Furthermore, coverage of pathogens is not uniform, with certain LMIC-specific priority pathogens, such as *A. baumannii,* having no drug in the pipeline at all.

Much of the pipeline is driven by small pharma players, as many large pharma companies have decreased their activity or left the antimicrobial research space altogether since the 2016 Political Declaration, including Astra Zeneca, The Medicines Company, Novartis, Sanofi, and Allergan. At the same time, some small biotechs have suffered high-profile bankruptcies (Melinta, Achaogen, Aradigm) or collapsed in value (Tetraphase), despite managing to bring new products to the market. The continued exits have resulted in a lack of specific expertise and capabilities in anti-infectives basic sciences and anti-infectives R&D.

To improve the ecosystem, new push funding and pipeline coordinating entities have been established. CARB-X has committed $550 million of funding through 2021 and supported 68 research projects to date[62], mainly in the research and early development stages. GARDP distributed €15.4 million on R&D in 2019, and has commitments in excess of €82 million through 2024 from a variety of public and private donors.[63] Overall, approx. $470 million of public push funding is provided annually through various public and private entities. Moreover, on 9 July 2020, a consortium of the world's leading pharmaceutical companies launched the $1 billion AMR Action Fund to invest in early-stage companies targeting novel AMR treatments. In collaboration with development and multilateral organisations, including the WHO and the European Investment Bank, the fund intends to bring two to four novel antibiotics to the market by 2030.[64] While this new fund is a complement to other push incentives in the market, it is widely seen as a bridge to fund late-stage development and does not solve the structural challenges of the antimicrobial development market.

In addition to push incentives, pull incentives are needed to develop and sustain a robust marketplace. Unfortunately, only a few pull incentives currently exist, and many are only in the ideation/early implementation stages. At the national level, the UK is currently in the tendering process for their 'subscription' style payment model pilot to incentivise pharmaceutical companies to develop new drugs for resistant infections, with NHS patients potentially receiving access to the drugs under this scheme as soon as 2022. Additionally, in April 2020, the US Congress began considering a subscription-style programme, PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act, to spur novel antibiotic development. One notable exception to this lack of pull funding is BARDA's December 2019 5-year, $285 million contract with Paratek Pharmaceuticals for its antibiotic omadacycline.

Large and small industry players coordinate their efforts through advocacy groups including the AMR Alliance, the Antimicrobials Working Group, the

[62] As of September 2020

[63] Global Antibiotic Research & Development Partnership. Financial & Performance Report 2019. Geneva: GARDP; 2020. https://gardp.org/uploads/2020/07/GARDP-Financial-Report-2019-English.pdf.

[64] Business Wire. New AMR Action Fund steps in to save collapsing antibiotic pipeline with pharmaceutical industry investment of US$1 billion. Business Wire 2020 9 July. https://www.businesswire.com/news/home/20200709005154/en/%C2%A0New-AMR-Action-Fund-steps-save-collapsing.

BEAM Alliance and the BIO-AMR Working Group, as well as through trade associations, such as the International Federation of Pharmaceutical Manufacturers & Associations or the European Federation of Pharmaceutical Industries and Associations. On the public side, the leading roles of the US and the UK have diminished since 2016 due to changes in governments and policy priorities. Under Germany's leadership, the G20 established and funded a Global AMR R&D Hub in 2017 to provide leadership on market-based reforms of the antibiotic market. In mid-2020 it launched a Dynamic Dashboard to track AMR R&D investment products in the pipeline as well as push and pull incentives. However, stakeholders still feel the need for an international body to provide more structured leadership on the public side of the debate.

Several coordination initiatives and entities are in place to help guide R&D efforts. The WHO, Pew, and others regularly review the global pipeline of antibiotics to assess its health and identify gaps. Furthermore, the WHO is implementing a global surveillance system to monitor AMR trends and produce reliable, country-level data, including in LMIC. Meanwhile, entities such as CARB-X help coordinate the pipeline through targeted funding rounds and balanced selection criteria.

Apart from the nascent AMR Action Fund, there is limited interaction between public and private stakeholders on AMR, with public stakeholders criticising the industry for lack of commitment to the field and companies wary of calls for punitive measures, such as pay-or-play solutions. Moreover, even when new antibiotics are brought to market, private companies bemoan the challenges associated with global registration – resulting in many products being selectively listed only in markets where they can garner the greatest return, predominately HIC.

Critical gaps in therapeutics

There is widespread agreement that there are not enough drug candidates to maintain a sustainable response to AMR. This would require an R&D ecosystem capable of supporting the development and commercialisation of drugs against a variety of pathogens.

Primarily, there needs to be a viable business model to sustain R&D. Since antimicrobials are relatively cheap and treatments short, compared to, for example, cancer drugs or treatments for rare diseases, many players prioritise those areas instead. Additionally, in the case of antibiotics, new drugs are also (rightly) kept in reserve for stewardship reasons – further diminishing returns. All experts noted that this lack of a sustainable and attractive business model is a key impediment to the development of new therapeutics.

A large-scale, global pull incentive as proposed by the Review on AMR or DRIVE-AB, could provide a systemic solution to incentivise investment, but is unlikely to materialise in the near-term. Such a pull incentive would ideally be de-linked from volume and tied to access requirements, increasing the likelihood of coverage for LMIC-specific pathogens. To help merge the current push incentives with any new pull incentives, the AMR Action Fund could position itself as a leading consensus mechanism and crucial link between early and late-stage development.

Various smaller scale interventions could improve parts of the R&D ecosystem but are unlikely to resolve the overall problem due to their limited size and impact. Current public funding comes mainly in the form of push incentives for research and early stages of development, such as grants and seed funding. However, there is a gap for financing late-stage clinical phases and post-approval expansion of indications, which are the most expensive stages of R&D. Clinical trial networks and shared control arms could accelerate and reduce costs, especially of Phase 2 and 3 trials, and are discussed in a separate section. More models like the collaboration between Entasis and GARDP could be a viable path forward. In 2019, Entasis and GARDP entered a partnership for their novel oral drug candidate, zoliflodacin, whereby GARDP fully funded the Phase 3 global clinical trial in exchange for commercial rights in up to 168 LIC and LMIC. Additionally, in lieu of rapid and affordable diagnostics, regulatory reform could provide a more practical framework for pathogen-specific label expansion rather than the current indication-based approval process. For example, a trial by Achaogen targeting Carbapenem-resistant Enterobacteriaceae

(CRE) infections found only 37 confirmed CRE patients out of around 2,000 they screened – and, as such, the trial was deemed insufficient to extend the drug label.

Priority of critical gaps for the overall AMR response

Given the current insufficient pipeline and spread of extensively resistant microbes, developing new therapeutics is critical to combat AMR. Indeed, almost all interviewed stakeholders name new therapeutics as their key priority. While other measures such as vaccines, improved sanitation, or better stewardship all reduce dependence on antimicrobial agents, only new therapeutics actually treat existing resistant infections. If a sustainable ecosystem is created and new drugs become available, these priorities might shift. However, until such a time, the critical gaps in therapeutics will remain the top priority to be solved. This is especially a concern in the context of the Covid-19 pandemic in which policy makers, healthcare providers, and the private sector have had their focus diverted away from AMR. It is still to be determined how, and to what extent, this will affect the AMR therapeutic pipeline (see Covid-19 section for more detail).

Image:
Thoko Chikondi, Wellcome Collection

Innovation: Vaccines (development and access)

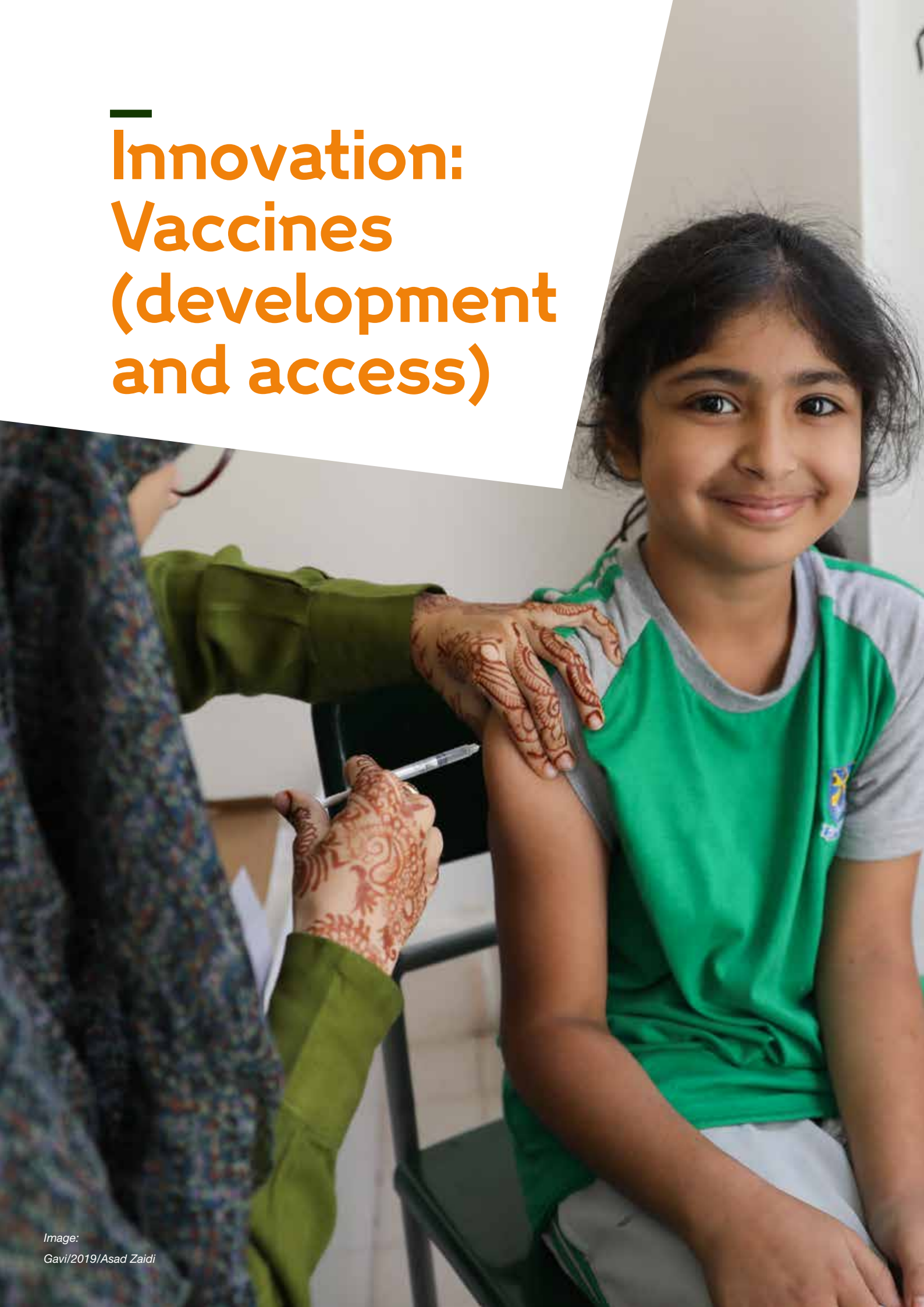


Image:
Gavi/2019/Asad Zaidi

Innovation: Vaccines (development and access)

Problem statement and context

Generally, vaccines can be segmented into those used for humans versus animals, and those that are AMR-specific versus AMR-sensitive. AMR-specific vaccines could play an instrumental role by directly preventing drug-resistant infections, controlling their transmission, and thus reducing the need for antimicrobials in the first place. Meanwhile, AMR-sensitive vaccines, such as the flu shot, prevent infections where antibiotics are commonly misused, as well as decrease the incidence of secondary bacterial infections, which generally require antibiotics.

Status quo

Since the 2016 Political Declaration, broad consensus has emerged that the use of vaccines is an important part of any solution to AMR, although the development of new antibiotics remains the priority of attention and funding. Many stakeholders suggest vaccines should play a larger role in the AMR response. Additionally, vaccines have garnered greater attention in the context of the Covid-19 pandemic.

Human vaccines

Among the WHO priority pathogens, effective vaccines exist for tuberculosis, *Haemophilus influenza,* Streptococcus pneumoniae and *Salmonella Typhi,* and their potential impact on AMR has been well documented. Several studies have shown a significant decrease in the prevalence of antibiotic-resistant pneumococcal disease after the introduction of pneumococcal conjugate vaccines (PCV).[65,66,67] In addition to this direct impact, multiple studies have observed indirect effects even of influenza vaccination on AMR, with antibiotic prescriptions decreasing by 13 to 50 per cent among those vaccinated compared to controls.[68] At the same time, research has mostly focused on those two vaccines referenced, with other research indicating no significant decrease in antibiotic use among vaccinated populations. Accordingly, more research is required to shore up the evidence base.[69]

The current clinical pipeline contains vaccines for previously unvaccinated pathogens, including Escherichia *coli, Shigella* and *Staphylococcus aureus,* along with next-generation versions of existing vaccines. However, most vaccines aimed at new pathogens are in the early stages of development and, like the innovation of therapeutics, the development of vaccines is an expensive, risky, and long-term undertaking. While push funding has focused more on therapeutics since 2016, there has been increased recognition of vaccines recently especially in the context of the Covid-19 pandemic. However it is still unknown how much this boost to vaccine research capacity will carry over into AMR-specific vaccines.

CARB-X included a specific call for vaccines and other biotherapeutics proposals in its 2019 funding round, while the UK government announced £20 million to support R&D of new vaccines and alternatives to antibiotics as part of GAMRIF. In addition, Wellcome and BCG have evaluated the development potential of vaccines against the WHO's list of priority pathogens to provide a guide for funders, product developers, policy makers, and potential investors.[70]

Interviewed experts also repeatedly pointed to the relative weight attached to vaccines in global and national AMR declarations today compared to three to five years ago. There is also increasing awareness and acceptance of the global AMR agenda within the vaccine space, which is very much aligned on increasing overall immunisation rates. In addition, the

[65] Hampton LM et al. Prevention of antibiotic-nonsusceptible Streptococcus pneumoniae with conjugate vaccines. Journal of Infectious Diseases 2012;205(3):401–11.

[66] Tomczyk S et al. Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. Clinical Infectious Diseases 2016;62(9):1119–25.

[67] Cohen R et al. Impact of pneumococcal conjugate vaccines for children in high- and non–high-income countries. Expert Review of Vaccines 2017;16(6):625–40.

[68] Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. Proceedings of the National Academy of Sciences of the United States of America 2018;115(51):12896–901.

[69] Buckley BS et al. Impact of vaccination on antibiotic usage: A systematic review and meta-analysis. Clinical Microbiology and Infection 2019;25(10):1213–25.

[70] Wellcome Trust, The Boston Consulting Group. Vaccines to Tackle Drug Resistant Infections: An evaluation of R&D opportunities. BCG; 2018.

new Immunisation Agenda 2030 frames AMR as one of the key threats over the next ten years, similar to outbreaks, requiring additional effort for vaccine R&D and implementation. So far, though, the inclusion of AMR into vaccine investment strategies frequently appears as a tool to boost the funding case for existing vaccines priorities; rather than a specific call to fund new AMR-specific development priorities.

Animal vaccines

Most antibiotics used in the world are used in animals. In the US, more than 70 per cent of antibiotics that are medically important for humans were used in animals as of December 2015.[71] Reducing the use of antibiotics in animals will therefore significantly reduce the use of antibiotics overall.

In terms of targeting future interventions, the ad hoc OIE Group on Prioritisation of Diseases for which Vaccines Could Reduce Antimicrobial Use presents detailed recommendations by species (such as *Helminth enteric parasites* in cattle, *Mycoplasma ovipneumoniae* in sheep, and *Fusobacterium necrophorum* in goats). It also includes an overview of coverage gaps, including R&D to develop a new vaccine versus lack of cross-protection, and the lack of efficacy against particularly prevalent strains.

The development of new animal vaccines has seen increased urgency in the animal space in recent years. The STAR-IDAZ International Research Consortium on Animal Health was launched in 2016 and includes a coordination of vaccine research at an international level as its first deliverable. The animal health industry itself has taken some strides to show leadership and ownership. In their 2019 Roadmap to Reducing the Need for Antibiotics report, Health for Animals committed to investing at least $10 billion in R&D, which includes delivering at least 100 new vaccines for animals by 2025.

Companion animal vaccination is likely not a priority of the future AMR response, as the use of antibiotics in companion animals is much lower than that in livestock. Based on interview findings, not only is reducing antibiotic use in pets unlikely to have a significant impact, pet vaccination in emerging economies is negligible anyway, while in HICs, pet healthcare tends to be an out-of-pocket expense. Therefore, large-scale preventative use is unlikely to sway consumers who often spend large sums on visits to veterinary clinics already.

Critical gaps in vaccines

Overall, the main gaps for developing new human vaccines are a lack of funding for R&D and barriers to access and uptake. As with novel therapeutics and diagnostics, expected returns are low and uncertain, while there are limited incentives to promote investment and R&D activity. Public-private partnerships with market guarantees for high-quality vaccines play an important role to spur action.

At the same time, the access and uptake of certain AMR-specific vaccines is relatively low – for example, global coverage for PCV is only around 40 per cent.[72] Major factors in LIC include poor overall health systems, insufficient supply chains and inadequate data collection systems leading to stock-outs. In MIC, the transition away from international financial support (for example, from Gavi), poses a significant challenge as the country crosses the income eligibility threshold. More rigorous evidence on the burden of disease and the economic as well as health benefits (including reducing the risks of AMR and not destroying the microbiota with antibiotics) can help strengthen decision making towards immunisation programmes. Finally, vaccine hesitancy and low patient adherence to schedules can lead to low coverage, even in HIC like the US, where PCV coverage of adults aged 19 to 64 was only 24 per cent.[73]

Within the vaccine space, animal health sees more immediate potential for impact in the context of the AMR response. Potentially low-hanging fruit are reducing barriers to uptake for aquaculture vaccines, especially in large industrial-aquaculture producers

[71] Food and Drug Administration. 2015 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. FDA; 2016.

[72] Jansen KU et al. The role of vaccines in preventing bacterial antimicrobial resistance. Nature Medicine 2018;24:10–9.

[73] Centers for Disease Control and Prevention. Vaccination Coverage Among Adults in the United States: National Health Interview Survey, 2016. CDC; 2018 8 February. www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/NHIS-2016.html.

across South-East Asia, where China, Indonesia, India, Vietnam, Bangladesh, and the Philippines account for 93 per cent of global aquaculture production as of 2016. The example of Norway in the mid-1990s shows that vaccines for many fish-borne diseases already exist, or can be developed and deployed quickly if industry and political stakeholders show will. More recently, pressure on Chilean fish farmers by domestic advocacy groups and consumers in export markets has led to an approx. 28 per cent reduction in antibiotic use in salmon from 2016 to 2018, with largely voluntary leadership from industry. At the same time, no other vector in animal health sees similar direct exposure of the environment to effluence as aquaculture, where antibiotics are directly poured into water in therapeutic concentrations.

Priority of critical gaps for the overall AMR response

In the overall response towards AMR, vaccines typically receive less attention compared to novel therapeutics because the lack of innovation in antibiotics represents a more pressing gap at this stage. At the same time, the vaccines space and its' funding are often distinct from AMR innovation discussions, and some interviewees advocate for stronger linkages between the two agendas.

While catalysing the development of new human AMR-specific vaccines would provide promising tools for several priority pathogens, the funding of new AMR-specific vaccines beyond existing priorities is not a large priority in the current vaccines landscape. Given that the community is still struggling to provide and improve access to the most basic vaccinations, any additional resources are unlikely to be channelled into new AMR-specific priorities.

At the same time, more and better evidence on the impact of vaccines on AMR (such as the reduction in antibiotic use and transmission of drug-resistant pathogens) is needed to mobilise investments for the vaccination agenda, particularly for vaccines for pathogens that are of priority concern from an AMR standpoint.

In animal health, there is already a seemingly robust vaccine pipeline in place and Health for Animals has committed to delivering 100 new animal vaccines by 2025. Here, increasing usage and reducing barriers of uptake around access and entrenched behaviours are a crucial precondition to ensure this goal is reached. Furthermore, many in the farming community believe that without improved husbandry practices, vaccines only address the symptoms but not the root causes of poor sanitation and biosafety.

The AMR community tends to see vaccines as more of a long-term priority that is not necessarily on the critical path in the short to medium term. Once there is a sufficient pipeline of new therapeutics, prevention and vaccines will likely rise in importance. Vaccines are potentially a key measure to ensure the longevity of the antibiotic toolkit. Therefore, there is still an important need for the AMR community to support advocacy for the overall immunisation agenda to increase access and uptake of vaccines on both the human and animal health sides, as this is very much an AMR-sensitive issue.

Innovation: Medicine quality

Innovation: Medicine quality

Problem statement and context

Poor-quality medicines lead to negative treatment outcomes, contribute to AMR and undermine trust in health systems. Substandard and falsified drugs – those which do not contain enough of the active ingredient, those which have degraded or those which are poorly formulated – can lead to subtherapeutic delivery of active pharmaceutical ingredients. In the setting of an infection, such substandard drugs apply selective pressure that encourages the growth and amplification of resistant microbes. Additionally, falsified products with insufficient or no active antimicrobial pharmaceutical ingredients will lead to treatment failure, prolonged infection, and an increased risk of spreading diseases – all of which encourage increased antimicrobial use in the future. Misattributing such treatment failure to resistance may also lead to increased use of reserve antimicrobials and deplete their efficacy more quickly.

Status quo

Poor quality in medicines has been brought up as a global health concern since the 1990s, with access to quality essential medicines enshrined in SDG 3: 'Ensure healthy lives and promote well-being for all'. While general awareness of the issue is comparatively low across the wider AMR community, campaigns like Meds We Can Trust and Fight the Fakes are increasingly highlighting the problem and calling on civil societies, foundations, governments and private partners to spur action (such as the Medicine Quality & Public Health Conference in 2018).

There have also been recent efforts to improve the evidence base on quality issues. The WHO published the first report from its Global Surveillance and Monitoring System in 2017, highlighting that antimalarials and antibiotics were the most commonly reported substandard or falsified products.[74] The Fleming Fund is providing a grant to support global sharing of data on suspect drugs and conduct quality surveys in Africa and Asia, as well as develop tools for detection. Moreover, the US Pharmacopeia (USP) Quality Institute was established in 2017 to gather evidence to support the link between poor-quality medicines and the emergence and spread of AMR, as well as to explore how certain procurement mechanisms may create a market for substandard or falsified medicines. Additionally, USP has created the Medicine Quality Database, a publicly available online database with over 17,000 records on medicine quality measurements. Finally, the Wellcome Trust is funding efforts to map the prevalence of low-quality medicines and model their impact on patient outcomes and resistance. Nevertheless, despite these early efforts, the overall evidence level remains low.

Strengthening national regulatory systems responsible for quality assurance has been a key focus in recent years. For example, USAID funded the Promoting the Quality of Medicines programme, which was implemented by USP and helped build quality control capacity and improve product registration, inspections, and surveillance in more than 20 countries. It's follow-on programme, Promoting the Quality of Medicines Plus, (PQM+) was awarded a $160 million cooperation agreement with USAID in October 2019 to further this mission. To harmonise and strengthen regulation, the African Union is seeking to establish an African Medicine Agency to aid national regulators. Finally, the WHO aims to provide transparency and guidance by developing updated global benchmarking of national regulatory systems.

Critical gaps in the quality of medicines

Lack of relevant data

There is very limited data available on the prevalence of substandard and falsified medicines, as well as on the quantitative impact of such medicines on infection and resistance rates. Prevalence studies are difficult and expensive to conduct at sufficient geographic scale, and since most regulatory agencies do not disclose their findings, publicly

[74] World Health Organization. Global Surveillance and Monitoring System for Substandard and Falsified Medical Products. Geneva: WHO; 2017. https://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/.

available data is limited. There is also not enough funding, with support often tied to specific diseases, such as malaria, rather than committed to quality issues more generally.

Consequently, few objective quantitative prevalence surveys exist, even though awareness of the problem has increased.[75] Therefore, there is also limited evidence quantifying the link between quality and AMR, and the weakness of evidence is exacerbated by gaps in AMR surveillance. Nascent research and findings from the USP Quality Institute and other research institutions underscore the need for additional surveillance efforts to generate data that will lead to insights about where risks from substandard or falsified medicines are most acute. One recent positive development is the launch of the Medicine Quality Literature Surveyor by the Infectious Diseases Data Observatory in July 2020. This tool tracks medicine quality across both geography and time. Finally, most efforts have focused on the quality of human medicines, while the quality of veterinary drugs is even less understood.

Solutions could tie into existing AMR activities, for example by including efforts to monitor quality in the national AMR surveillance system. Precedents for more systematic quality monitoring exist in the form of the WHO Global Surveillance and Rapid Alert system or the WWARN surveyor of anti-malarial quality.[76]

Weak regulatory authorities

National regulatory agencies and relevant regulations need to be strengthened and enforced. This includes ensuring good manufacturing practices in both human and animal sectors through monitoring and inspection of production sites, including those producing products for export, and supply chains. To support national agencies, pre-qualification could be expanded to cover more antibiotics, as studies suggest that medicines provided under that programme are much less likely to be substandard.[77]

However, there are also political hurdles to achieving a solution. Drug-producing MIC may resist reform to protect local industries, while others are unwilling to acknowledge the problem to avoid reputational damage. Moreover, this risk will continue to increase as more LMIC increase domestic production of cheap antimicrobials. The drive towards universal health coverage also creates friction between ensuring wide access and tackling quality issues and has led to a renewed interest in procurement systems which prioritise low cost, sometimes at the expense of quality.

Lack of a holistic view on quality impact in decision making

In purchasing decisions, price is often the dominant factor for both funders and MIC health systems. For example, MIC transitioning away from financial support provided by the Global Fund, and the resultant decrease in available funding, leads to a low prioritisation of quality considerations. To address this, a holistic assessment of the total societal and economic cost of low quality against low purchasing costs is required and needs to involve multidisciplinary input from health economists, epidemiologists, etc. It would include the impact of prolonged or untreated infections, the risk of further spreading the disease and the additional medication needed for treatment.

Priority of critical gaps for the overall AMR response

Quality is not likely an immediate priority, as it cuts across all medicines, while the magnitude of its impact on AMR is not yet clear. Solving the problem also requires a complex combination of evidence generation, reform of medicine regulation and market incentives, and systems engineering to prevent, detect, and respond to low-quality drugs. Within this required response, the AMR community could contribute through AMR-specific data collection to form a solid fact base and advocacy to raise awareness, which would require only limited resources and attention compared to other priority themes or enablers.

[75] Tabernero P et al. A random survey of the prevalence of falsified and substandard antibiotics in the Lao PDR. Journal of Antimicrobial Chemotherapy 2019;74(8):2417–25.

[76] Nwokike J et al. Medicines quality assurance to fight antimicrobial resistance. Bulletin of the World Health Organization 2018;96:135–7.

[77] ACT Consortium Drug Quality Project Team and the IMPACT2 Study Team. Quality of artemisinin-containing antimalarials in Tanzania's private sector: Results from a nationally representative outlet survey. The American Journal of Tropical Medicine and Hygiene 2015;92(6 Suppl.):75–86.

Innovation: Clinical trial networks

Image:
Thoko Chikondi, Wellcome Collection

Innovation: Clinical trial networks

Problem statement and context

Establishing networks of clinical trial sites can be a significant driver for improving the efficiency, effectiveness, speed, and cost of new antimicrobial development by standardising a costly element of the development process (this is especially so for therapeutics, where few large pharmaceutical players remain active in the space that are able to deploy resources at scale). Importantly, networks of clinical trial study sites are needed in locations where AMR is prevalent and drug-resistant infections have a high incidence. In addition, continuously running studies through clinical trial networks retains site infrastructure and capacity, lowering start-up costs and maintaining access to well-trained staff.

Status quo

Given the potential to improve the cost, efficiency, and quality of trials, clinical trial networks represent a necessary addition and follow-up to creating a more robust R&D environment. In fact, some experts noted significant concerns that some of the projects supported in their early stages by CARB-X may struggle with financial viability as soon as CARB-X support finishes, driven in large part by the significant costs associated with the trial stages.

Currently, few antimicrobial- (and especially antibiotic-) focused clinical trial networks exist. Two examples are the US Antibacterial Resistance Leadership Group and the European COMBACTE-NET network. Experts explain this paucity by pointing to coordination problems among industry players, as well as the historical dearth of promising antimicrobial candidates that would have generated sufficient demand to sustain a network.

Two initiatives are expected to further shift this in the near term. First, the European Clinical Research Alliance on Infectious Diseases (ECRAID) aims to establish a trial network focused on various infectious diseases. While the network is not limited to antimicrobials, early public documents and consultations around the ECRAID launch suggest that AMR will receive significant attention. ECRAID plans to commence operations in 2021. Second, while existing initiatives and ECRAID are Europe or US focused, the Wellcome Trust is supporting the creation of a clinical trial network focused on Asia. This region is expected to be particularly hard-hit by AMR (with around 30 per cent of the global burden of resistance in South-east Asia alone). Currently, the regional pipeline to combat this is limited, with only three clinical trials ongoing in South-east Asia, which equates to only 5 per cent of all global clinical trials.

Critical gaps in clinical trial networks

Under the status quo, overall clinical trial capacity and capabilities are simply insufficient and present a critical gap in accessing sufficient numbers of patients with drug-resistant infections.

Recent activity in the US and Europe and, to a lesser degree, in South-east Asia and Africa, is on the right trajectory. Nevertheless, some critical gaps remain. The set-up of clinical trial networks is likely to be a multi-year process with significant impact on overall R&D cost functions several years out. Experts mention the difficulty in finding new sites with sufficient quality standards and skilled personnel to meaningfully expand networks without diluting quality.

In addition, the existing clinical trial network expansion plans are geographically limited. Further geographic expansion will be necessary to provide sufficient scale and allow access for a broad set of organisations developing innovative products.

Priority of critical gaps for the overall AMR response

Clinical trial networks can function as an important enabler of therapeutic innovation and increase efficiency of development, but are in and of themselves not direct drivers of innovation, and are therefore secondary to multiple other innovation enablers in this landscape analysis (e.g. therapeutic innovation, discovery and translational research).

While significantly improving the economics of antimicrobial development, they are likely to be insufficient on their own to create a step change in attracting new players to the development of antimicrobials, without accompanying changes to market incentives.

National action

Image:
Dave Sayer, Wellcome

National action

Problem statement and context

The national and subnational levels present the implementation context for all activity aimed at reducing AMR and preventing resistance development. While global governance can support the enabling environment through awareness raising, coordination, and donor funding, national policymaking and implementation is ultimately required to achieve impact on AMR.

The AMR community has used national action plans (NAPs) as both a tool to spur national action and to monitor its success. NAPs, though, are by definition a plan and do not automatically translate into action, and even less so into impact.

Status quo

The 2016 Political Declaration promoted national action by mainstreaming the issue of AMR at the global intergovernmental level. On the ground, human-health professionals (healthcare professionals, researchers, etc) describe the communicative benefit of the Political Declaration in clearly marking AMR as a shared global concern, not just an HIC topic.

In addition, while NAPs existed as one-offs in a handful of countries prior to 2016, a large-scale Tripartite push in 2017 to support countries in adopting them ensured that (as of March 2019) 116 out of 158 surveyed countries had a developed NAP.[78] In multiple countries (e.g. the UK, Australia), NAPs are now entering their second iterations, with significant progress on ambition with regard to their comprehensiveness from a One Health perspective. Moreover, other countries (e.g. Thailand) have conducted mid-term reviews of their NAPs to assess their impact thus far and recalibrate moving forward.

Yet while the need for national-level action is increasingly clearly accepted, expert interviews revealed a surge in critical questions around whether NAPs have allowed activity to be mistaken for impact. Causes for this are mostly found in the lack of enabling environments, especially with regard to funding, coordination, and political leadership.

No significant funding challenges were observed in HIC at the domestic level. Policymakers mention no major capacity challenges to implement AMR programmes. Funding is earmarked for a number of AMR interventions, including the US Congress's $170 million FY 2020 appropriation to the CDC to continue implementation of the Antibiotic Resistance Solutions Initiative, and the UK government's September 2019 spending review suggesting £8 million to support the Department for Environment, Food and Rural Affairs with animal antimicrobial use reductions. At the intergovernmental level, room for significantly more funding exists for both international market entry incentives and donor support for LMIC implementation.

In LMIC, lack of funding remains a barrier to implementation. Funding requirements are not clearly specified beyond the O'Neill review's estimate of $40 billion over 10 years, but experts across all levels and geographies of the AMR response agree that current levels constrain implementation.

Sufficient domestic policy leadership exists in the US and EU/EEA, although leadership is unclear in other HIC. In addition, HIC action has managed to spur ownership among non-governmental actors, like in the animal health and food industries, although this remains incomplete (see sections on antimicrobial use in animals and food safety and security). In LMIC, levels of political will are insufficient to enact national action across the One Health spectrum, with few exceptions (see below).

Coordination is one of the key bottlenecks to national action. This is true for coordination across ministries and across the One Health spectrum (see below). In addition, in countries with federalised systems, experts describe coordination failures between national and local/regional levels. For example, in India, the complexity of health systems forced individual states (e.g. Kerala, Madhya Pradesh) to develop state-level action plans. In Switzerland, a lack of clear competencies across cantonal borders hampers the AMR response to zoonotic disease outbreaks, for example.

[78] UN Secretary-General. Follow-up to the Political Declaration of the High-level Meeting of the General Assembly on Antimicrobial Resistance: Report of the Secretary-General. New York: UN General Assembly; 2019 10 May. https://digitallibrary.un.org/record/3807197?ln=en.

Nevertheless, national action is crucial to achieve impact, especially where MIC are concerned, given the rise in antimicrobial use in these countries. MIC have rapidly caught up to or overtaken HIC with respect to antimicrobial consumption in recent years. In 2000, HIC consumption of broad-spectrum penicillins was 2.3 times that of UMC and 3.3 times that of LMC (as measured in defined daily doses per 1,000). By 2019 this had narrowed to 1.3 times and 1.6 times, respectively, and by 2015, to 1.1 times and 1.2 times, respectively. With respect to fluoroquinolones, HIC consumed 2.3 times the levels of UMC and 4.0 times that of LMC in 2000, but this narrowed to 1.0 times by 2010; by 2015 both UMC and LMC had overtaken HIC in relative use. A similar trend has also been observed with cephalosporins.[79]

A similar trend has emerged with respect to agricultural production. In terms of gross agricultural production value, HIC accounted for 54.7 per cent of all production in 1991, while UMC and LMC combined accounted for 43.8 per cent. LIC accounted for 1.5 per cent. By 2016, HIC's share had decreased to 25.8 per cent, while UMC and LMC accounted for 71.9 per cent. The LIC share remained relatively low at 2.3 per cent. A similar trend emerges when one considers meat production alone, with UMC production values significantly overtaking HIC. Given the widespread awareness of the low regulatory and/or practical barriers to antimicrobial use in agriculture, these trends indicate that agricultural use of antimicrobials in MIC will significantly outpace that of HIC and LIC over the medium term.[80]

Critical gaps in national action

Implementation in LMIC

Experts across both HIC and LMIC broadly share a perception that NAPs have not equated to national action in many, but not all, LMIC. There is still a lack of NAPs in several countries. More significantly, concerns exist that even where NAPs are present, some countries are conducting 'copy-and-paste' exercises from global action plans.

Some experts have urged taking stronger action to incentivise or perhaps compel country-level implementation, such as including AMR or broader health system preparedness into IMF Article IV consultations. In this way, a lack of action could result in direct negative effects on countries' credit ratings.

More broadly, ownership should be taken not just at the national level, but at the regional and local levels as well. One strategy that experts raised was to leverage microplanning initiatives that have been successful in other public health areas (such as vaccination campaigns in India) to drive local ownership and successful implementation.

Additionally, experts highlight that almost no LMIC have successfully implemented their NAPs at scale without an external injection of funds. Solving this funding gap will be crucial in helping transform plans into action. Some LMIC that have received external funding and started to scale implementation have managed the external donor process through a central 'clearing house' mechanism for in-country services and funds (such as those in Malawi, Kenya, and Zambia). While it is important to ensure that such a mechanism does not become another redundant forum, this approach can help a country manage, focus, and prevent the duplication of efforts.

Coordination and inclusion of all relevant actors

Policymakers and experts across LMIC and global governance institutions agree that the process of drafting NAPs in LMIC commonly fails to bring all relevant actors to the table (for example, the Fleming Fund begins country consultations by encouraging multi-stakeholder roundtables to prevent this dynamic). This is replicated within the policymaking process, with frequent low levels of engagement outside of human health ministries. This leads to limited awareness and ownership among other One Health sectors, such as in agriculture (Morocco

[79] Analysis of ResistanceMap data: Center for Disease Dynamics, Economics & Policy. ResistanceMap. CDDEP; 2020. https://resistancemap.cddep.org/.

[80] Analysis of FAOSTAT data: Food and Agriculture Organization of the United Nations. Food and agriculture data. FAO; 2020. http://www.fao.org/faostat/en/.

presents one high-profile exception, with broad engagement across various agricultural sectors). Critically, this also often implies that actors with the 'power of the purse' (e.g. treasuries) are not included in the process. As a result, few LMIC NAPs are costed, much less included, in national budgets. Public health officials and non-governmental actors (e.g. clinicians) frequently describe the more basic problem of being unable to 'make the case' for AMR as a priority vis-à-vis competing health and other public policy causes.

In MIC, attention to AMR from the human health communities at least, is usually present. However, this does not necessarily translate into funding or political will, and consequently, implementation is still lacking. Brazil is an example of a country with an NAP that experts describe as strong and detailed, but has translated into limited action without a dedicated budget.

In LIC, this attention may be less apparent due to more immediate public health concerns. As a result, levels of national engagement diverge widely. Often, such divergences are explained by the presence or absence of 'local champions': individual officials included in global dialogues around the importance of AMR due to their interest or personal connection to the topic and who have a voice and/or credibility to shift national health policy dialogues towards AMR. Nevertheless, even where such local champions are present, they are obstructed by an inability to make the AMR case to actors at the central level 'holding the purse strings', as described above.

Upward feedback loops from national to global level

Currently, despite data being a key bottleneck across several themes and enablers, most information on interventions and best practices cascades downward from the global to the national level. Where information translates upward, it is mostly with regard to monitoring the status of the AMR response per country, such as GLASS, the WHO's self-assessment survey or the OIE's Annual Reports on Antimicrobial Agents Intended for Use in Animals. While these are a key part of enabling the global response, few data points around best practices or experiences with implementation are collected.

In addition to information challenges, issues with regard to influence also persist. LMIC experts reported a persistent perception that the global response to AMR is driven by a small group of mostly HIC countries, with little room for LMIC to shape the global agenda. At the same time, policymakers in HIC and global governance organisations describe difficulties in engaging LMIC officials on the importance of AMR (e.g. frustrations about limited G-77 engagement at the UN level). Improving communications and participation are an important step to strengthening commitments to impact at the national level.

Redefining the NAP narrative: Data and story

All of the critical gaps on national action relate to the lack of availability (and level of granularity) of AMR data. This makes it especially difficult to translate momentum from NAPs, should they have been developed, into effective implementation. However, hard data in and of itself is not enough to spur policymakers into action. There is a clear need for a compelling narrative to 'sell' the story on AMR. Given that no convincing narrative has emerged since the 2016 Political Declaration, some experts noted that there is a potential opportunity to frame AMR in the 'language of pandemics' (i.e. as a 'slow-moving pandemic'). Covid-19 has spurred an increase in awareness on infectious diseases, both from policymakers and the population more broadly. It should be noted, however, that this increase in awareness is accompanied by broad fatigue on healthcare advice in general, and this is an obvious risk for any reframing of AMR. (See the Covid-19 chapter for a more detailed discussion of the reframing opportunity for AMR).

Priority of critical gaps for the overall AMR response

National action is a critical arena for the overall AMR response. Without national action, no implementation occurs.

Generating actionable country-level data is necessary to allow the AMR community to demonstrate the scale and urgency of AMR to policymakers. Ideally, this data should be gathered at the regional and local levels wherever possible so as to create accurate financial implication assessments. These, in turn, can be used by policymakers to make informed trade-offs over resource prioritisation (which may or may not be responding to AMR).

Yet the AMR community may benefit from more strict differentiation between national contexts. In some countries, deprioritising AMR vis-à-vis a range of other public health concerns may well be appropriate from a public and health policy perspective. Rather than expending political capital and attention on the topic of urging 'copy-and-paste' exercises of the global action plan, the AMR community might instead focus on promoting AMR-sensitive interventions (e.g. certain IPC measures in healthcare facilities). Additionally, including relevant LMIC success stories could provide a platform to celebrate action and an impetus to develop best practices and spur interest.

Given that many NAPs are either coming to an end (e.g. 5-year plans) or approaching their mid-terms, the next few years could serve as a useful time to conduct analytic mid-term/exit reviews. These could serve to chart progress, ensure renewed policy interest (especially with much attention diverted to Covid-19) and allow for integration into broader national health policy initiatives.

Comprehensive national action could focus on actionable and pragmatic data generation for policymakers, while implementing a limited set of the most promising known interventions (IPC, WASH, stewardship guidelines, bans on certain types of animal and plant use). Funding and trialling such an approach in a small set of pilot countries could serve as a tactical move to re-energise the AMR community by demonstrating impact and focus. Such pilots would have the advantage of reducing a problem to a limited scale, while also presenting a broad One Health response.

Image:
Luuk Rombouts

Global governance

Global governance

Problem statement and context

Global governance can be a crucial enabler of the response to AMR. Yet, policymakers are divided in their opinion on whether strong global governance institutions are the most effective way to combat AMR, compared to intergovernmental action relying on a small set of nations championing the topic on the international political agenda, or even national action. In addition, when assessing global governance, it may be difficult to distinguish between simple activity, and impact.

Currently, the WHO, FAO, and OIE Tripartite serves as the main governance institution leading the AMR response at the global level. Following the 2016 Political Declaration and the resulting IACG process, the IACG recommended the AMR Leadership Group establish three main governance structures (the Global Leaders Group, the Independent Panel on Evidence, and the Partnership Platform). At present, the public discussions process has been completed for the Global Leaders Group and the Independent Panel on Evidence, and is currently ongoing with respect to the Partnership Platform, but experts were unable to provide further details on the advancement and implementation of this new structure.

Status quo

One of the key successes of the 2016 Political Declaration has been to firmly anchor AMR as a priority on the global health agenda. Yet experts, including policymakers, global AMR leaders, and leaders among global health more broadly, voiced significant concerns about the underlying health of the global governance response (see section on critical gaps).

Leadership and ownership are clearly regulated at the level of the global agencies, with the Tripartite generally considered an effective coordinating body that has improved over time. In addition, AMR has received stronger traction across the entire UN ecosystem (albeit at different levels, given ongoing frustrations such as engagement with the UN Environment Programme). The newly created IACG-recommended Leadership Group hopes to provide an additional forum on global leadership.

Among global action, funding remains a major limiting factor, especially with respect to resources for non-human health. The WHO's AMR budget of $41.7 million is >35 per cent larger than the entire OIE budget of $30 million. The FAO's full-time resource commitment to AMR reportedly consists of two junior staff members.

Intergovernmental action represents the second pillar below global agencies. Importantly, multiple experts in national and global-level policy positions lament having been forced into an improved awareness of simply how reliant AMR global governance was on the initiative shown by the UK-US axis. The almost simultaneous shift in geopolitical priorities in both countries since 2016 was described as a significant 'double whammy'. One particularly grave consequence is a perception that, in 2016, the global AMR community was substantially closer to agreeing on a large-scale pull incentive for therapeutic innovation than it is today. This sentiment has only intensified in the context of the Covid-19 pandemic and the increasing difficulty in getting AMR attention from policymakers.

Several HIC policy representatives voiced frustrations about the difficulty in convincing LMIC political leaders of the importance of sustained global political action on the problem of AMR (e.g. very limited engagement by the G-77 at UN level). Equivalently, some countries expressed concerns about perceptions of global leadership dominated by a small set of Western countries.

Critical gaps in global governance

Focus and prioritisation

Based on conversations with leaders at all levels of the response to AMR as well as some additional global health leaders more broadly, a clear message emerged. Bringing all elements of the response to AMR to the table over the past few years has been a substantial and necessary achievement. At the same time, the complexity of the AMR landscape, combined with a dearth of evidence allowing policymakers to quantify the relative contribution to resistance of different themes, has led to a state of paralysis – the metaphorical 'deer in the headlights'.

Consequently, some prioritisation of actions is now needed to prevent sleepwalking into a crisis where the collective level of belief in its urgency has not been matched by impactful action. The global community at large, but especially the new Leadership Group and Independent Panel on Evidence, should take into consideration how the critical path forward looks for the AMR response. Again, this sentiment has only strengthened in the context of the Covid-19 pandemic with the need for action even more acute.

Losing momentum

Analogous to other social issues for which awareness must be built in a multi-year process, demonstrable impact often naturally lags behind awareness levels. This creates an intermediate plateau phase in which a sense of urgency is not matched by visible success, and which, if lasting for too long, can result in demotivation and a shift in attention and resources to other causes.

In the case of AMR, this is exacerbated by the fact that due to regular turnover in policy communities, many of the policy 'veterans' of 2016 may no longer be in their positions, resulting in a loss of institutional memory. This loss of institutional memory is again intensified in the context of the Covid-19 pandemic, with many infectious disease and policy experts shifting their attention to the immediacy of vaccine/therapeutic developments for Covid-19.

The current global response to AMR appears firmly lodged on this plateau. The adoption of the IACG recommendations may break through this deadlock, but experts demonstrated scepticism for two reasons. Firstly, the almost three-year period between the establishment of the IACG and the presentation of its recommendations is viewed by some as lost time. In the words of one expert, "the IACG would have achieved much more had it been completed in 6 to 10 months". Secondly, a related, broader criticism of AMR global governance in the past years has been a perception of selling activity for impact and presenting talking shops without reaching implementation. It is unclear to what extent the new institutions can provide the needed momentum and visible success to re-energise the community.

Achieving accountability

Experts disagreed to what extent an insufficient global governance response has been a failure of resourcing (which, they generally agreed, is insufficient) or, at a more fundamental level, of political will. In parts, this hinges on definitional difficulties with what constitutes 'political will'. One possible framework to conceptualise political will sees three levels of hierarchy:

I. **Championing:** At the most basic level, political will is expressed by championing an issue in the domestic or international agenda. In concrete terms, this may be expressed by ensuring an issue is simply on the agenda in political discussions with other policymakers. AMR found strong national champions prior to the 2016 Political Declaration (especially in the US and the UK), and is by now sufficiently mainstreamed into the global political agenda (see above).

II. **Funding commitments:** The second stage requires political actors to "put their money where their mouth is". The global response to AMR has achieved partial success in this area, with significant funds at the WHO level, some national levels, and some elements of ODA (e.g. the Fleming Fund). At the same time, some segments remain underfunded – most evidently a global pull incentive to spur therapeutic innovation.

III. **Accountability:** At the final stage, political actors expose themselves to (external or internal) accountability by setting measurable targets, monitoring progress towards them and correcting course where their achievement fails. AMR has not reached this final stage in almost any setting, with few countries committing to clear and measurable reduction targets. Notable exceptions include the UK's 2019 five-year strategy and its June 2020 announcement that the NHS will begin paying pharmaceutical companies "up front for access to their [novel] antibiotic product, based on a product's value to the NHS, rather than how much it is used."[81] At the international level, no clear and agreed-upon reduction targets have been adopted by the global community, and the IACG process itself has so far resulted only in recommendations.

[81] UK Department of Health and Social Care. World-first scheme underway to tackle AMR and protect UK patients. DHSC 2020 17 June. https://www.gov.uk/government/news/world-first-scheme-underway-to-tackle-amr-and-protect-uk-patients.

Priority of critical gaps for the overall AMR response

The need for focus and prioritisation affects all fields of the AMR response. The new institutions emerging from the IACG recommendations should take this into consideration from the outset and lead the global AMR community to impact along the critical path.

While taking near-term actions to prevent the AMR community from losing momentum is not the highest-impact action in a direct comparison to other themes and enablers of the overall AMR response, its effect may be of substantial counterfactual value. Leaders who mention this risk point to it as a serious *downside* risk of inaction. Fears include that such a loss of momentum could very significantly dent the enabling environment, leading to even less funding, reduced awareness-generating efforts and limited participation in coordinating bodies. Moreover, this momentum challenge is doubly important in the context of the Covid-19 pandemic. It is thus of the utmost importance that action be taken to prevent the unravelling of a significant share of the progress made in the run-up to and wake of 2016.

Appendix 2: Overview of the methodology, sources, and sampling

Overview of the methodology, sources, and sampling

Structuring the AMR landscape

A comprehensive landscape analysis mapping out all elements of AMR rather than looking at a predefined subset requires a framework. Such a framework must both fulfil criteria of being collectively exhaustive (to the greatest extent possible) and simultaneously draw clear distinctions between these elements.

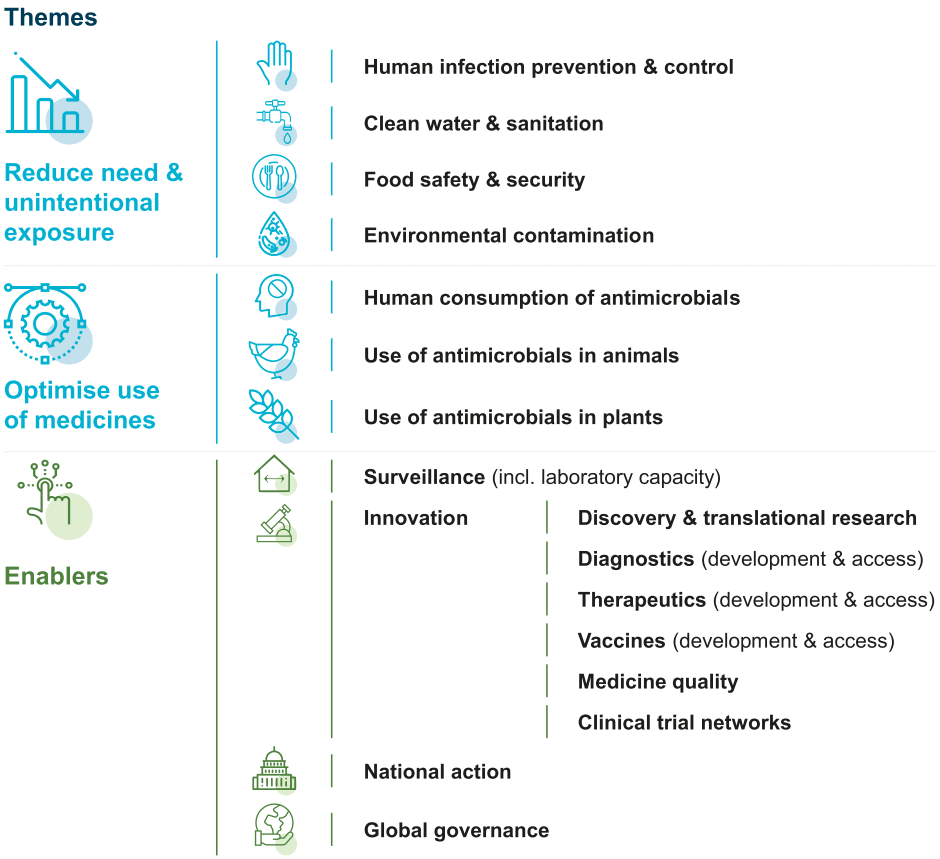
To map out the landscape, the present effort relied on a modified version of the 2017 IACG AMR Framework for Action. This provided multiple benefits: firstly, the IACG framework shared the ambition of the current project to present a comprehensive map of the AMR landscape. Secondly, the IACG framework was the result of a multi-month stakeholder consultation process, representing the closest thing to a consensus framework across the entire AMR community. Thirdly, it was designed to achieve compatibility with both the 2016 Political Declaration and the Global Action Plan.

Some minor adaptations to the framework were made. Most significantly, levers were replaced by potential gaps as the horizontal axis of the frame, which represents the 'lenses' through which each theme and enabler is analysed. This decision was motivated by the fact that not all levers are applied to all themes and enablers, and that questions around problem definition and solution space were insufficiently addressed by levers. Lastly, levers did not allow an overarching analysis of the implementation status per theme and enabler.

Adjustments to individual themes and enablers include adding health security, separating out use in plants as a standalone theme and including food security as an addition to food safety – see Appendix 1 for further detail. In addition, innovation topics were

AMR landscape framework

Exhibit 6



considered as overarching enablers rather than as individual themes.

The framework divides themes into two broad categories: reducing the need for and unintentional exposure to antimicrobials, and optimising the use of antimicrobials. Several overarching enablers cut across all themes and support sustainable progress. The problem and ambition for each theme and enabler is clearly delineated:

- **Human IPC:** Reducing antimicrobial use by reducing the need for antimicrobial treatment through preventing the occurrence of infection and controlling its spread
- **Clean water and sanitation:** Reducing antimicrobial use through preventing the transmission of drug-resistant infections via clean water and improved hygiene
- **Food safety and security:** Limiting the transmission of resistant pathogens to humans through the food supply, and mitigating risks to food security from AMR impact on food animal and plant health
- **Environmental contamination:** Limiting the transmission of resistant pathogens to humans through the environment (mainly soil and water systems), and limiting de novo resistance development in environmental systems
- **Human consumption of antimicrobials:** Reducing the development of pathogen resistance through good stewardship (limiting misuse for wrong indications, in improper dosage, or for the wrong treatment duration, while ensuring access is sufficient to effectively prevent and control infections), and therefore slowing the rate at which existing therapies lose efficacy
- **Use of antimicrobials in animals:** Reducing the development of AMR from antimicrobial use in livestock, aquaculture and companion animals, and reducing its transmission to humans
- **Use of antimicrobials in plants:** Reducing the development of resistant pathogens in plants, their transmission to humans through horticultural products (mainly fruit and vegetables, but also flowers, etc), and the effects on environmental resistance development from applying high concentrations of antimicrobials directly to soil and water systems on fields or in groves
- **Surveillance (including laboratory capacity):** Building comprehensive, accurate and actionable resistance databases in humans, farmed animals and plants, and the environment, to enable and monitor an effective AMR response and to appropriately allocate resources within AMR and between AMR and other public (health) challenges
- **Discovery and translational research:** Ensuring a healthy early-stage research environment and pipeline from target and lead identification to translational medicine to support therapeutic innovation to combat AMR
- **Diagnostics (development and access):** Developing affordable, accurate and timely point-of-care diagnostic tests, ensuring adequate access to them, and reducing barriers to their use, to enable antimicrobial stewardship
- **Therapeutics (development and access):** Developing new therapeutics (e.g. new classes of antibiotics) to overcome resistance developed to older treatment options, ensuring adequate access, and creating a sustainable R&D ecosystem and market environment for them that supports a healthy long-term pipeline
- **Vaccines (development and access):** Reducing the need for antimicrobial use by preventing infection through developing and ensuring access to effective vaccines in humans and animals
- **Medicine quality:** Tackling substandard and falsified medicines to ensure drugs have the required therapeutic efficacy, limiting resistance pressures due to suboptimal dosing
- **Clinical trial networks:** Establishing networks of trial sites to improve efficiency, speed and cost of new antimicrobial development. Continuously running studies through clinical trial networks would lower start-up costs and provide access to well-trained staff
- **National action:** Securing implementation of the global AMR response at the national level through policymakers and other in-country stakeholders
- **Global governance:** Creating and maintaining strong global institutions that can enable and support the response to AMR

For more detailed information on the problem statement and context for each theme and enabler, please refer to the detailed profiles in Appendix 1.

Assessment of themes and enablers

The progress, momentum and gaps in each theme were assessed along eight questions, as shown in Exhibit 7.

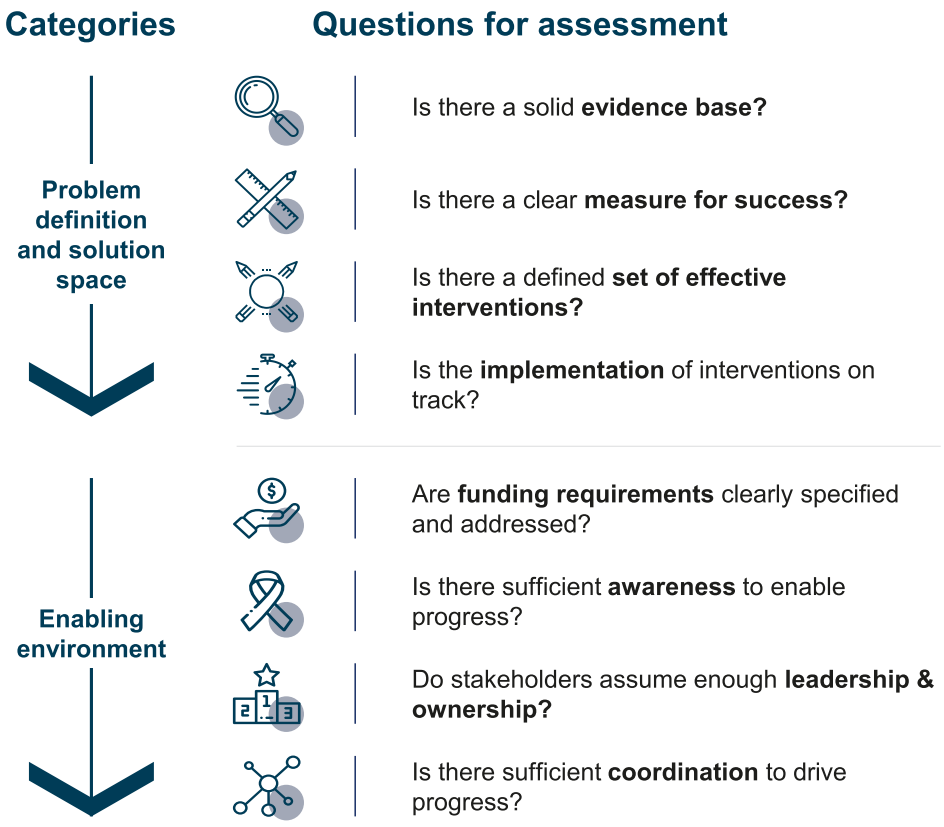
The first four questions refer to each theme's or enabler's problem definition and solution space (both in terms of a known set of solutions and their implementation level). The other four questions analyse the enabling environment.

Sources of insight: Sampling and analysis

The landscape analysis draws on insights gathered across two phases of expert sourcing. The original landscape analysis, conducted in July-September 2019, collated insights from over 90 interviews and over 255 reports, articles, and data repositories. Interviews represented the focus of data collection, with desk research used to buttress hypotheses and fill gaps.

Assessment questions for themes and enablers

Exhibit 7



Interviewees were selected from a pool of recognised experts on each theme and enabler, covering different geographies (HIC, MIC, LIC) and sectors (policy, private sector, research, social sector, advocacy). Gaps were filled through review by the wider project team. In addition, interviewees were routinely asked for suggestions on additional experts to contact in their fields.

Insights and results were scored across the eight questions and aggregated to the landscape level. Scoring metrics were carefully tailored to each question, as depicted in Exhibit 8.

Scoring metrics

Exhibit 8

Categories	Criterion	Low maturity	Medium maturity	High maturity
Problem definition and solution space	Evidence base	Problem and impact on AMR not understood (hypotheses only)	Despite general understanding several evidentiary gaps remain	Widely accepted and quantified evidence of importance for AMR response
	Measure for success	No measures defined and no monitoring attempts	Imperfect measures with limited consensus	Metrics for success defined and agreed
	Intervention design	Effective interventions not clearly described	Some interventions described, impact not well understood	Full set of interventions that can sufficiently address the problem
	Intervention implementation	No meaningful implementation of interventions observed	Implementing in progress in some settings, and not started in others	Implementation of effective interventions on track globally
Enabling environment	Funding requirements	Funding needs not identified or specified	Needs identified, but considerable room for more funding	Needs identified and well-known, and funding needs met
	Awareness	No awareness among any relevant stakeholder population	Awareness among some stakeholders, but insufficient to address all relevant angles	Broad awareness and understanding across stakeholders in line with scale of AMR risks
	Leadership & ownership	No leadership and ownership among relevant stakeholder population	Limited leadership and/or ownership, e.g., in some sectors or geographies	Strong leadership and clear ownership across sub-themes and geographies
	Coordination	No meaningful coordination among main stakeholders observed	Limited coordination but not enough for effective collaboration	Clear roles, aligned agenda, and effective working mechanisms

The refinement of the analysis and update in light of Covid-19 in July-September 2020 captured the perspectives of over 80 experts, in a mixture of workshops with on average 5-8 participants, covering priority topics; as well as in a series of individual interviews. Some of these experts had been contacted in the first phase in 2019, while others were newly selected based on e.g. their Covid-19 expertise.

Methodologically, two key differences persisted due to the different nature of the exercise. Firstly, conversations were deliberately no longer "double-blinded" as in the first round of interviews. Secondly, workshop results were not scored according to the above metrics, but rather reviewed by several participating reviewers, and synthesised into updates to the landscape (where appropriate) through multiple iterations.

Defining impact and an underlying normative frame

For the analysis above – and especially where prioritisation is concerned (see chapter on critical path) – impact is defined as reducing or avoiding drug-resistant infections in humans. Where animal or plant health is considered, this is regarded from a human health standpoint: reducing AMR in animal and plant pathogens with the target of reducing their transmission to humans. With a different underlying normative framework that saw human health as equally important to animal (and perhaps plant) health, different conclusions could be drawn from the landscape analysis.

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DOI: 10.6084/m9.figshare.13221710