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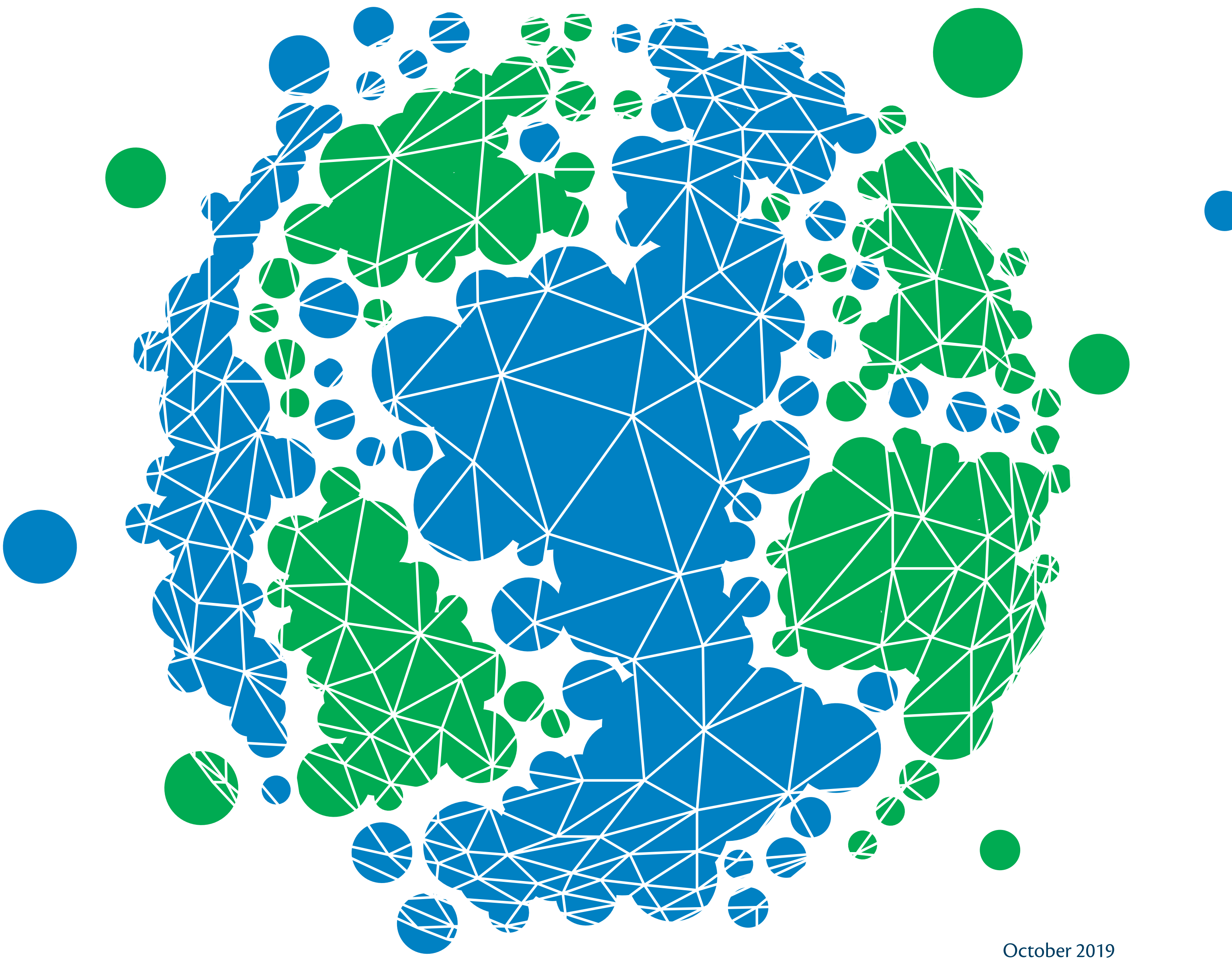
Pulling Together to Beat Superbugs

Knowledge and Implementation Gaps in Addressing Antimicrobial Resistance



October 2019

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Foreword

Imagine a world rife with infectious diseases that are impossible to cure, even with powerful antibiotics. Or living with the threat of virulent new strains of malaria and tuberculosis that are resistant to tried and tested medical interventions. For millions of people, especially newborns and the elderly, this is becoming a terrifying reality.

Anti-microbial resistance (AMR), which reduces our ability to treat infectious diseases and breeds 'superbugs' that are difficult to stop, has emerged in the last decade as a growing threat to public health. This silent pandemic is already leading to 700,000 deaths per year. If not addressed, AMR could cost millions more lives — or as many as 10 million deaths annually by 2050, which is higher than the death rate for cancer, currently the second leading cause of death globally. People living in developing countries and those affected by fragility, conflict and violence are particularly vulnerable.

AMR is not just a health problem, it's a development problem. Unchecked, it will impact people's health and life prospects, and ultimately, countries' human capital. It will also hamper progress towards the 2030 Sustainable Development Goals and harm economies. If unabated, AMR's economic impact is projected at more than US$ 1 trillion annually after 2030.

What can we do to put people everywhere on a safer path?

This report finds that countries can make AMR-related investments more efficient and cost-effective by improving technical capacity and data quality, enhancing interagency coordination and building public awareness of the AMR challenge.

It also lays out an agenda for the research community by identifying knowledge and implementation gaps. In particular, implementation research, which focuses on improving the effectiveness of interventions through policies, programs and practices, will be key in moving AMR knowledge from laboratory settings into the real world. It is vital that all stakeholders know what works in diverse and challenging development contexts and tailor solutions to specific country circumstances.

Finally, the report urges the development community to go beyond technical solutions that focus exclusively on the misuse of antimicrobials. We need to redirect development efforts more broadly, so that they become "AMR-smart."

This means being more conscious of how investments can affect AMR and using available financing more astutely. This will require applying a rigorous and imaginative AMR lens to all investments.

In addition to interventions specifically aimed at AMR, a diverse set of actions across multiple sectors — such as improving public health systems, increasing access to clean water and sanitation, building resilient agriculture and food systems, educating younger generations on AMR, or designing urbanization and infrastructure to stop contamination — will be part of the effort to curb the rise of AMR.

There is no simple cure-all for the AMR challenge, but a more holistic approach will help ensure that everyone can look forward to a healthier future.

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Executive summary

Antimicrobial drugs such as antibiotics have revolutionized medicine and saved hundreds of millions of lives since their discovery some 70 years ago. People no longer fear that a simple graze or cut will become septic and that they could die as a result, and most people now have the freedom to routinely undergo life-enhancing surgery previously thought impossible due to the high risk of untreatable infections.

The rise of antimicrobial resistance (AMR), if not stopped, threatens to plunge humanity back into an era of health uncertainty few people alive today can remember. AMR does not follow national borders; its consequences affect the lives of everyone on the planet and blight the prospects of future generations. Yet with the right approach and intelligent investment, the AMR tide can be turned. This report sets out a fresh way to look at the AMR crisis. It uses a new narrative to identify areas where knowledge gaps exist and further investigation is needed. It suggests that too much effort is spent searching for the right solutions in the wrong places, and proposes ways of "pulling together" across traditional institutional and disciplinary boundaries to contain and reduce AMR.

Antibiotics and other antimicrobials have become an essential infrastructure of modern society. They are ingrained in our health systems, in our food systems, and in our relaxed approach to risks of minor ailments and injuries. Modern societies are totally reliant on antimicrobials and their continued effectiveness. From a broader perspective, humanity's relationship with antimicrobials can be considered in terms of (a) norms and behaviors—our assumptions, beliefs, and attitudes to antimicrobials in areas such as human medicine, agriculture, livestock, and the environment; (b) use and governance—the roles and responsibilities of different actors, industries, institutions, and countries; and (c) external trends beyond the system of antimicrobials—such as global population growth, urbanization, globalization, climate change, and conflicts—that create the conditions for the rapid emergence and spread of AMR worldwide.

The threat of AMR is not new. It is a natural phenomenon that Alexander Fleming publicly warned about in the early days of penicillin. Scientists have long been aware that the misuse of antimicrobial drugs could accelerate the evolution of resistant microbes. Over the past three decades, the public health and agriculture communities recognized AMR to be an economic and health problem caused by inappropriate and excessive use of antibiotics, exacerbated in turn by the dwindling supply of new, more effective drugs coming onto the market. At the same time, the AMR literature has grown exponentially from less than 2,000 scientific journal articles per year in 1990 to over 11,000 in 2018. This report's extensive bibliographic review found a broad spectrum of interventions to control AMR across three main action areas: (1) establishing and maintaining an enabling environment for AMR control through agenda setting, regulation, legislation, and surveillance and monitoring; (2) reducing the need for antimicrobial usage through measures to prevent infection such as better hygiene, vaccination, and improved livestock husbandry; and (3) limiting the use of antimicrobials by means of economic incentives and disincentives, as well as education and awareness raising of prescribers and users.

The vast majority of published knowledge and evidence covers AMR from the perspective of high-income countries (HIC) across a narrow range of subjects. While progress on abating AMR has been achieved in some HIC situations, there remains a significant gap between proposed technical solutions and the reality of implementing them in practice. This implementation gap is even more acute in low- and middle-income countries (LMICs), which will bear the greatest burden of AMR's rising social and economic impacts.

Through several country-based case studies, this report illustrates factors that either enable or block interventions for controlling AMR in specific LMIC contexts. The report identifies knowledge and implementation gaps that merit research attention, together with actionable interventions that can be applied now. It particularly focuses attention on the importance of local context in carrying out implementation actions by proposing a typology of countries in terms of the interventions likely to provide the greatest benefits. An international summit of AMR experts convened by the Wellcome Trust (2016) agreed: "…even if some evidence gaps remain, meaningful actions need to be taken immediately to counter AMR, with individual countries tailoring implementation according to their particular national circumstances."

In contrast to HIC nations, countries at lower levels of economic development tend to be more exposed to key contextual risk factors that exacerbate the spread of AMR. Given the significance of AMR risk factors that increase the transmission of AMR in LMICs—such as poor sanitation, lack of access to clean water, poor governance, insufficient public health-care expenditures, or poorly regulated private health services—efforts to promote prudent and responsible use of antimicrobials, while desirable, are not enough for controlling the spread of AMR, particularly at lower levels of economic development. In LMIC contexts, interventions that act indirectly on AMR such as water and sanitation improvements, termed AMR-sensitive actions, may have greater impact and be more cost-effective in controlling AMR than direct interventions such as banning antibiotics in animal feeds, termed AMR-specific interventions.

Two intertwined findings of this report are that (1) AMR needs to be reframed as a global development issue that cannot be solved with technical solutions alone; and (2) AMR-sensitive interventions are often the most cost-effective way, especially in LMICs, to overcome the underlying weaknesses in establishing an enabling environment for successful application of AMR-specific interventions aimed at reducing the unnecessary use of and overreliance on antimicrobials.

Curbing the rise of AMR demands that it be refocused as a development problem. Addressing AMR is necessary to attain many of the sustainable development goals (SDGs), and it is likewise true that making progress on several SDGs and their specific targets also will contribute to tackling AMR. This virtuous synergy should be recognized more widely and exploited more fully.

Knowledge gaps exist, but they are overshadowed by a "doing" gap. Efforts to address AMR are seriously compromised by the low level of implementation, the fragmentation of interventions, their poor sequencing in time and geography, and their deployment in environments that are not conducive to the AMR control measures selected. Abundant knowledge exists, yet people do not seem to know what to do, or how to do it. This calls for major efforts in the field of implementation research to bridge knowledge and actions in real-world settings.

To this effect, it is paramount to build research agendas in the specific contexts of countries to bridge the implementation gap and overcome the shortcomings of best practice approaches. Out of twenty-three key knowledge and implementation gaps identified in the course of this study, one stands out: It is our limited capacity to identify and measure potential cobenefits across a broad array of AMR-sensitive interventions in country-specific contexts.

Introduction

A SLOW-MOTION TSUNAMI

You wake up one morning, reach over and grab your phone. Your heart sinks when you read a message explaining that one of your dearest friends is in critical condition after pulmonary infection and is heading into intensive care. You hope she will come through the experience and you might assume that the antibiotics she needs will work. It's exactly that assumption that many of us take for granted. Every day people across the world rely on antibiotics; they've done so for decades. They are used to treating life-threatening bacterial infections in organ transplants, chemotherapy, and caesarean sections, as well as to control diseases and pests in agricultural crops and livestock production. Antibiotics and other antimicrobials have become ingrained in our health systems, our food systems, and our societies. We are now heavily reliant on their effectiveness.

That reality is now disappearing as the emergence and spread of antimicrobial resistance (AMR) threatens the health and well-being of people across the world. A world without effective antibiotics is a problem on many fronts. It has been estimated that AMR already costs up to 700,000 lives per year (O'Neill 2016), although the true burden of resistant infections remains uncertain. The number of deaths caused by multidrug-resistant organisms (MDROs) could be more than six times higher than the widely cited figures (Burnham et al. 2019). And the actual number of treatment failures is probably much larger, since there is a strong focus on consequences of resistance to last-resort antibiotics, while the likely much larger number of treatment failures due to resistance to first-line drugs is virtually unknown.

AMR stands to take millions more lives; unaddressed, it could inflict an economic impact in excess of $1 trillion annually after 2030 (World Bank 2017a). Moreover, AMR will disproportionately affect those in low- and middle-income countries (LMICs), making the issue an important development challenge. Far beyond public health, AMR and the rise of superbugs threaten to undermine several of the development gains made in the 20th century.

Imagine a world where a simple graze or cut could be life-threatening. In addition, simple surgery—not to mention organ transplantation—could only be conducted at an unacceptable risk.

The report aims to reach a broad audience, beyond those conversant in AMR. For those unfamiliar with antimicrobial resistance, a primer on AMR is an annex to the report.

In April 2016, addressing a high-level dialogue on AMR with UN member countries, Dr. Margaret Chan, at the time director-general of the World Health Organization (WHO), described antimicrobial resistance as "a slow-motion tsunami." It may be a slow-moving crisis, but it is nonetheless a global crisis that must be managed with the utmost urgency, since we know that it is already with us and the costs and consequences will only increase with time.

The burden of infections with antibiotic-resistant bacteria in the European Economic Area (EEA) already appears substantial (Cassini et al. 2019). There are increasing reports of patients with infections caused by drug-resistant bacteria associated with increased risk of worse clinical outcomes and death, and consuming more health-care resources than patients infected with susceptible strains of the same bacteria. For example, an unprecedented epidemic of typhoid caused by a multidrug-resistant (MDR) clone of the bacterium, known as H58, has rolled across parts of Asia and Africa (Wong et al. 2015; Klemm et al. 2018). An outbreak occurred in the Sindh Province in Pakistan between 2016 and 2018 with 5,274 people reported to be affected by extensively drug-resistant typhoid (WHO 2018f). MDR enteric fevers increase the cost of treatment and lead to more complications (Azmatullah et al. 2015).

Globally, resistance in tuberculosis (TB) would by itself account for a third of the AMR burden. In a recent study following a large multicentered cohort of patients who were diagnosed with TB between 2013 and 2016, drug susceptibility testing revealed that 62 percent of strains


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were pan-susceptible, 7 percent were resistant to only one antibiotic, 26 percent were multidrug-resistant (MDR), and 5 percent were pre-extensively or extensively drug resistant (XDR). Mortality ranged from 6 percent among patients with pan-susceptible (PDR) TB to 57 percent for patients with resistant TB who were undertreated (Zürcher et al. 2019).

Gonorrhea is another example of infection where MDR is a threat (ECDC 2018). The number of gonorrhea cases is rising worldwide, and an increasing proportion of cases are multidrug-resistant. WHO reports that about 78 million people are infected with gonorrhea each year around the world. Ninety-seven percent of the countries surveyed reported the presence of drug-resistant gonorrhea strains, and 66 percent—particularly in high-income countries, where surveillance is best—reported the emergence of resistance to last-resort drug treatments for the infection (Wi et al. 2017; Alirol et al. 2017). In the United States between 2009 and 2017, the number of reported gonorrhea cases increased by 75.2 percent (CDC 2018). Meanwhile, some strains of the causative agent of gonorrhea (*Neisseria gonorrhoeae*) have developed resistance to all but one recommended drug combination treatment.

In general, resistance is already high in many countries, but it is projected to grow even more rapidly, particularly in LMICs (World Bank 2017a). In Brazil, Indonesia, and Russia, for example, 40 to 60 percent of infections are already caused by drug-resistant bacteria, compared to an average of 17 percent in OECD countries (OECD 2018). In these countries, the growth rates of AMR between now and 2050 could be four to seven times higher than in other OECD countries. There are already inequalities among countries. For example, the average resistance proportions in Turkey, South Korea, and Greece are about seven to eight times higher than in Iceland, the Netherlands and Nordic countries (Norway, Sweden, Finland, and Denmark), which have the lowest proportions (OECD 2018). In this study, inequalities in AMR risk are also related to age, with children and the elderly being most vulnerable.

Different population groups can be at higher risk. AMR adds to the devastation of conflict by increasing medical costs, blocking hospital beds because patients need care for a longer time, by reducing productivity and earning potential, and by leaving more people with life-long disabilities (Jakovljevic et al. 2018). Fragility, conflict, and violence can be factors of emergence (locally) and spread (locally and beyond) of resistance (de Smalen et al. 2017; Aro and Kantele 2018).

AMR is a catchall term that encompasses a diversity of resistance determinants, emergence, and spread mechanisms. Discussions about AMR often oversimplify this biological complexity. A recent study in the EEA shows that different types of resistance vary in terms of the number of cases and the number of attributable deaths (Cassini et al. 2019). AMR also is a dynamic process. It is a function of time and use: the larger the quantity of antimicrobials consumed and the longer the time for which they are consumed, the greater the selection pressure for resistance. First-line antimicrobials change as AMR evolves, as illustrated by ceftriaxone, which is now a first-line treatment for gonorrhea, although it was developed as a third-generation cephalosporin. The levels of resistance to first-line treatments can be expected to increase with time; however, the rates of resistance to second- and third-line antibiotics could increase even more rapidly. A recent study estimates rates will be 70 percent higher in 2030 compared to 2005 for the same antibiotic-bacterium combinations (OECD 2018).

Beyond resistance to antibiotics and the rise of resistant bacterial infections, there is rising concern about resistance to (a) antiviral drugs, such as HIV/AIDS drugs; (b) antifungal drugs, such as treatment for infections with *Candida auris*; and (c) anti-parasitic drugs, such as first-line treatment for malaria (artemisinin-based combination therapies, also known as ACTs). This report focuses on AMR, primarily understood as resistance to antibiotics. It also focuses on AMR as the mechanism by which infections become difficult or impossible to treat. Superbugs is a popular name for multidrug resistant bacteria making AMR a global threat.

The antimicrobial resistance wave has already hit and many are suffering in the flood.

KNOWLEDGE AND IMPLEMENTATION GAPS

The current global political agenda on AMR has been shaped by a small number of countries. Among these countries, the UK, Nordic countries, and several other EU member states have been champions. They have worked through the European institutions, the G7 and G20 forums, as well as the United Nations (UN) and its technical agencies (such as WHO, FAO, and more recently UNEP) and OIE, embracing a broad spectrum of the issue's multiple facets. For example, Mexico, Ghana, and Thailand have taken an active role on AMR. Countries from around the globe have participated in regional and global coordination of AMR efforts through various constituencies of the UN system, and 193 countries supported the adoption of a political declaration in September 2016. A great number of these countries have prepared national action plans (NAPs), which provide a framework to assign responsibilities to institutions and sectors. Mainstream media have reported on the AMR issue, often covering specific aspects such as the role of livestock or conditions of health wards in conflict zones. Since 2010, the world has moved to some AMR awareness, but the implementation gap remains huge (IACG 2019a and b).

In April 2016 the Wellcome Trust organized an international multidisciplinary summit, bringing together policy makers and researchers from more than 30 countries and 14 multilateral institutions to discuss the evidence underpinning a range of AMR policy interventions. The summit concluded that, even if some evidence gaps remain, meaningful actions need to be taken immediately to counter AMR, with individual countries tailoring implementation according to their particular national circumstances (Wellcome Trust 2016).

There is a substantial and rapidly growing body of evidence on AMR. A bibliometric analysis of global scientific research on carbapenem resistance over the period from 1986 to 2015 shows a significant increase in the number of publications in the past few years (Sweileh et al. 2016). Such an increase in publications is occurring in many areas of the AMR issue. A PubMed search using "antimicrobial resistance" [performed on March 18, 2019] resulted in 219,113 hits (including 51,138 for the past 5 years), showing that more than 9,000 peer-reviewed scientific papers have been published in English every year since 2012 (with a record of 11,158 in 2017). Despite existing knowledge, the challenge posed by AMR remains formidable. Efforts to address AMR—particularly in low- and middle- income countries (LMICs)—have been complicated and are compromised by the low level of implementation, the fragmentation of interventions, their poor sequencing in time and geography, and their deployment in difficult environments for AMR control measures to be effective.

By the end of May 2019, 127 countries had a NAP. In most countries, however, the challenge is not about writing a plan; it is about implementing the plan once it has been written. According to the ad hoc Interagency Coordination Group (IACG), six factors in particular have made implementing NAPs a challenge: awareness, political will, coordination, monitoring, data quality, and technical capacity (IACG 2018 b). There is insufficient knowledge regarding the local (or national) nature and extent of the problem, which interventions to implement, and the ability to predict the positive effects of perhaps costly interventions.

There is an urgent need to address these knowledge and implementation gaps, to facilitate local implementation of policy interventions, and to support the development of longer term solutions. Important evidence gaps will continue to exist, but there is abundant evidence to support immediate action, and the risks justify action even in areas of scientific uncertainty. Further research can provide a clearer picture, supporting prioritization as well as the development of more targeted AMR countermeasures. In addition, "learning from doing" and sharing knowledge and experience of implementation in different contexts will provide further evidence to support national efforts to combat this very real threat to human development (Wellcome Trust 2016).

NOT JUST A COMPLEX ISSUE; A WICKED PROBLEM

Although the probability of AMR becoming a problem was first raised before the beginning of the modern antibiotic era, and the emergence of AMR was recognized as a real problem in the 1970s, only much later has AMR started to be defined as falling into the "wicked problem" category (Hutchinson 2017).

The term "wicked problem" was first used by Rittel and Webber (1973) with reference to the complicated social issues affecting urban design and planning, in which "... the search for scientific bases for confronting problems of social policy is bound to fail, because of the nature of these problems. They are 'wicked' problems, whereas science has developed to deal with 'tame' problems."

Understanding the true nature of wicked problems may not only help to explain the relatively slow pace achieved so far in dealing with AMR, but also provide new insights into how to approach and implement actions that will accelerate progress in its containment.

Rittel and Webber (1973) proposed ten characteristics of wickedness associated with social or cultural problems that are difficult or impossible to solve. Of relevance to AMR are issues—such as incomplete or contradictory knowledge; difficulty in clearly defining the problem and solution; the number and social diversity of people and opinions involved; the large economic burden of the problem; and the intertwined nature of the problem with other problems—that are particularly significant features of AMR.

Approaching AMR as a wicked problem—and accepting that success can only be measured in terms of "better versus worse" outcomes, rather than "true or false" options—will help identify and understand the need for new social compacts, the inadequacy of the existing fragmented disciplinary approach to AMR, the importance of context, and the current lack of consensus among global, regional, and national actors on the most effective way to address the issue. Furthermore, given that wicked problems have no definitive problem statement, being characterized as an evolving set of intertwined questions and constraints, the linear process of first understanding and only then solving is doomed to fail.

Coming to grips with real world wicked problems—such as AMR, climate change, or child stunting—requires not only research to develop successful interventions, but more importantly greater efforts to understand how to implement these interventions effectively in diverse real-world contexts. Implementation research (Peters et al. 2014) is a powerful—yet largely neglected—tool for interdisciplinary investigation of the multiple interactions between what can be achieved in theory and what happens in practice in an iterative way with a much greater emphasis on social sciences than is currently the case.

PIECING THE AMR PUZZLE TOGETHER

This report aims to identify and organize critical gaps in knowledge and implementation in relation to AMR. It brings pieces of knowledge and experience together to document these knowledge and implementation gaps, not as pure academic gnosis but as meaningful areas where there is some prospect to better address the AMR challenge. By bringing those puzzle pieces together, the report highlights areas of need for further research. It also explores the gap between the technical solutions that we know can address AMR and the reality that they are often not adapted or well implemented in the places where they are most needed.

Chapter 1 takes a new look at the old challenge of AMR. It builds a cross-disciplinary evidence-based narrative. In many cases the use of antimicrobials is a substitute for imperfect infrastructures and failing systems, a starting point to expanding the horizon of what can be done to address the challenge. We reframe AMR as a global sustainable development challenge; one that requires both a technical and adaptive approach, and an approach that acknowledges how and why the use of antimicrobials has become ingrained in our societies.

Chapter 2 aims at reviewing approaches used to date to control AMR and further explores knowledge and implementation gaps. Much has been done to understand and address AMR. Here we survey and categorize most common interventions designed to establish and maintain an enabling environment for AMR control, those designed to reduce the need for antimicrobial usage, and those self-limiting the use of antimicrobials. We also examine how interventions have played out in practice.

Chapter 3 aims to assess and organize key knowledge and implementation gaps. The focus of this chapter is the critical knowledge that is needed—in particular contexts—to support countries, more particularly LMICs, in better understanding and addressing AMR. The report identifies areas where needs exist for further translational, implementation, and policy research. Furthermore, it offers a framework to support national decision making and action. Much of the action on AMR to date has focused on the use, overuse, and misuse of antimicrobials. However, a country's risk profile in terms of AMR also is determined by context. Building on this understanding, we propose a typology for countries to better understand risk related to AMR, preparedness, susceptibility, and needs for research.

This report has a strong focus on country-level actions and options. It offers a selection of case studies that illustrate AMR issues in specific contexts. The case studies highlight interventions along with key factors that enable or block their success. The case studies have been selected to represent a number of AMR issues across different national contexts, spanning low-, middle-, and high-income countries to enrich the analysis and provide illustrations to the reader. The case studies are by no means country case studies, nor are they remotely comprehensive. They have been developed through literature reviews followed by consultation with first-hand observers and national stakeholders. Hence the possibility of bias in the data collected and subjectivity in the observations reported here may not be ruled out.

We have used a hashtag [#KKIG] to flag key knowledge and implementation gaps as they are identified throughout the report. All #KKIGs have also been collated into Table 1, so that the reader can easily refer to this synopsis of gaps, either as they appear in the text, or later, as they are collectively discussed in chapter 3.

TAKING A **NEW LOOK** AT AN **OLD CHALLENGE**

Chapter 1

Taking a new look at an old challenge

In this chapter we build a cross-disciplinary evidence-based narrative on AMR, emphasizing that, in many instances, the use of antimicrobials is a substitute for failing systems and infrastructures. We propose to reframe AMR as a global development challenge; a challenge that requires both a technical and adaptive approach, as well as an approach that acknowledges how and why the use of antimicrobials has become ingrained in many societies. Appreciating the tensions around antimicrobials—the way we think about them as socio-technical objects, the way we use them, and external factors—can be the starting point to expand the horizon of what can be done to address AMR.

AN ENDLESS RACE

Antimicrobial resistance (AMR) is not a new phenomenon. Antibiotic-producing organisms have existed on earth for millions of years. Due to the process of evolution by natural selection, however, microbes also have been developing resistance for millions of years. Scientists have now detected functional antibiotic-resistant genes in microorganisms found in ancient permafrost (Kashuba et al. 2017) and even caves isolated from the earth's surface for 4 million years (Bhullar et al. 2012), supporting our understanding that AMR is natural, ancient, and hard wired in the microbial nature of things. Hence the origin of AMR long predates the use of modern antibiotics, but its existence was previously inconspicuous due to lower selection pressure.

Alexander Fleming warned the public that microbes were capable of accelerating their development of resistance under the increased selection pressure of widespread use of antibiotics and other antimicrobials (see Fleming's discourse to the Nobel Academy). Indeed, resistance to penicillin was formally demonstrated already in 1940 (Rammelkamp and Maxon 1942). Ever since then, a vicious cycle has emerged; as drug discoveries have added new molecules to the arsenal against infectious diseases, so resistance occurred as predicted. Figure 1 illustrates the timeline of successive discovery, clinical introduction in the United States, and [subsequent] detection of resistance for antimicrobial drugs over the past 70 years. In many instances, resistance was known before the drugs were even clinically introduced. Resistance itself does not necessarily mean drug obsolescence; in many instances, drugs continue to be used despite resistance being known to occur because not all microorganisms develop resistance to these drugs, everywhere and at the same time.

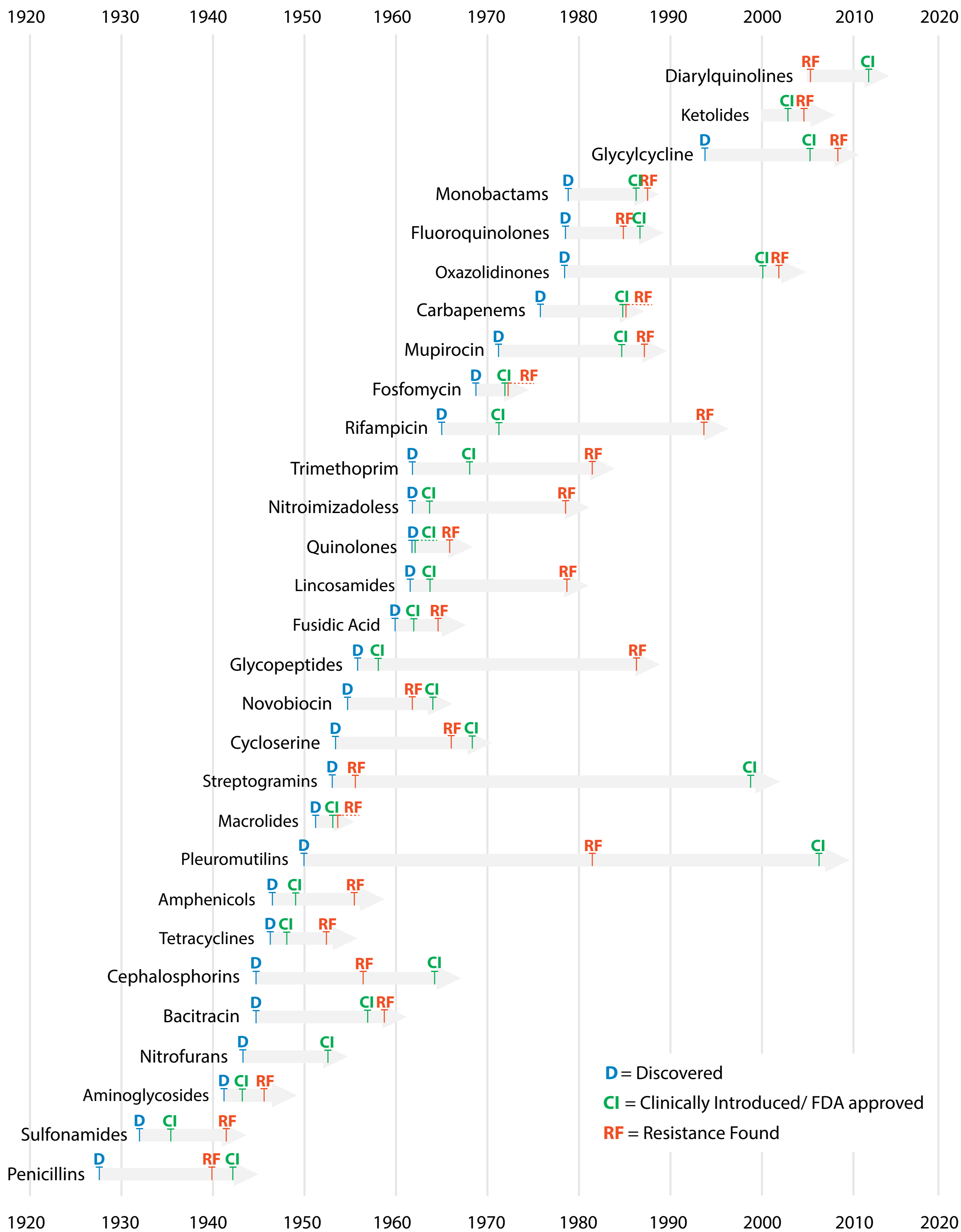
WHO has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine. This list (updated in 2018) is essentially intended to contribute to risk management of AMR due to non-human use of antimicrobials. In 2018, an OECD analysis focused on the following antibiotic-bacterium combinations: third-generation cephalosporin-resistant *E. coli*, fluoroquinolones-resistant *E. coli*, penicillin-resistant *S. pneumoniae*, meticillin-resistant *S. aureus* (MRSA), carbapenem-resistant *K. pneumoniae*, third-generation cephalosporin-resistant *K. pneumoniae*, carbapenem-resistant *P. aeruginosa*, and vancomycin-resistant *E. facealis* and *E. faecium* (OECD 2018). The significance of a specific resistance determinant, and how this translates in terms of treatment options—or drug obsolescence—should be better understood and communicated in order to focus on priority questions (#KKIG 1).

Figure 1 also shows that the pace of new molecules being discovered has dramatically slowed down since the 1980s. The discovery pipeline has currently largely dried up as pharmaceutical companies exit this unprofitable race, faced with high development costs and the short useful life of any new drugs they do bring to market (Nel-

FIGURE 1

Timeline of antibiotic discovery (D), clinical introduction (CI), and [subsequent] detection of antibiotic resistance (RF)

Note: Resistance is not necessarily synonymous with obsolescence. Sources: Nelson and Levy 2011; CDC 2013.



son 2003; Burki 2017)—or even what could become the imperative of not putting on the market newly discovered drugs. Furthermore, there have been no new classes of antibiotics since the 1970s. New drugs on offer are now dominated by derivatives of established classes of antimicrobials, and most candidate molecules for further development display limited innovation (WHO 2017e; Theuretzbacher et al. 2018). New antimicrobial drugs without preexisting cross-resistance are in very short supply, despite being still urgently needed, especially for certain geographical areas and infections.

What is the significance of a specific resistance determinant? How to translate this in terms of risk of absence of treatment options or drug obsolescence? How can this help to focus on priority resistance determinants? **— #KKIG 1**

A traditional approach to combating AMR—inventing and producing new antimicrobial compounds, which in the past may have been a lucrative business model— sowed the seeds of its own demise and has now burned itself out. It has essentially resulted in a "treadmill" or arms race between new drugs and constantly evolving resistant microbes. The rise of AMR has proven to be an endless race between microbes and humans, which we are losing and cannot win in the absence of a clear understanding of the fundamental drivers of resistance emergence and spread.

Drug discovery has a crucial role to play in maintaining our ability to successfully treat infections, but without addressing the underlying causes of the AMR crisis we will remain on the same broken treadmill, constantly reliving a self-fulfilling prophesy. Furthermore, it can be expected that we will eventually run out of finding new targets in bacteria that are sufficiently different from those in eukaryotic cells to allow for use without damaging effects on the animal or vegetal patient. Not to mention that new drugs will be reserved, hence having a very limited market, if any access to market.

New drug development is in itself a large and complex issue, which has been well discussed and analyzed elsewhere (McKenna 2019; see also relevant sections of the UK review in O'Neill 2016 and World Bank economic analysis 2017). In this report, we mainly focus on the increasing influence of factors that predispose the emergence and spread of AMR, hence slowing down this arms race between superbugs and humans.

TIME TO BROADEN THE TENT

The AMR conversation has largely been carried out within a circle of technical professions and experts focused on the science of AMR. With the exception of economists, who have recently studied the costs and benefits of AMR containment and investigated market failures in the pharmaceutical development and distribution system, relatively little space has been created for social scientists to join the global conversation (Roope et al. 2019). This has led to an exaggerated sense that AMR is a purely technical problem that will eventually be solved through technical solutions, ignoring that science's solutions can become science's problems (Beck 1992). This may have created a mistaken belief in science as our savior by disregarding human, social, and cultural elements that are intimately involved in driving the "wicked" rise of AMR.

Social scientists have studied medicines and the ways in which humans relate to them for many years (Smith 2015). This body of work has generated valuable insights of relevance to AMR, such as how the role of antimicrobials has influenced health and healthcare practices over a range of regions, cultures, social worlds, stages of development, infrastructure, and governance arrangements. Not only can this knowledge be used to understand diverse societies' reliance on antimicrobials and their reactions to reducing them, but also the consequences—intended and unintended—of doing so. In some societies and cultures, medicines, including antibiotics, have been found to take on other meanings and roles far beyond their purely biological effects (Chandler et al. 2016). Moreover, they take on practical roles that enable them to become a quick fix for the challenges of everyday life in modern societies (Denyer Willis 2019), and social research can explicate how antibiotics are connected to multiple strands and scales of modern globalized life—for example, understanding antibiotics as infrastructure (Chandler 2019). Such findings and approaches are highly relevant for understanding the social compacts around antimicrobials, interpreting how they are used, prescribed, marketed, and integrated into people's lives across a broad spectrum of actors, including patients, livestock keepers, prescribers, pharmaceutical companies, governments, and regional and global bodies. Moreover, pharmaco-epidemiologists, social scientists and humanities scholars are equipped with toolkits for exploring the current architecture of AMR science and policy, and can thereby open up alternative framings for action (Landecker 2016 and 2019; Podolsky 2015).

Behavioral and social sciences—which include but are not limited to psychology, anthropology, sociology, economics, and political science—are all pertinent to AMR and the understanding of how this knowledge can contribute to the conscious suspension of sectoral interests for the good of public health (#KKIG 2).

What areas of the AMR problem would behavioral and social sciences be most effective and impactful? How should AMR research and implementation activities best incorporate the social sciences to add value and improve progress? What proportion of overall AMR control effort should be devoted to social science research? **— #KKIG 2**

The AMR global dialogue now needs to open up to a broader range of stakeholders, including the development community, civil society, and the public at large (IACG 2018 d and f; 2019 b). There is an obvious parallel between AMR and the climate change issue, which was hidden from public awareness and engagement in a shroud of scientific discourse for far too long, only gaining real traction internationally once ordinary citizens became engaged (Gough and Shackley 2002).

ANTIMICROBIALS IN MODERN SYSTEMS

The discovery of arsanilic acid, sulfa drugs, and penicillin—and the initial recognition of their therapeutic potential in the first half of the 20th century—has been one of the greatest advances in fighting infectious diseases and in the evolution of modern medical practice (Aminov 2010; Landecker 2019). The large-scale production of these drugs enabled a transition from dependence on scarce life-saving substances in limited supply into widely available medicines. This, combined with the availability of vaccines, has led to the misconception that infectious diseases would no longer be a challenge; that is, a false sense of security that the world had entered a post-infectious era. Nevertheless, globally, outbreaks of infectious diseases have actually risen (Smith et al. 2014). And while the number of people dying from different types of infections has decreased over the long term (although the trend varies markedly by socioeconomic levels), infectious diseases remain an important cause of death globally.

Antibiotic consumption in humans shows a steady growth trend. Between 2000 and 2015, antibiotic consumption in humans is believed to have increased 65 percent from 21.1 billion to 34.8 billion DDDs (Klein et al. 2018). This increase was greatest in low- and middle-income countries (LMICs), where rising consumption was correlated with increasing GDP per capita. In high-income countries (HICs), overall consumption increased much less and showed no correlation with GDP. If current policies remain unchanged, projections of worldwide human antibiotic consumption to 2030 indicate an expected tripling of 2015 levels.

Quantitative information on use patterns in animals—including species, antimicrobial agents or class of antimicrobial agents, route of administration, and type of use—should be collected by OIE member countries in order to evaluate antimicrobial exposure in food-producing animals (OIE 2019). This applies to veterinary medical use (to treat, control or prevent infectious disease) or non-medical use (including growth promotion). It is widely accepted that—in absolute tonnage—use in animals far exceeds that in humans. In the United States, for example, the total annual use of antimicrobials rose sixteen-fold from 1950 to 1978 (Black 1984). Over the same period, antibiotic use as a livestock feed additive increased from 16 percent to 48 percent of total use, representing a fifty-fold rise in their use for growth promotion in animal rations. Studies estimated the global consumption of antimicrobials by livestock will continue to increase by 67 percent between 2010 and 2030 (Van Boekel et al. 2015). About a third of this increase will be due to intensification of farming systems in middle-income countries. In some countries—such as Brazil, Russia, India, China, and South Africa—the increase in antimicrobial consumption by livestock is projected to double.

Global estimates of the total antibiotic use and trends are not currently available (#KKIG 3), not least because use in humans and animals are quantified in different ways, or figures carry a high level of uncertainty. Other factors explaining why consumption has been hard to measure—and why this remains a gap—include the lack of reporting requirements at the national level (or reporting limited to specific antimicrobial class), and the lack of transparency from different sectors. However, better knowledge of the use, the purpose for use, and where it is deemed necessary in the value chains is critical to target interventions and change practices.

What is the current level of consumption (use) of antimicrobials in humans and animals? How can this be reliably quantified in practice? How this can be used to set targets and monitor progress on reducing the use of antimicrobials? **— #KKIG 3**

Although antibiotic consumption rates in most LMICs remain lower than in HICs despite higher bacterial disease burdens, human consumption in LMICs is rapidly increasing (Klein et al. 2018). It is now evident that antimicrobials have largely been used as a substitute for good quality public health systems with the necessary and sustainable practices to prevent and control infection. Still, the lack of access to affordable and quality antimicrobials for many people is a greater problem, and has currently more fatalities, than the effects of AMR. Globally, 5.7 million people die each year from treatable infections due to lack of access to antibiotics (Daulaire et al. 2015). Strategies are needed to simultaneously address the double burden of access and excess (#KKIG 4). In some settings, antimicrobials may simply not be available, while in other settings—such as urban and peri-urban informal settlements—antimicrobials are there and cheap but people cannot afford them, prioritizing food rather than a full course of antibiotics. The question of access is not limited to LMICs and raises the broader question of social connectedness.

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The discovery of antimicrobials—and their mass production—has been rapidly integrated into societies' approach to health in both human and veterinary medical domains. It has created space for the notion that infectious diseases were a thing of the past. In many respects antimicrobials have been used as substitutes for preventive health systems and sustainable agricultural practices (Chandler et al. 2016; Kirchhelle 2018), masking development deficiencies in many sectors and areas. From this perspective, antimicrobial resistance can be viewed as an extremely relevant development issue.

How to adequately capture the issue of access, especially in the context of acute and chronic poverty? What strategies can be developed to simultaneously address the double burden of access and excess? **— #KKIG 4**

Progress against infectious diseases started well before the antibiotic era. While the discovery of antimicrobials has been one of the greatest advances in fighting infectious diseases and in the evolution of modern medical practice, another great advance has been introducing washing hands and hygiene habits at the end of the 19th century. For example, a rapid decrease of maternal mortality occurred in England after doctors started to wash their hands before helping deliver a child, following the example of nurses (Chamberlain 2006). Figure 2 shows that progress in mortality rates from tuberculosis and other microbial respiratory diseases made great progress well before the beginning of the antibiotic era in the United States. Such progress in the US and other similar HICs was essentially achieved through improved infection control and sanitation. As shown in Figure 2, some countries have not yet reached the death rate level of a high-income country such as the US at the beginning of the antibiotic era (arbitrarily dated in 1945), or struggle to bring it down to the current level in the US. Part of the AMR challenge is to address the underlying development weaknesses to AMR and identify the most cost-effective AMR investments across contexts and interventions to be able to prioritize where and how funding should be used for the greatest global benefit (#KKIG 5).

What would be the most cost-efficient relative distribution of AMR-related investments across countries and regions and between intervention types (research, implementation, AMR-specific, AMR sensitive etc.)? How could this help prioritize where and how funding should be used for the greatest global benefit? **— #KKIG 5**

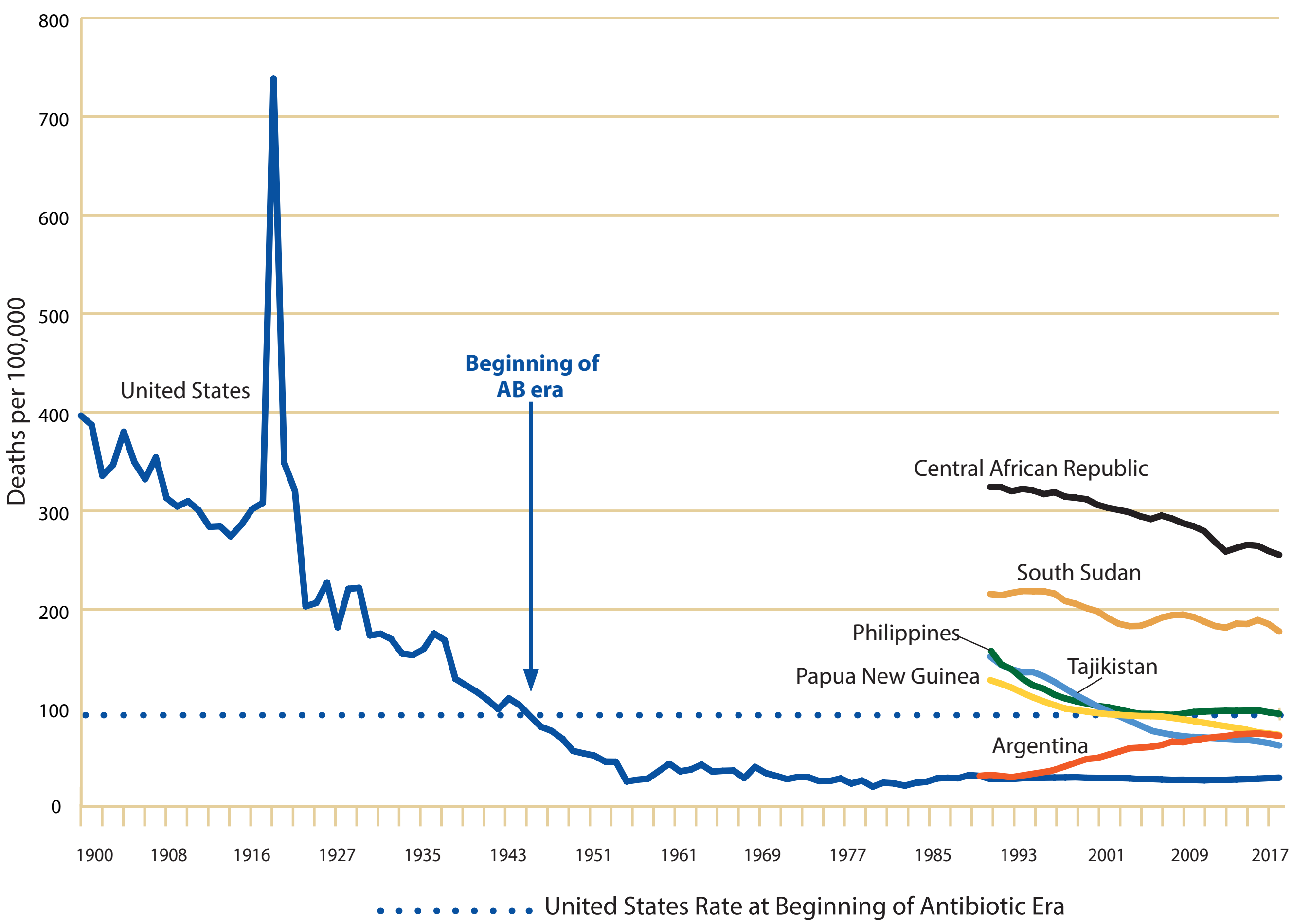
OECD recently has advanced an ensemble of modeling techniques to provide support for policy action on AMR (OECD 2018). This mainly covers the human health sector; other sectors should be included in the near future. OECD has reviewed public health interventions that would provide affordable and cost-effective packages in the fight against AMR. These packages include: (a) in hospitals, improved hand hygiene, stewardship programs, and enhanced environmental hygiene in healthcare settings; (b) in community settings, delayed prescriptions when there is no objective clinical emergency, mass media campaigns, and use of rapid diagnostic tests; and (c) mixed interventions, stewardship programs, enhanced environmental hygiene, mass media campaigns, and use of rapid diagnostic tests. These packages would reduce the burden of infectious diseases, improve how antibiotics are used, and consequentially reduce AMR rates by, respectively, 85 percent, 23 percent, and 73 percent (OECD 2018) while producing savings of USD purchasing power parity 4.1, 0.9 and 3 per capita per year. According to this study, the mixed intervention package would save 47,000 lives each year across the 33 participating countries, and millions of people would avoid AMR-related complications and health problems. AMR-sensitive interventions—although they are designed and implemented for various reasons—also can have AMR impacts (benefits) while addressing other important rationales (e.g., related to objectives of development, sustainability, and equity). More AMR-sensitive interventions should be included in this type of analysis and their expected contributions to AMR (cobenefits) should be determined. Furthermore, these packages of interventions should be assessed for national contexts, and a frame of multisectoral accounting for costs and benefits may be used for galvanizing political support in line with the SDGs (#KKIG 5).

It is widely accepted that antimicrobials have been a game changer for the food sector and animal production

FIGURE 2

Rate of death from tuberculosis and other respiratory infections in the United States before and after the beginning of the antibiotic (AB) era, compared with selected countries in different regions of the world, 1989–2017

Sources: Adapted from Hall, McDonnell, and O'Neill (2018). Authors' calculations using Center for Disease Control (death rate by tuberculosis, pneumonia and influenza) for United States (before 1990) and Institute for Health Metrics and Evaluation (death rate by respiratory infections and tuberculosis) for all countries from 1990 onward.



in particular (including aquaculture). Since the early 1960s, meat consumption has grown significantly; currently, the total biomass of animals raised for food by far outweighs that of humans. Livestock is one of the fastest growing sectors in agriculture, and based on projected increases in demand for animal source food, consumption is likely to maintain this growth trend for the foreseeable future, particularly in middle-income countries where demand is expected to increase significantly. This situation has been accompanied by profound transformations of the food-producing sector in response to the increasing appetite for animal-sourced foods in a growing global population. Transformations include the systematic use of antimicrobials, a substantial proportion of which is used at subtherapeutic doses for growth promotion purposes (Van Boeckel et al. 2015). Another part of the antimicrobial usage in livestock is prophylactic use to overcome the shortfalls of poor husbandry and animal management systems. However, taking the perspective of historically situated animal health concerns, rather than present-day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public health concerns, sheds a different light on antibiotics in the landscape of disease prevention and control (Woods 2019). In the course of industrializing animal production, farmers and veterinarians recognized the roles played by housing, husbandry, vaccination, nutrition, and pathogens in the production of animal diseases, suggesting multiple possible points of intervention, including antibiotics. Similarly to progress against infectious diseases before the antibiotic era, industrialization of animal production did not rely solely on antibiotics.

CASE STUDY 1: **AMR AT THE CROSSROADS OF ECONOMIC DEVELOPMENT**

In Vietnam, the production of meat—including pork, beef, and chicken—increased by 90 percent from 2002 to 2012 (FAO 2018). At present, most meat is produced on small farms, but the scale of production is increasing. Aquaculture is also an important sector, producing 4.15 million tons of fish and shellfish in 2018. This intensification, along with expanding human population density in urban and peri-urban areas and the demand for inexpensive food products, has increased the threat of infectious diseases and the use of antibiotics to limit their impact.

A lack of information about appropriate antibiotic use contributes to the overuse and misuse of antibiotics. In the animal sector, they are mainly used prophylactically: the amount used to raise chickens in the Mekong Delta is estimated to be six times that used in many European countries, expressed in quantities per unit of livestock (Carrique-Mas et al. 2015). The use of tetracycline and tylosin is common in pig and poultry farming (CDDEP 2010). Quinolones and sulfonamides are also common in fish, shrimp, and crab production, and antibiotic residues are found in many livestock and aquaculture-derived food products. This in turn can lead to antibiotic residues in the environment, in the food chain, and to a subsequent rise in AMR. Implementing good husbandry practices, increasing routine monitoring of animal food products, and supporting consumer education on food safety can limit risk associated with antibiotic use.

National Action Plans on Drug Resistance issued by the Ministry of health (for 2013–20) and by the Ministry of Agriculture (for 2017–20) were introduced in Vietnam to control AMR by promoting responsible use of antimicrobials, including antibiotics, in the human and in the plant and livestock sectors, respectively, as well as to strengthen surveillance for AMR (Dang and Nguyen 2017; MARD 2017). These plans, however, face challenges in implementation as demonstrated by the occurrence of residues of nonauthorized molecules in the food chain (such as e.g., chloramphenicol, nitrofurans, and ivermectin in aquaculture products).

Food safety is widely perceived by consumers, agro-business operators and government to be a major problem in Vietnam (Wertheim-Heck et al. 2016; Nguyen-Viet et al. 2017; World Bank 2017b). The government has responded by developing public advertisements on food safety (Nguyen-Viet et al. 2017), establishing a modernized policy that promotes a shift from traditional informal (wet) markets to supermarkets (Viet 2014), and addressing food safety risks at the farm level (Dang and Nguyen 2017). A 2010 food safety law charged the Ministries of Health, Agriculture and Rural Development, and Industry and Trade with control of antimicrobial use, with each ministry assigned control of specific products with a value chain. Although the Ministry of Health, through the Vietnam Food Administration, maintains overall responsibility for regulation of antimicrobials, the dispersal of control through several ministries may be an impediment to implementing comprehensive measures to ensure food safety. For example, within the Ministry of Agriculture and Rural Development, the use of antimicrobials in the animal sector is regulated not only by the Department of Animal Health but also the Department of Livestock Production, with oversight of agriproduct quality by the National Agroforestry-Fisheries Quality Assurance Department (NAFIQAD).

The World Bank Livestock Competitiveness and Food Safety (LIFSAP) project in Vietnam supports food safety protection and a reduction in AMR by promoting good animal husbandry practices in the agriculture and livestock sectors and increased monitoring of animal food products for antimicrobial residues. Previous projects to limit the risk of avian influenza had provided a proof of concept for a model of cooperation among government agencies, and a 2017 World Bank report recommends a risk-based approach to food safety in Vietnam that relies on intersectoral collaboration and input from the private sector to reduce antimicrobial residues in agriproducts that inhibit their sale in international and domestic markets (World Bank 2017b). Bridging the various ministries and departments with responsibilities for AMR will require similar strong leadership and the coordination of good practices across sectors. Recently, the academic sector also has played a role in promoting good animal husbandry: the Oxford Clinical Research Unit has partnered with the government of Vietnam to implement randomized controlled trials of the development of farm health plans, training of farmers to raise healthier meat with less antibiotic use, and diagnostic support for 91

farms (IACG 2019 a). Finally, as civil society organizations have become increasingly important in the debate about food safety, with a focus on "clean meat" and the absence of chemical residues in food products, a greater emphasis on AMR could contribute substantially to raising awareness of appropriate antimicrobial use.

This case study, focusing on Vietnam, provides an example of economic growth of the food sector as a driver for the use of antimicrobials. It illustrates how they are an important component of this growth and the challenge of governing their use requires addressing multiple issues. These issues include a culture of self-medication; the continuing gap between awareness about how AMR develops and the appropriate use of antimicrobials; compartmentalization of food safety oversight into different ministries; a growing market for cheap food in response to an expanding urban population; and the informal food system, which predominates in this context. This case study shows that laws and regulations regarding food products and antimicrobial use are unlikely to address the problem on their own, and that alignment of food safety concerns in civil society with concerns over the emergence and spread of resistant infections are a potential avenue to advance the national AMR agenda.

FOR DRIVERS OF AMR, CONTEXT MATTERS

The 2016 Wellcome Trust Summit identified three specific areas of meaningful actions: (1) reduce antibiotic use in agriculture; (2) improve local understanding of antibiotic use and resistance levels in human and animal medicine and agriculture; and (3) optimize antibiotic use in public health systems (Wellcome Trust 2016). The rise of AMR has often been seen primarily in terms of use and misuse, including overuse of antimicrobials.

The inappropriate, indiscriminate, and unregulated use of antimicrobials—both for human health and for raising crops and animals—is widespread in many parts of the world, although we are far from knowing the entire range of uses (#KKIG 6). In many settings across medicine and agriculture, antimicrobials have become substitutes for poor and fragmented systems. This reliance on antimicrobials has crept into our systems and become a part of the way much of our world operates, with most of us not giving this pause for thought. However, with their efficacy beginning to fade, we begin to see how significant their roles are in maintaining the systems we currently operate. This reliance has made it difficult to govern their prudent and responsible use. Farmers use a low dosage of antibiotics to boost the growth of their livestock, while patients seek antibiotics for viral infections that do not require antibiotics. Antimicrobials are injected into the trunks of fruit trees and are used by the clothing industry. Aquatic ecosystems are being contaminated by effluents from production plants, hospitals, human waste, and intensive livestock facilities. These are just snapshots of the wide range of everyday human activities that are leading to continued exposure to antibiotics, biocides, chemical preservatives, and metals in different settings and may result in the emergence of resistance. Chemicals with antimicrobial properties are widely used in domestic cleaning products, cosmetics, plastics, and building materials. Such chemicals leave long-lasting residues, yet their effect on indoor resistome dynamics is little known or understood. Even less is known about how they relate to the transmission of latent and infectious drug-resistant pathogens to humans, though the threat has been demonstrated (Fahimipour et al. 2019).

What are the multiple applications of antimicrobials—including their disposal—and their contextual drivers in anthropogenic activities? How do we assess their relevance to the AMR threat? **— #KKIG 6**

Baker et al. (2018) have used whole-genome sequencing to study the temporal and spatial evolution of AMR in bacterial pathogens. It leads to thinking about AMR in terms of emergence and spread. Exposure of susceptible bacteria to antimicrobials will result in the local emergence of resistant mutants. This happens continuously, as a genetically diverse pool of bacteria are exposed to a range of different compounds at different concentrations. Once a resistant clone is locally successfully esta-

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blished, opportunities may come for further expansion, such as broader geographical dissemination or spillover into another host population. Such opportunities depend, among other factors, on the mode of transmission of the bacteria (Baker et al. 2018). At a broad level, antimicrobial use (AMU) has a bearing on the emergence of resistance, but the spread of resistance, sometimes referred to as "contagion," is understood to be driven by biological factors along with a number of socioeconomic conditions, depending on the local and national context (Hendriksen et al. 2019; Collignon et al. 2018). Clarifying the relationship between use and other contextual drivers, and the distinction between the emergence and spread of AMR, may be crucial to optimizing interventions to curb resistance (#KKIG 7). Furthermore, in some cases, targeting the context rather than the use might be easier, cheaper, and more effective.

What factors contribute to the spread of AMR? How can their importance be assessed, in locally and regionally specific contexts (e.g. urban vs rural; rich vs poor, community vs hospital)? **— #KKIG 7**

Emergence is only one part of the story. AMU can explain only some of the variation in resistance levels across countries and regions (Hendriksen et al. 2015). Reducing antibiotic consumption alone will not curb the rise of AMR because the spread of resistance is also determined by other contextual factors (Hendriksen et al. 2019; Collignon et al. 2018).

The spread of resistance is associated with a range of socioeconomic, health, and environmental risk factors, articulated by recent country-level analyses. There is good understanding about the spread of infectious diseases, and there may be very few aspects that are specific about the spread of resistance determinants. But knowledge gaps exist regarding how changes in drivers of spread—such as the lack of adequate sanitation infrastructure, inappropriate waste management, low expenditures on health per capita, low public shares of total health expenditure, weak governance, and corruption—might impact AMR, and how to make these changes with maximum impact (#KKIG 8).

Poor sanitation infrastructure is consistently associated with higher levels of infectious diseases, part of which are caused by bacteria resistant to antimicrobials. Where sanitation and waste disposal infrastructures are lacking, or inadequate, antibiotic residues, resistant bacteria, and resistance genes are more likely to be released directly into the environment, with higher potential for human contagion (WHO 2014). Country health expenditure levels also are inversely correlated with antimicrobial resistance levels. In countries where financial protection against out-of-pocket health costs is low, utilization of preventive health care services is lower, and self-medication is more common (Ocan et al. 2015). This may ultimately lead to increased demand for and consumption of antimicrobials in instances where they would normally not have been needed, and suboptimal use even if they were. A third example relates to weak governance and corruption. Lower scores on governance and corruption indexes have been shown to be associated with higher levels of antibiotic resistance (Collignon et al. 2015). Countries with stronger, more transparent governance systems and lower levels of corruption might be better able to introduce regulations limiting the misuse and overuse of antimicrobials and mandating their safe disposal, and succeed at enforcing those regulations. Weak governance also might be associated with increased diffusion of substandard and falsified antimicrobials on the market.

How might changes in drivers of spread—such as the lack of adequate sanitation infrastructure, inappropriate waste management, low expenditure on health per capita, low public share of total health expenditure, weak governance, and corruption—impact AMR? **— #KKIG 8**

AMR AND SUSTAINABLE DEVELOPMENT

AMR could bring economic consequences more severe than the 2008–09 financial crisis with a disproportionate and lasting impact on LMICs because (1) losses would be sustained over a long period, up to 2050 and probably beyond; and (2) the impacts would likely be worse for LMICs (World Bank 2017a). A follow-up question, though, is to know how this translates into impact for particular countries; decision makers need more granular localized evidence to act.

The threat of drug-resistant infections compromises some of the most significant health achievements of the 20th century and poses a serious development challenge. If AMR is not contained, prospects for achievement of a number of the sustainable development goals (SDGs) by 2030 are particularly at risk. Drug-resistant infections jeopardize the prospect of ending extreme poverty and promoting shared prosperity, the World Bank's twin goals. The intersection of SDGs with AMR has been acknowledged in several reports (World Bank 2017a; IACG 2019 a and b), including ending poverty, ending hunger, promoting healthy lives and well-being, and achieving sustained economic growth (Figure 3a).

The emergence and spread of AMR will impede progress toward the 2030 agenda, yet there are a number of SDGs that will contribute to containing AMR (Figure 3b). For example, ensuring the availability and sustainable management of water and sanitation for all will help reduce infectious disease risks, hence limiting the need for antimicrobials and reinforcing AMR control. Water supply and sanitation measures are typical examples of AMR-sensitive interventions that indirectly impact AMR and provide cobenefits.

In addition to economic inequities between countries, unabated AMR will increase gender inequality. Women and girls already commit significantly more time than men to unpaid care giving, which AMR would exacerbate. This heavy and unequal responsibility, which affects the equality of women worldwide, will only get worse with AMR (WHO 2018d). For example, worldwide nearly 70–80 percent of the impaired elderly are cared for at home by their family members. While estimates vary across countries, they indicate that 57–81 percent of caregivers of

FIGURE 3A

The emergence and spread of AMR will impede progress toward the 2030 agenda

SDGs 1, 2, 3, 8, 11, and 17 are particularly at risk

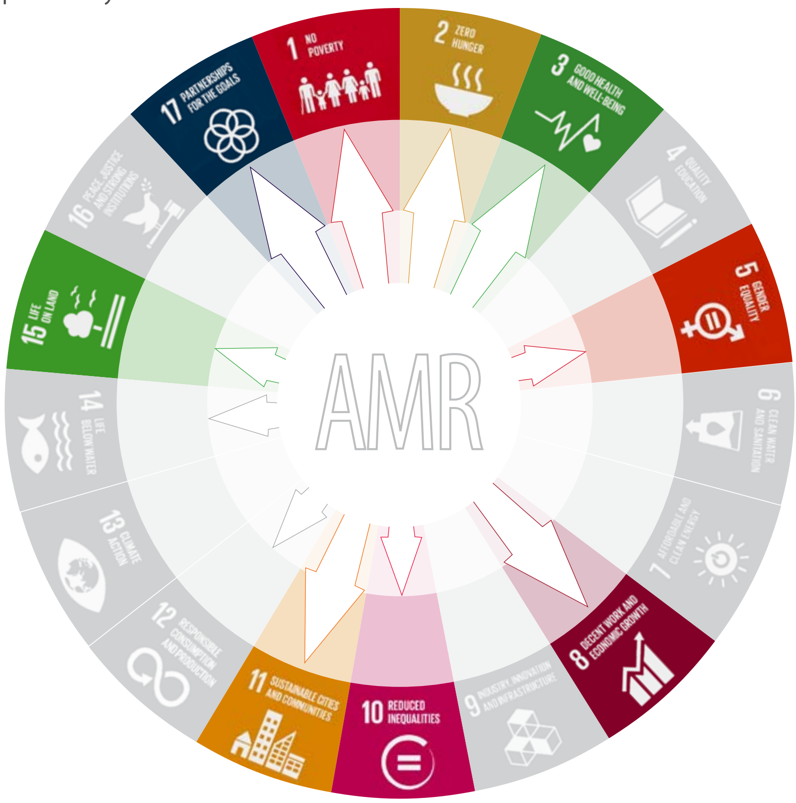
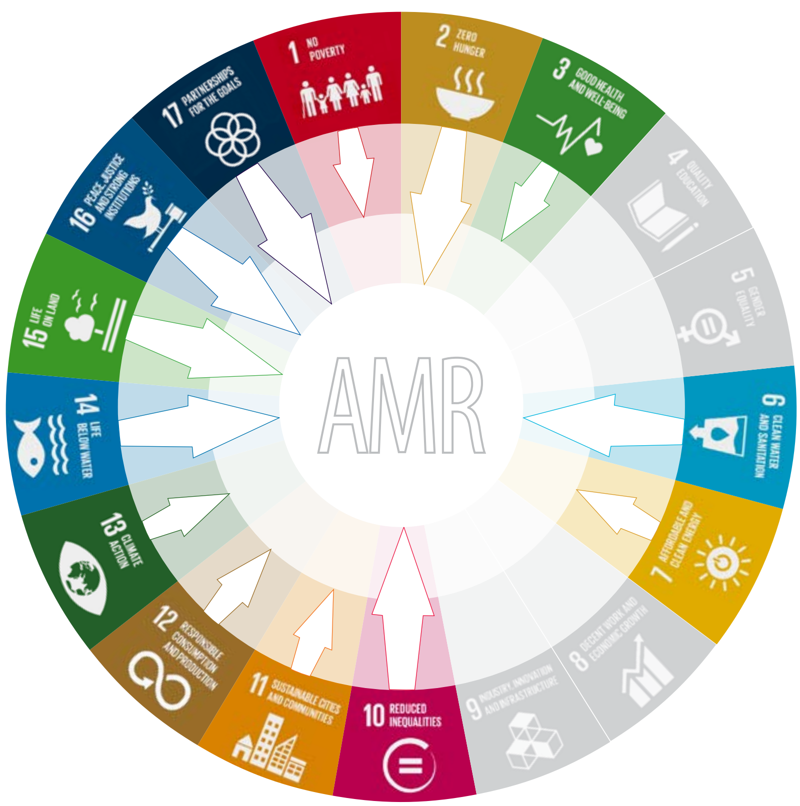


FIGURE 3B

Progress made on some SDGs will contribute to containing AMR

SDGs 2, 6, 10,14, 15, 16, and 17 are particularly relevant to AMR



the elderly alone are women (Sharma et al. 2016). AMR exacerbates gender inequality because women and girls, who provide care for family members with prolonged illnesses related to AMR, would face a greater burden. In addition, AMR will increase women and girls' risk of exposure to drug-resistant infections during pregnancy, miscarriage, and childbirth, especially as these events may take place in healthcare settings without safe or hygienic conditions. AMR also can lead to complications in infections that disproportionately affect women, such as sepsis or the much most common urinary tract infections.

To reduce the global threat of AMR, AMR-sensitive interventions are necessary. These include increasing access to clean water, investing in education and infrastructure, and ensuring good governance, as well as increasing public health care expenditures and better regulating the private health sector. The global effort to contain AMR could be undermined by neglecting the development dimension of AMR (Figure 3b).

TENSIONS SURROUNDING ANTIMICROBIALS, BEYOND THE WAY WE USE THEM

A gap exists between the technical solutions that we know can address AMR and the reality that they are often not adapted and implemented adequately, or not at all, in the places where they are most needed.

The human and animal health communities have long been aware of AMR as a scientific certainty, and, for more than two decades, have recognized it to be a serious problem with far-reaching and severe consequences of no available treatment options for infectious diseases. Despite the voluminous and ever-growing body of scientific knowledge on the subject, we are still far from bridging the gap between knowledge and the ability to reliably contain and reduce AMR as a risk. To replicate achievements of the few successful countries that have made progress on reducing use, and to a certain extent on abating AMR, we must learn more about the persistent problem of converting knowledge into realistic policy and practices, especially in LMIC environments.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Advances can be made through technical approaches. These include improving guidelines and incentives to prevent the emergence and spread of infection, improving global surveillance of antimicrobial use and resistance, promoting new diagnostics to prevent unnecessary use, developing new vaccines and antimicrobials, and improving incentives to promote investment in new drugs. Relying on technical approaches alone, however, will not solve the problem in a replicable and reliable way across the globe. Encouraging people, societies, and nations to change their norms, behaviors, and use of antimicrobials presents an adaptive challenge.

Adaptive challenges can be understood as challenges that are underpinned by a difference between values and circumstances (Heifetz 1998). People might easily say they value antibiotics and want to preserve them, but the way societies are deploying them is contrary to that reality. Addressing this gap requires changes in values, roles, and relationships at all levels within and across societies. It requires engagement with people across multiple different sectors and regions (renewing social compacts). It requires change in numerous places and across organizational boundaries (suspending sectoral interests). Solutions may require experiments and new discoveries. For example, several countries have had standards and awareness campaigns on the sustainable use of antibiotics. These standards and protocols are well known, but are difficult to implement in countries where perceptions of the quality of medical care are entwined with receiving antibiotics at any routine medical appointment, irrespective of need. Guidelines—and technical solutions—alone will not be sufficient to change those behaviors.

As discussed earlier, because antimicrobials are now socially, politically, and economically ingrained in our societies, antimicrobials and their roles need to be rendered visible in terms of:

- **Norms and behaviors related to antimicrobials,** which refers to people's assumptions, beliefs, and attitudes in life and livelihoods around antimicrobials in domains such as human medicine and agriculture and imperatives for progress. These have also developed and solidified in the context of a broader modernity, including social, economic, and political norms.
- **Use and governance of antimicrobials** across different sectors, industries, institutions, and countries, which refers to their respective roles and responsibilities. Standards and protocols on the sustainable use of antimicrobials exist with different levels of effective implementation, regulation, and enforcement. The challenge of governing antimicrobials is about the way we use antimicrobials.
- **External trends beyond the system of antimicrobials** such as population growth, migration, urbanization, climate change, organic and inorganic pollution, and loss of biodiversity. These have contributed to conditions for the emergence and further spread of antimicrobial resistance. These factors can influence tensions around antimicrobials, and contribute to optimizing conditions for emergence or the spread of resistance.

Multiple factors influence the rise of AMR across these three broad areas. As a result, the problems and challenges of addressing AMR are becoming more and more complex, they are difficult or impossible to solve. As mentioned earlier in this report, incomplete or contradictory knowledge, the difficulty of clearly defining the problem and solution, the number and social diversity of people and opinions involved, the large economic burden of the problem, and the intertwined nature of the problem with other problems are among the most significant features of AMR as a wicked problem.

Figure 4 represents the three areas described above as a conceptual model to AMR. The way we think about antimicrobials, the way we use them, and the broader factors influencing this system constitute three areas of influence, which interact with each other in diverse ways.

The first and central area in Figure 4 can be viewed as the system of how we currently use antimicrobials. It pertains to antimicrobials themselves, understood as socio-technological objects, their discovery, and the rules that govern access to them across different sectors, industries, institutions, and countries. Standards and protocols on the sustainable use of antimicrobials exist with different levels of effective implementation, regulation, and enforcement. Already authorized products contain antimicrobials, some of them at low dosages or in irrational combinations with other non-antibiotic products, are available on the pharmaceutical market.

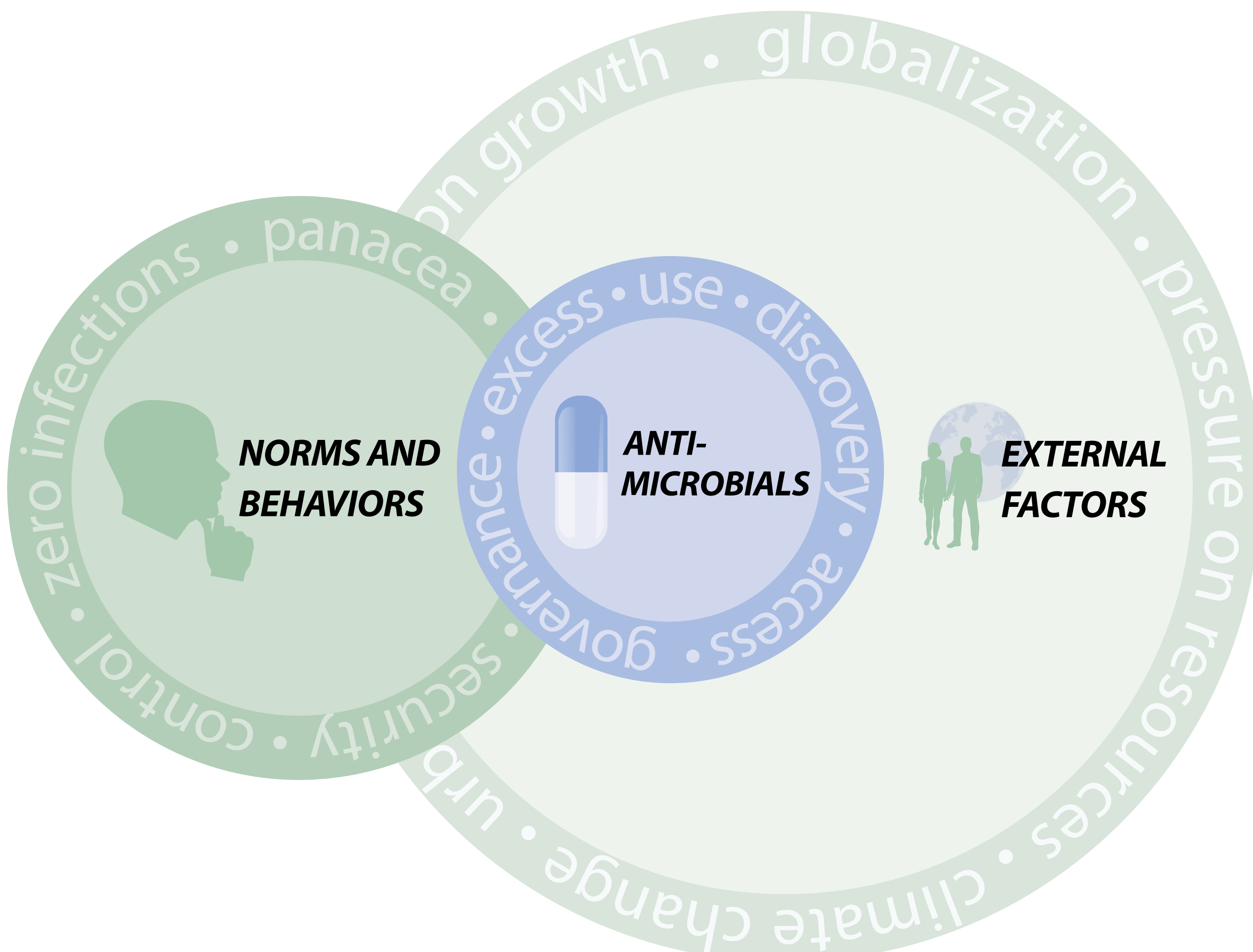
This first area is influenced by a second area—norms and behaviors—regarding how we think about antimicrobials. This second area includes, for example, the view that antimicrobials are modern panaceas that mark the "end of infectious diseases" and characterize times of biosecurity and control.

For example, in many LMIC and HIC settings drugs can still be purchased without a prescription. Examining the purchase of antimicrobials in Manila drugstores, 66.3 percent of the transactions were made without prescription (Lansang et al. 1990). In a more recent study, 60 percent of pharmacy visits by a simulated patient led to antimicrobials being dispensed without prescription (World Bank 2017a). Antimicrobial availability without prescription is becoming an established norm, often facilitated by the lack of regulation and poor enforcement of prescription guidelines. As a result, antibiotics are increasingly available over the counter and are being overly used in situations where they could be having no effect at all and where they are not necessarily indicated. As noted above, the interaction between norms and behavioral and governance drivers can be thought of within the antimicrobial system. In this conceptual model, the issue of excess—as opposed to prudent and responsible use—clearly appears as subjective rather than objective.

A parallel could be drawn with vaccines and vaccine hesitancy, defined as a delay in acceptance or refusal of vaccines despite availability of vaccination services. The

FIGURE 4

Tensions around antimicrobials: the way we think antimicrobials (norms and behaviors), the way we use them (use and governance), and external factors



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trend has been reported in many countries worldwide, prompting WHO to declare it one of the biggest threats to global health. For example, lower levels of immunization are believed to have resulted in a 30 percent rise in measles cases globally, even in countries where measles had been previously eradicated. A recent Eurobarometer study on attitudes of EU citizens toward vaccination indicates that 85 percent of responders believe vaccination is an effective way to prevent infectious diseases, protecting themselves and the others (European Commission 2019). Herd immunity is crucial, particularly when one has a compromised immune system and cannot be vaccinated. Children who survive cancer, for example, should not be put at risk because their peers are not vaccinated. The Eurobarometer also shows that approximately half of EU citizens have been vaccinated in the last five years. While 79 percent consult and trust healthcare professionals to get information about vaccinations, 48 percent believe that vaccines can often produce severe side effects and even 38 percent think vaccines can cause the diseases against which they protect. The parallel of vaccine hesitancy illustrates the potential influence of "norms and behaviors" on "usage."

The third area in Figure 4 represents a wider context, and drivers outside the antimicrobial system itself that may have an influence on antimicrobials and the rise of AMR. This area includes, among others, the growth of human populations, urbanization, globalization, increased pressure on natural resources, and climate change, as well as systemic factors that affect behaviors, such as the way hospital and health workers are paid or reimbursed, who provides education and training, etc. This third area does influence the first two, namely norms and behaviors as well as governance.

Following up on the previous example of country settings where drugs can be purchased without a prescription, this established norm may be facilitated by the lack of regulation and enforcement of prescription guidelines, self-medication as a way to avoid paying a doctor consultation, as well as increasing demand by a growing population of urban dwellers.

Fragility, conflicts, and violence are another example of an external factor that can drive a particularly fertile breeding ground for AMR because of worn-down health systems and a shortage of antibiotic supply (Arie 2013; Abbara et al. 2018; Jakovljevic et al. 2018). Even though doctors know the right technical protocols to prevent AMR, the situation means they cannot always follow them. Patients take incomplete courses of antibiotics or are prescribed an inappropriate mix because the right medicine is not available; in some cases, because they do not have enough money to afford the complete course. Other shortages—water; power and fuel for generators; gloves and gowns; and chlorine tablets for disinfecting water—mean doctors cannot always meet basic hygiene standards, making it easier for any drug-resistant infection to spread. One of the consequences of conflicts, violence and fragility in states is the displacement of refugees and asylum seekers, which seems to play a role in the spread of AMR (de Smalen et al. 2017; Aro and Kantele 2018).

External trends—beyond the system of antimicrobial use—are of critical importance as a wider context to AMR. The link between climate change or biodiversity loss and AMR may not be readily understood. There could be more exposure to pathogens from geographical expansion of vector ranges, resulting in increased disease incidence and more demand for antimicrobial treatment. In addition, there may be more frequent interruptions to healthcare services from extreme weather events that limit access to antimicrobials, or changes in vegetation leading to soil erosion that facilitates runoff and dissemination of antimicrobial-contaminated effluent. These are context-specific illustrations of the links that are not commonly made but potentially critical for optimizing cobenefits and reducing trade-offs in achieving the SDGs.

Many reports, studies, papers, consultation meetings, and workshops have extensively described the technical aspects of interventions that can be undertaken to address the threat of AMR (WHO 2015a; World Bank 2017; IACG 2019 a). According to OIE, responsible and prudent use is determined taking into account the specifications in the marketing authorization and their implementation when antimicrobials are administered to animals as part of good veterinary and good agricultural practice (OIE 2019). From a user standpoint, however, what constitutes "prudent" and "responsible" use can be a matter of judgment (#KKIG 9). Practically, it probably combines a triad of knowledge at hand, cost for the user, as well as a form of signaling (i.e., tacit or explicit code of what is expected to be done or not to be done). Such a combination is subject to huge variations among individuals and communities. The use of this knowledge, cost, and signaling triad could prove powerful in implementation research. The COM-B model has been proposed to address capability, opportunity, and motivation in behavioral or organizational changes (Essack and Sartorius 2018). This model identifies three preconditions for behavior change: capability (i.e., knowledge and skills), opportunity (physical and social), and motivation (Michie et al. 2011; 2014). The model covers the behavioral and social sciences, which include psychology, anthropology, sociology, economics, and political science. Behavioral and social influences should be given more consideration in the design and evaluation of interventions to improve prudent and responsible use of antimicrobials (Lorencatto et al. 2018).

How can "prudent and responsible" be better defined? What factors determine individuals' adoption of the "prudent and responsible" principle? **— #KKIG 9**

In the first case study (Vietnam and AMR at the crossroads of economic development), we have identified drivers belonging to (a) norms and behaviors, such as antimicrobials being needed to produce food, and a perception of residues being invisible; (b) governance, such as easy access to antimicrobials, or the lack of enforcement of the regulation; and (c) external factors, such as urbanization, demand for animal-sourced food, and economic growth.

Our second case study, below, will provide another illustration of how this conceptual model applies to address persistent and multiple AMR-related questions.

CASE STUDY 2: **ACCESS TO QUALITY MEDICINAL PRODUCTS**

Senegal is actively engaged in addressing the issue of substandard and falsified (SF) veterinary medicinal products (VMPs). These SF drugs may have limited effect or even lead to adverse health outcomes. Because they may contain adulterated or insufficient active ingredients, they can also contribute to the emergence of AMR. Circulation of such products is a threat to animal health and disease control, and Senegal has set a national target to eliminate them by 2023.

Since 2006 Senegal—with other member states of the Union Economique et Monétaire Ouest Africaine (UEMOA)—has been working to develop a common approach to regulation of VMPs, including registration and authorization of antimicrobials. This harmonization is recognized as essential to controlling the quality of antimicrobials and other medicinal products in the region. In 2006 a UEMOA Minister's Counsel was established, supported by fees from new drugs entering the market. In addition, a network of laboratories was established across the region to monitor the quality of available drugs (UEMOA 2006a and b).

A substantial share of VMP sales occur outside formal markets in the country (Tchao 2000; Abiola et al. 2005; Walbadet 2007). From 1979 to 1997, many public services in Senegal, including veterinary services, were shifted to the private sector (Gobbers et al. 2000). However, the private sector has been slow to take over and is still insufficiently developed to deliver the needed animal health services at scale. This has left gaps in service provision. SF VPMs have become freely available in local informal markets, making it difficult to track their origin, control quality, control trade, monitor the effects of these drugs (either in individuals or the animal population at large), and assess the likely impact on AMR.

Reducing the market for these drugs will require focusing on veterinary pharmacies, veterinarians and animal health professionals, and farmers and herders, as well as addressing the culture in which the systems developed. By themselves, communication campaigns, regulation of VMPs, and increased laboratory capacity for quality control do not sufficiently address all the issues associated with substandard and falsified products. Much of Senegal's livestock sector is based on pastoralism. Borders between Senegal and neighboring Mauritania, Mali, Guinea, Guinea-Bissau, and the Gambia are porous, in part because of the seasonal movement of herders and their livestock in search of land to graze or access to markets. Traffickers, including of substandard and falsified VMPs, take advantage of this ease of movement to distribute products to farmers and herders (Didier 1986; Vallée 2006).

Pressed by droughts in the 1980s, agricultural traders and seasonal migrants increasingly settled in cities in Senegal in search of stable incomes (Didier 1986). Sales of medicines offered an economic opportunity for these migrants. In the absence of a strong private veterinary medicine sector, many filled this role as informal and unregulated purveyors of VMPs and began diagnosing and counseling herders on the best treatment for their livestock. Medicines for sale in this unregulated market are obtained from two primary sources: (1) hijacking of products bound for public sector outlets, and (2) smuggling of drugs from neighboring countries (Didier 1986). Consumers drive this informal market because of the lower cost of drugs here than in pharmacies. Others value the knowledge, accessibility, and flexible arrangements of informal sellers or consider it unnecessary to visit a licensed veterinary specialist for "easy-to-treat" conditions. Absent recognition of the value of licensed providers of veterinary medicines, consumer demand for informal markets has been persisting.

Senegal's experience illustrates that ensuring access to quality VMPs will require a more effective system—such as an established list of authorized VMPs, better laws and regulations, and changes to a sectoral structure that allows various players to provide veterinary services, along with changes in norms and behaviors such as a cultural preference for informal markets and lack of appreciation of veterinarians and pharmacists—to limit substandard and falsified VMPs. Our analysis has identified regional regulations established by UEMOA, strong laboratory capacity to conduct quality control, political awareness, and outspoken support by senior members of government as important to addressing the issue of substandard and falsified VMPs and key contributions to the national and regional AMR agendas. Applying our conceptual model to this case, we have also identified major drivers of AMR in the areas of governance, norms and behaviors as well as the existence of external factors in action, such as the pastoral and cross-border movements of livestock and herders.

UNDERSTANDING OUR **APPROACHES** TO **DATE**

Chapter 2

Understanding our approaches to date

This chapter examines our most common approaches to understand and address AMR. More specifically, we review interventions establishing and maintaining an enabling environment for AMR control, those reducing the need for antimicrobial usage (adaptation), and those limiting the use of antimicrobials (mitigation). We also examine these interventions, to document key knowledge and implementation gaps. The efforts have mainly focused on use of antimicrobials, broadly ignoring the underlying causes of emergence and spread of AMR such as imperfect infrastructures and failing systems.

TAKING A COUNTRY STANDPOINT

AMR is a wicked problem; it cannot be solved, but it can be managed. It requires interventions by many actors across many sectors. Efforts to address AMR are often compromised by the low level of implementation and lack of coordination. The fragmentation of interventions, their poor sequencing in time and geography, and their deployment in non-enabling environments for AMR control measures often compound progress.

A number of technical solutions to contain risks related to AMR have been proposed. They have been essentially designed as technical solutions to be implemented by the human and animal health sectors, focusing on use of antimicrobials. In this chapter, we review a number of interventions that seek to reduce the emergence and spread of AMR.

These interventions have been identified in papers and reports published over the past few years. They are essentially the IACG discussion papers and reports (IACG 2018a to f, and 2019a and b), the World Bank (World Bank 2017a), Wellcome Trust (2016), and UK (O'Neill 2016) reports, and the global action plan on Antimicrobial Resistance (WHO 2015a). A second body of literature was then used to further extract interventions, drawing on published literature, studies, comments, and review articles.

Interventions have been organized into three functional groupings or "action families." One family deals with establishing and maintaining an enabling environment for AMR control through agenda setting, regulation, legislation, and surveillance actions. Another focuses on reducing the need for antimicrobial usage through measures to prevent infection such as vaccination, better hygiene, and improved livestock husbandry. A third family relates to self-limiting the use of antimicrobials by means of economic incentives and disincentives, as well as education and awareness-raising among users. These proposed action families cut across sectors and are equally applicable to diverse national contexts, broadly encompassing public health, animal health, and environmental health in a way that removes discipline silos around the AMR question and enabling "One Health" approaches to its containment (Robinson et al. 2016).

Interventions need to be context-specific and the "best practice" approach is likely to fail, especially when directly translating success stories in high-income countries into the context of low- and middle-income countries without adaptation. This observation is not solely related to resources; it also encompasses cultural, social, and environmental dimensions. Our review of interventions emphasizes the predominance of AMR-specific interventions in national agendas. We observe that AMR-sensitive interventions are vastly overlooked. This is a missed opportunity in view of their expected capacity to contribute to the battle against AMR.

CASE STUDY 3: **ANTIMICROBIAL POLLUTION IN THE ENVIRONMENT**

In India there are over 8,000 pharmaceutical manufacturing plants. The release of pharmaceutical waste products into the environment—particularly water systems—is believed to be a driver of AMR (Bengtsson-Palme et al. 2018). The potential routes of exposure to resistant bacteria from environmental pollution include dependence on natural water bodies—for irrigation, water for livestock, bathing, drinking water in the absence of safe water sources in many parts of the country—as well as dispersion during seasonal flooding. The issue of pharmaceutical waste products into the environment is also globally regarded as critical (Lübbert et al. 2017; The Review on Antimicrobial Resistance 2015; Changing Markets Foundation 2016). Perhaps nowhere is this problem more pronounced than in India. Industrial effluent treatment plants are frequently overloaded with more effluent than they can effectively process. In addition, only part of all pharmaceutical waste in India is thought to reach treatment plants, and a significant portion is illegally dumped into bodies of water.

The two regions with the highest concentration of pharmaceutical manufacturing plant effluent are Hyderabad and Visakhaptanam. Hyderabad was declared a "critically polluted area" in 2009 by the Central Pollution Control Board (CPCB). Similar problems may exist in many other areas, given the large number of antibiotic manufacturers in the country (Gandra et al. 2017).

A number of challenges exist to regulate and monitor manufacturing effluents and limit them as a pathway for the emergence of AMR. These challenges include providing sufficient resources for a strong and independent regulatory authority (or authorities), including a budget, mechanisms to ensure that existing regulatory agencies in different ministries/departments work closer together, human resources capacity, and confidentiality in reporting. For example, there may be conflicts of interest between departments—such as environment and industry—that may have diverging agendas within the government. Furthermore, the private sector may challenge the governmental authority, when for example, a lobbying group representing a large number of India's pharmaceutical manufacturers disputed reports of pollution, claiming that foreign clients regularly audit plants (Siddiqui 2016).

Another challenge is the lack of defined standards—either globally or nationally—for the allowable level of antimicrobial residues in the environment. There are no specific laws aimed at reducing antibiotics in wastewater in order to limit AMR in India (Bengtsson-Palme and Larsson 2016). India's Central Pollution Control Board (CPCB) sets standards for pharmaceutical effluents, but these standards do not include antibiotic residues. Consequently, antibiotic residues are not monitored as part of other effluent monitoring activities (Gandra et al. 2017). India intends to regulate antibiotic discharges in its National Action Plan 2017–21.

The government of India seeks to improve manufacturing standards, with multiple initiatives aimed at strengthening good manufacturing practices (GMP). The government recently attained a high "maturity level" grading from the WHO Global Benchmarking Tool for its regulation of vaccine manufacturing (WHO 2017 c). A draft of India's pharmaceutical policy released in 2017 suggests the state will procure antibiotics and pharmaceuticals only from GMP-compliant manufacturing units (Government of India 2017). However, enforcement remains a challenge. Proposed GMPs for environmental conditions might include proof of monitoring discharge or proof of implementation of adequate cleaning technologies for effluent. As part of this, policy instruments could include shifting part of the responsibility for ensuring diligent waste processing at effluent treatment plants onto the manufacturer.

The government also has provided substantial subsidies to support the manufacture of common effluent treatment plants (Kaur et al. 2017). Given reports that such plants are chronically overwhelmed by high volumes of waste, it may be that even more plants need to be constructed, properly maintained, and include an additional clarification stage such as ozone treatment or activated carbon filtration. In parallel, resources and political will must be deployed to ensure that existing infrastructure is maintained and functioning as expected.

The adoption of voluntary standards—such as the AMR Industry Alliance's Common Antibiotic Manufacturing Framework (AMR Industry Alliance 2018)—benefits from strong industry buy-in (depending on what proportion of manufacturers sign onto the standard), potentially

speedy roll-out compared to other avenues for standard-setting, and a low administrative burden on governments. Aside from obvious concerns about conflicts of interest, voluntary enforcement may be hampered by limited expertise both in AMR and in the environmental impact of pharmaceuticals, the high cost of current technology, and relatively few low-cost alternatives.

When registering a new pharmaceutical product to take to the market, companies in many countries are required to report to a government agency regarding where and by whom the active pharmaceutical ingredient is produced. Often, countries are aware of where medicines and their active pharmaceutical ingredients are produced, but they are not necessarily aware of the environmental impact of pharmaceutical effluents. Similarly, consumers are usually not aware of the environmental impact of effluents where the pharmaceuticals were produced. In India this is complicated by the lack of central procurement of antimicrobials. The government, as well as private hospitals and other countries, can leverage buying power to support manufacturers that are able to demonstrate adherence to high manufacturing and waste disposal standards, while ensuring that this does not lead to greater economic inequity or access to antimicrobials by effectively limiting the ability of smaller manufacturers to participate.

Poor infrastructure is associated with higher levels of AMR (Collignon et al. 2018). Only a few laboratories—given the size of the country—are reported to be involved in AMR surveillance (Das et al. 2017) for human health, and the INFAAR network for AMR surveillance in animal health has only recently been established. Insufficient data have created uncertainty in the precise contribution of water treatment, including proper handling of industrial effluent, to reducing AMR. This lack of comprehensive surveillance—along with the lack of an implementation and monitoring framework for one health in the country to track AMU and dissemination in humans, animals, and the environment—means the true burden of AMR in India remains unknown.

Establishing an enabling environment for AMR control is our first family of interventions, including agenda setting, regulation and legislation, and surveillance (discussed in the next section). In this case study, we have illustrated the complexity of addressing AMR issues in contexts of conflicting interests and poor capacity of underlying systems. Opportunities to address the particular issue of waste disposal from the manufacturing sector in India include the following: (1) government support and enforcement; (2) implementation of good manufacturing practices (GMP); (3) preferential procurement from high-standard manufacturers; and (4) comprehensive AMR surveillance that includes the environmental sector. All four can contribute to create an enabling environment to reduce AMR. The case study also illustrates challenges and difficulties to address AMR issues across sectors and the need to roll out suites of interventions.

ESTABLISHING AN ENABLING ENVIRONMENT FOR AMR CONTROL

Agenda Setting

Agenda setting refers to the shaping of policies and country-level plans to address threats posed by AMR. National action plans require governance structures, including targets and lines of accountability, to turn political will into action effectively.

National Action plans

National action plans (NAPs) are important in agenda setting because the implementation of AMR interventions requires long-term vision and investments in areas such as surveillance, research, laboratories, health systems, institutions, and professional education. WHO developed a manual (in collaboration with FAO and OIE) to assist countries in preparing or refining their national action plans (WHO 2016). Birgand et al. (2018) explored different governance approaches by three European governments and suggested that a decentralized bottom-up approach in the development of a NAP is more effective, since it allows for flexibility and modification as needed and develops a sense of accountability and ownership in communities and across the governance structure.

The scope of a NAP should include a "One Health" approach to bring all sectors on board and align respective contributions to a common set of targets. For example, 10-year targets to reduce unnecessary antibiotic use in agriculture should be consistent with a country's economic development and availability of funding.

How to increase the level of implementation of NAPs? — **#KKIG 10**

Countries fall into four broad categories in terms of their progress so far with NAPs: (1) countries with no plan or strategy on AMR (including very fragile and very small states); (2) countries preparing a plan or in the process of approving a plan; (3) countries with a plan but experiencing difficulty in implementation; and (4) countries with a plan or strategy that is being implemented (IACG 2018b). Many LMICs fall into the third category (#KKIG 10); this is partly due to organizational and staffing deficiencies, and lack of substantial amounts of government funding.

Links with other Agendas

Universal health coverage means that all people and communities can use the preventive, curative, rehabilitative, and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship (Kieny et al. 2018). As acknowledged in the 2017 World Bank report, expanding healthcare coverage, improving oversight and quality of care, and smarter and fairer financing all contribute to AMR containment in hospitals and community settings (World Bank 2017a). The AMR-sensitive nature of universal health coverage (UHC) has potential to strengthen AMR containment through expanding health coverage to all citizens.

At least half of the world's population still does not have full coverage of essential health services. UHC provides an enabling framework to tackle AMR because AMR in many ways reflects the weaknesses in existing health systems. Moving toward UHC requires strengthening health systems and robust financing structures. A robust UHC approach builds coordination and governance structures that are critical for AMR containment, as well as enhanced regulatory capacities (Kieny et al. 2017). One example is health facility accreditation, where requirements for improved antimicrobial stewardship can be built into accreditation processes for hospitals and clinics.

Chapter 1 shows the strong relation between the sustainable development goals and AMR. Here as well, we can connect AMR with various development agendas. Better understanding of the specific contributions of SDGs and other relevant agendas to AMR, and ability to quantify these contributions (cobenefits) in different local contexts would be critical (#KKIG 11).

Another important agenda addresses water, sanitation, and hygiene (WASH). The WHO WASH Strategy (2018) responds to a member-state resolution and the broader SDGs. It also recognizes the human right to safe drinking water and sanitation, adopted by the UN General Assembly in July 2010. Evidence suggests that improving access to safely managed drinking water and sanitation (indicators for SDG 6.1 and 6.2)—such as regulated piped water

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or connections to sewers with wastewater treatment—can dramatically improve health through improved hygiene and reduced diarrheal disease deaths. Studies also demonstrate how WASH interventions significantly reduce the emergence and transmission of antimicrobial resistant organisms.

The WHO WASH Strategy (WHO 2018c) aims to empower countries through (a) multisectoral technical cooperation, advice, and capacity building to governments, practitioners, and partners regarding sector capacities; (b) public health oversight roles; (c) national policies and regulatory frameworks; (d) national systems for water quality and disease surveillance; (e) national systems for WASH monitoring; and (f) national WASH target-setting. Every dollar invested in WASH is expected to yield $3 in economic benefits. The integration of WASH with AMR initiatives will yield additional cobenefits in health and economic gains over and above the direct outcomes of WASH programs alone. It is estimated that 2.3 billion people around the world still lack access to toilets and 4.5 billion people do not have access to safely managed sanitation—that is, to a system that safely conveys, treats, and disposes of household waste. Given that over a third of the world's population still has no access to safe sanitation, most development agencies, national governments, NGOs, and other civil society groups are currently involved in the WASH agenda in some way. This creates a very significant opportunity for strong links to the AMR agenda for synergy and greater impact.

Overall, there are several agendas that can connect to AMR. The global health security agenda (GHSA) is another example of an AMR-sensitivity, since preparedness for pandemics holds many synergies with AMR (International Working Group on Financing Preparedness 2017). One pillar of GHSA is AMR. A number of other pillars— such as legislation and laboratory capacity—include AMR, making this agenda both specific and sensitive. The GHSA is a voluntary consortium of countries that not all WHO members have adopted. Nonetheless, the GHSA includes a dedicated action package on AMR, and, more broadly, it also can be leveraged for AMR-sensitive interventions. For example, some countries still lack adequate diagnostic capabilities, including for common bacterial infections, and GHSA can help strengthen overall systems for better diagnosis of known and novel infections and can build in capabilities for AMR testing in the context of overall laboratory capacity strengthening.

What are the specific contributions of the Global Agenda for Sustainable Development and other relevant agendas to AMR? How can these be quantified for AMR-sensitive interventions (cobenefits) in different contexts? **— #KKIG 11**

Regulation and legislation

Effective legislation and regulation enable responsible production, distribution, and usage of antimicrobials across the food production, health, and pharmaceutical dispensing systems. Regulation is aimed at ensuring access and reducing excess in the use of antimicrobials and their disposal into the environment. The goal of regulating antibiotic use is to focus on the end-to-end supply chain leading up to the dispensing point, as well as the operations of the dispensing points. Regulating antibiotic use can vary from strict bans to restrictions or "gating," with the ultimate goal of optimizing the use of antibiotics in public health and agriculture.

While regulation and legislation are necessary, they are not sufficient to impact the AMR problem without the necessary level of enforcement and substantive punitive measures for lack of compliance (see case studies 1, 2, 3 and 4). This is a major impediment in many countries where enforcement is weak and corruption is rife at all levels due to factors such as the highly lucrative trade in antimicrobials spanning the whole supply chain from international imports to local street markets. Collignon et al. (2015 and 2018) found a positive correlation between indices of good governance and levels of AMR.

Agriculture and food

Improved husbandry and food processing requirements can balance the need for access to antibiotics and consequences of excessive use in agriculture, animal and plant production.

Antimicrobials are used in agriculture principally in the livestock and aquaculture sectors for three purposes: (1) growth promotion, (2) prevention of infection based on known risk of exposure (prophylaxis and metaphylaxis), and (3) treatment of clinical infection. Experience suggests that improved husbandry practices often can replace the use of antibiotics for growth promotion and disease prevention (OECD 2015).

To reduce the amount of antimicrobials employed in livestock farming, some countries have banned or restricted their use for growth promotion. According to a survey conducted by OIE (2017), 86 out of 146 (59 percent) responding countries did not authorize any antimicrobial agents for growth promotion in animals in their countries as of 2016. The 60 remaining countries (41 percent) reported use of antimicrobials for growth promotion, either with direct authorization of some compounds, or because the country had no regulatory framework on this issue. Where countries have only banned antimicrobial use for growth promotion, total antimicrobial use may not have declined, since usage may have simply been reclassified as prophylactic. Countries that have banned use of antimicrobials as growth promotors may experience a transitory increase in therapeutic use.

Specific antibiotics, listed by WHO as highest priority critically important for human medicine, should not be used in animal husbandry or agriculture to lower risks of resistance emergence (WHO 2017d); however, not all countries have introduced or enforced their prohibition in livestock, aquaculture, and agriculture regulation.

There are examples of successful antibiotic bans—or restrictions of some classes of antibiotics—in several European countries, particularly in the use of antibiotics in specific animal species when accompanied with other measures (see case study 5). However, some of these countries, while having achieved excellent results in reducing antibiotic use, also have introduced alternatives—such as zinc oxide in Denmark—that have turned into a problem (Jensen et al. 2018).

Enforcement of regulations and voluntary uptake of recommended standards can be greatly enhanced by the provision of support measures, such as advisory services to farmers and insurance schemes that protect farmers from financial hardship while phasing out the use of antibiotics. This is particularly relevant in LMICs, where the withdrawal of antibiotics in food production, a low margin industry, is likely to have greater negative financial impacts compared to HICs, where management practices are generally better (Laxminarayan et al. 2015).

Regrettably, many countries still report no regulatory framework for the manufacture, registration, distribution, commercialization, and pharmacovigilance of veterinary medicinal products (OIE 2017; World Bank 2017c). In many LMICs, there are essentially no controls over the veterinary use of antimicrobials. These are generally available over the counter without prescription, as well as in pharmacies, general stores, and informal markets, with serious concerns over quality of VMPs (see case study 2). They are routinely added to commercially produced animal feeds as standard ingredients. Implementing targeted interventions thus remains difficult in many LMICs.

The AB supply chain

Banning or restricting certain classes of antibiotics must be carefully enforced throughout the entire drug supply chain.

Legislation to enhance "gating" of antibiotics will ensure that their use is exclusively routed through trained healthcare professionals rather than over the counter by unqualified sales people. In addition, restrictions can be placed on certain types of highly critical antibiotics such as last-line antibiotics that are reserved for tertiary care facilities. Recently WHO proposed the *AWaRe* classification for antimicrobials in three categories: Access, Watch, and Reserve (Hsia et al. 2019). Strict regulation for at least Reserve antibiotics is critical.

The levels of resistance to second- and third-line antibiotics is expected to increase rapidly (70 percent higher in 2030 compared to 2005 for the same antibiotic-bacterium combinations) compared to first-line antibiotics (OECD 2018). Removal of second- and third-line antibiotics from general and online sale can be an intervention where indiscriminate over-the-counter sale of antibiotics is widely seen as a primary driver of AMR. According to the WHO AWaRe classification, efforts should be focused on Watch or Reserve antimicrobials, which never should be sold without prescription. Tanzania provides an example of a successful antibiotic gating intervention. The government and its Pharmacy Council and Management Sciences for Health have set up a national network of 12,000 accredited drug dispensing outlets, which sell appropriate antibiotics and educate people on the prudent use of ABs and AMR risks (Wellcome Trust 2018).

Last but not least, a revision of the products containing antimicrobials marketed in countries is needed, as there are still many pharmaceutical products containing antimicrobials at dosages lower than those effective, and fixed-dose combinations of antimicrobials with other drugs, without evidence of efficacy in clinical practice, but which contribute to the presence of antibiotics in the environment.

Labeling

Labeling and transparency requirements can affect industry norms in both food supply chains and medicine supply chains involving antibiotic use.

The information provided on the packaging (i.e., a bottle label, package leaflet, and outer carton) is critical to ensure the correct and safe use of the product. Standards and regulation on how medicines and food are labeled can empower users and consumers to make better informed decisions and recognize the unique nature of antibiotics. Standard labeling requirements can emphasize the "protected" status of certain antibiotics, support tracking mechanisms to ensure drug quality, and inform customers when antibiotics are included in products like animal feed (Wellcome Trust 2016).

More importantly, labeling can set industry norms around appropriate antibiotic use. Labeling of products containing antibiotics may increase awareness of antibiotic usage at all levels of supply chains and is a potential tool to reduce the circulation of substandard and falsified drugs. The UK AMR Review has called on governments and international health organizations to agree to global labeling standards for antibiotics (O'Neill 2016).

In India, the "Red Line Campaign" for antibiotic packaging was intended to draw attention to antibiotics as a special type of medicine, targeting consumers and other actors throughout the supply chain. If distinctive labeling were widely adopted, common labeling standards could become

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a condition of sale of antibiotics. Another option would be to include information that is in a relevant local language so that people can understand when they can use a medicine and how. Consistent international labeling of antimicrobials, agreed among all countries, has the potential to reduce existing confusion and misuse among prescribers and users.

No such international standards are currently in force, and each country can interpret existing guidance in its own way. As for VMPs, not all countries follow "good practices" on labeling. A recent survey indicated that only 18 of the 57 countries require that precautions on disposal of unused or waste materials are included in labeling (World Bank 2017c). In the United States, for example, The Pew Charitable Trusts (2016) found that labeling measures to be introduced by FDA in 2017 would result in a third of all antimicrobials intended for livestock use not fully meeting judicious use standards after implementation of FDA policy. This parallels the situation regarding agricultural pesticides, where after 40 years of efforts to establish and enforce international labeling standards, they are still only regulated through voluntary guidelines (FAO and WHO 2015).

A number of interventions can contribute to creating an enabling environment (including surveillance, which is discussed in the following section); however, the question remains regarding what constitutes an enabling environment for local context (#KKIG 12).

What are the essential characteristics of an enabling environment for AMR control? How should countries prioritize efforts toward establishing an enabling environment within their contexts? **— #KKIG 12**

Surveillance

Country surveillance systems to track antimicrobial use (AMU) and AMR in humans, animals, and the environment are an important component of AMR containment and are captured in the second objective of the Global Action Plan (WHO 2015a). Surveillance and monitoring provide a clear picture of the local situation, which over time builds a knowledge base to assess the impact of other interventions. Surveillance priorities for countries will depend on national technical, economic, and human resource capacities, as well as governance and the general socioeconomic context.

Standardized data collection and systems integration is the key to surveillance of drug resistance and antimicrobial consumption.

What are the critical data and data models for meaningful surveillance and monitoring of priority AMR determinants? How can they be incorporated into facility and population surveillance, monitoring, and reporting systems? **— #KKIG 13**

While there is consensus regarding some key principles of data collection and integration, many LMICs still lack the basic capacity to establish and maintain surveillance systems. It is important to focus on how to integrate AMR surveillance into existing data collection systems, which will maximize the efficiency of resource use and provide more complete data. Other suggested practices (IACG 2018c) include:

- Shared data platforms enable countries to analyze information on AMU in different sectors and locations (e.g. public hospitals and private hospitals) and assess the prevalence of resistance in humans and animals.
- Surveillance of the quality of medicines can help minimize and contain AMR.
- Data collected by local and national monitoring systems should be incorporated into regional and global surveillance systems.
- Implementation of point prevalence surveys (PPS) from a few sentinel sites in remote regions can provide a relatively quick assessment that is less resource intensive than continuous surveillance.
- Collecting quantitative data will enable tracking of progress and accountability for AMR interventions.

The technical design and data collection standards of country surveillance systems should be informed by global guidance so that data is comparable between countries and contexts. The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide global standardized methods for determining susceptibility to antimicrobial agents among clinical pathogens.

Resources and guidelines available to LMICs in developing their laboratory facilities include FAO's assessment tool for laboratory and antimicrobial resistance surveillance systems (ATLASS), which provides recommendations for improving laboratories and ensuring use of standardized data collection methods. The OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals provides standards on laboratory methods for bacterial antimicrobial susceptibility testing, and the Terrestrial and Aquatic codes provide guidance on AMR and AMU surveillance and monitoring. WHO's Global Antimicrobial Resistance Surveillance System (GLASS) provides epidemiological standards for surveillance in humans, and additional guidance on analysis and sharing of data on AMR. As of June 2019, seventy-one countries had enrolled in GLASS, including eleven lower-middle-income countries and six low-income countries (WHO 2018 b). In 2017, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) updated its guidance on integrated surveillance of antimicrobial resistance in foodborne bacteria (WHO 2017e).

In other sectors—like plants and the environment—there are few, if any, international guidelines and standards for surveillance of AMR and AMU. The Tripartite Integrated Surveillance System for AMR/AMU (TISSA) is working toward harmonizing data from different AMR and AMU surveillance systems (IACG 2018 c). This remains an important gap in terms of knowledge and implementation (#KKIG 13).

Microbiology laboratory facilities are important because improving antimicrobial susceptibility testing is key to enabling the overall surveillance system. Not all countries may be able to reach the same antimicrobial susceptibility testing capability, but shared regional infrastructure can be effective in both human health and veterinary health. The key for LMICs is the cost, portability, and reliability of equipment. Thus, the technologies employed in HIC contexts may not be directly transferable to lower resource settings. The development of laboratory capabilities also requires human capital planning and the collaboration of technical training institutions.

Most surveillance focuses on phenotypes, while resistance determinants require genotyping. New developments in the use of next-generation sequencing (NGS) may change the ability to perform comparable global surveillance of AMR. This includes the use of NGS for analyzing single isolates (Zankari et al. 2013), as well as using the technology directly on samples and quantifying the entire resistome by using the metagenomics approach (Munk et al. 2018; Hendriksen et al. 2019). There are new real-time detection of antibiotic resistant genes with portable and geo-tagged systems, which could allow surveillance even in remote places without microbiology laboratories.

CASE STUDY 4: **SMART USE OF ANTIBIOTICS**

Thailand has had a strong political commitment to tackle AMR in the last decade and is following through with practical actions. In 2016 the cabinet endorsed a five-year National Strategic Plan on Antimicrobial Resistance for 2017 to 2021. Understanding the complex network of stakeholders was essential in developing the national strategic plan. Prior to approval of the strategic plan, there were roughly 24 committees, subcommittees, and working groups under the Ministry of Public Health and the Ministry of Agriculture and Cooperatives that were related to AMR. These were consolidated under the new plan, and the participatory approach to implementation of the plan has given legitimacy and raised public awareness about AMR efforts. The National Health Assembly—which brings together representatives from government, academia, the private sector, and civil society from all 77 provinces—adopted a resolution on AMR that incorporated various actions for the Ministries of Public Health, Agriculture, and Education, other governmental agencies, national and provincial health assemblies, local governments, civil society organizations, and the private sector (Sumpradit et al. 2017).

Thailand has been grappling with the overuse of antibiotics for at least the last decade. A 2010 study on the health impacts of AMR in Thailand found that 87,751 hospitalizations led to antibiotic-resistant infections with one of five major bacteria *(Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and MRSA), accounting for 3.24 million additional days of hospitalization and 38,381 deaths (Pumart 2012). Norms and behaviors around antibiotic prescriptions and use have contributed to this problem. In a study published in 2017, simulated patients visited community pharmacies and reported non-infectious diarrhea in a 14-month-old child. The results showed that, of 91 pharmacies visited in Khon Kaen Province, 7.7 percent provided oral rehydration salt solution according to guidelines, whereas 68.1 percent dispensed antibiotics inappropriately (Jaisue et al. 2017). These continuing challenges have suggested the need to directly address existing norms and behaviors that underlie prescriptions and the use of antibiotics. In Thailand, both physicians and pharmacists are allowed to prescribe and dispense controlled-class antibiotics to consumers and they receive either direct or indirect benefits for doing so. Other antibiotics—those classified as cautionary in Thailand, such as ciprofloxacin and cotrimoxazole—can be dispensed without a prescription (Jaisue et al. 2017). In rural areas, many more antibiotics can be purchased illegally (WHO 2015b). The Thai Food and Drug Administration is working to reclassify drugs to limit those in the cautionary class, hence reducing access to certain antibiotics (Sommanustweechai et al. 2018). Thailand aims to reduce antibiotic consumption in the human health sector by 20 percent and in veterinary medicine by 30 percent by 2021, as outlined in its National Strategic Plan on Antimicrobial Resistance (Sommanustweechai et al. 2018).

This case study describes an initiative to encourage the smart use of antibiotics in clinical settings as a primary approach to limiting AMR in Thailand. The Antibiotic Smart Use (ASU) program aims to both reduce patient demand and educate providers on appropriate use of antibiotics in clinical care. The ASU program is a collaboration between the Ministry of Health and universities in educating consumers and providers on the appropriate use of antibiotics for respiratory infections,

diarrhea, and simple wounds with the ultimate goal to change social norms (Sumpradit 2012a).

The ASU program has been rolled out in three phases (Sumpradit 2012a; So 2014). In 2007–08, education and training reforms were piloted in Saraburi Province, with Phra Nakhon Si Ayutthaya Province serving as a control to measure effectiveness. Training included educating prescribers and providing posters and videos for patient waiting areas, posters with treatment guidelines for clinicians, and white light illuminators for patients' visualization of their own throat infections (So 2014). Seed money was given to hospitals to support implementation and evaluation. Overall, phase I resulted in an 18–46 percent decrease in use across hospitals (Sumpradit 2012b). In 2008–09, this pilot program was scaled up to 44 hospitals and 621 primary health centers in three provinces, including one public and one private hospital network. Within the program, a pay-for-performance scheme was initiated by the National Health Security Office. There was no single package of interventions. Examples of innovative methods to reduce antimicrobial use included the use of concave mirrors with photos of bacterial infections so patients could compare clinical signs for themselves; the provision of herbal medicines as alternatives to antibiotics (ReAct 2016); and the availability of materials that addressed common misconceptions related to antibiotics, such as their ability to reduce inflammation (Sumpradit 2012 a). In 2010, Thailand began scaling up this program to 15 of the 77 provinces in the country, and the payment mechanism to limit prescription of antibiotics remains sustained. The sustainability and success of this phase is still to be evaluated.

The ASU program addresses the drivers of inappropriate antibiotic use that can contribute to AMR. Specifically, this program aims to provide education to both providers and consumers—both of whom have been implicated in the misuse antibiotics—to change the norms and behaviors associated with antibiotic use. For providers, this means, in part, reducing the incentives to overprescribe (e.g., direct fees) and rewarding appropriate use of antibiotics. For consumers, this means reporting about the ineffectiveness of antibiotics for some illnesses, as well as the direct and indirect harms of inappropriate use (e.g., clinical consequences). Because norms and behaviors (e.g., rural vs. urban purchasing habits) are likely to differ across the country, the flexibility built into implementation of the ASU program may allow Thailand to contend with diverse underlying drivers of excessive and inappropriate antibiotic use. As effectiveness of the campaign is assessed across the 15 provinces, lessons on what messages and education methods scale best and change critical norms and behaviors of antibiotic use may become apparent.

This case study addresses the norms and behaviors that determine antibiotic use. The program certainly benefits from an existing nationwide enabling environment. It shows how a pilot is currently being scaled up to meet the needs of the country. It will benefit from enablers such as a decentralized network of AMR interventions with potential for innovation, regulation of controlled-class antimicrobials, and training and other incentives for appropriate antimicrobial use for clinical practitioners. The case study also highlights how all elements that will allow scale-up from discrete successes to an integrated functioning system are not yet identified. Finally, we note the recurring issue of illegal medicines in informal markets.

This case study emphasizes the importance of addressing key issues around antimicrobials—that is, the way they are situated in our health and other architectures, the way we use them, as well as external factors to the system. Finally, it showcases an array of interventions that benefit from an enabling environment and seek to reduce the need for and use of antimicrobials.

REDUCING THE NEED FOR ANTIMICROBIAL USE (ADAPTATION)

Rather than being afraid of a world without antibiotics with the advent of AMR, we can prepare for this by building our systems and structures in ways that antibiotics are less needed. Prevention of infections that require the use of antimicrobials to treat them is fundamental to reducing the emergence and spread of AMR. One of the five objectives of the Global Action Plan for controlling AMR is to reduce the incidence of infections by infection prevention and control (IPC). Other objectives, which also contribute to infection prevention, include reducing risk at the human-animal-environment interfaces, expanding access to clean water and sanitation, and access and use of basic hygiene practices. Preventing infections in the first place is one of the most efficient ways to address AMR (World Bank 2017a). IPC practices apply to both human health and animal health. Good hygiene and sanitation have been highlighted as one of the most powerful intervention tools in combating AMR, yet basic steps are often lacking: across the world today, 2.1 billion people lack reliable access to safely managed drinking water services and 4.5 billion lack safely managed sanitation services.

Hygiene, infection prevention and control

Although IPC practices are often seen as basic or even taken for granted, good hygiene—in the hospital, community, and at home—is at the root of preventing infection and must be addressed explicitly as with other, seemingly more complex interventions. Studies show that most healthcare-associated infections can be prevented through good hygiene (WHO 2014). High standards of hygiene—personal hygiene as well as hygiene in hospital, community, and home environments—to reduce the presence and survival of microbes in the environment and reduce human and animal exposure usually correlates with conditions and practices that maintain health and prevent the spread of diseases.

In the human healthcare setting, the importance of good hygiene—particularly cleaning the facilities, and good hand hygiene through hand washing with clean water and soap or alcohol-based products—is well established. Successful AMR interventions highlight the need to monitor compliance (Mölstad et al. 2017). Studies show that adherence to hand washing protocols is frequently suboptimal. Other IPC measures, such as patient screening and isolation, can play an important role in AMR containment. All may not be able to implement these measures given their cost (Wellcome Trust 2016). Beyond cost, factors such as fragility, conflict, and violence (see chapter 1) may also hamper implementation. A better understanding of these obstacles and how to overcome them is needed (#KKIG 14).

What are the major obstacles in implementing effective hygiene, infection prevention, and control in specific contexts? How can we overcome them? **— #KKIG 14**

In the agriculture and food setting, effective preventive AMR interventions can be applied to basic infrastructure such as building design, drainage, and effluent management at all stages of the food chain from primary production to processing and retail outlets. The consistent application of good animal husbandry practices (GAHP) for livestock rearing with higher biosecurity—like the simple act of showering, changing clothes, and shoes before entering a livestock facility—can significantly reduce the risk of introducing infectious agents and the subsequent need for antimicrobial use in livestock (Lhermie et al. 2017). This is important with regard to risks related to the food chain and to pollution of the environment.

Food safety remains a challenge in many LMICs. For example, a study from Ethiopia found that abattoirs were lacking in basic amenities such as soap, hot water, and even bathroom facilities for staff (Dulo et al. 2015). Globally, productivity losses associated with foodborne diseases in LMICs are estimated to cost $95.2 billion per year, and the annual cost of treating foodborne illnesses is estimated at $15 billion (Jaffee et al. 2019). Measures to improve food safety will have an indirect positive impact on AMU and consequently AMR control (World Bank 2017a). The food and agriculture sector can do more to limit consumer exposure to drug-resistant microbes. For example, regulations on surface cleansing methods in food processing set-

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tings are not employed in all countries, but could reduce the spread of bacteria (Wellcome Trust 2016).

A better understanding of obstacles in implementing good practices in agriculture, biosecurity, and food safety and how to overcome them is needed (#KKIG 15).

What are the major obstacles in implementing good agriculture practices, biosecurity, and food safety in specific contexts? How can we overcome them? **— #KKIG 15**

Water and sanitation

Every year, 361,000 children under 5 years of age die due to diarrhea related to poor sanitation and contaminated water, which are also linked to transmission of diseases such as cholera, dysentery, hepatitis A, and typhoid. Improving access to clean water and sanitation is consistent with the sustainable development goals. It would reduce the incidence of infections, and therefore reduce the need for antimicrobials and spread of infections with resistant microbes. Although this intervention is not specific to AMR, it constitutes a vital step toward better health and fewer infections and is an AMR-sensitive intervention (#KKIG 16).

What are the major obstacles in accessing clean water and sanitation? How can we overcome them? **— #KKIG 16**

Poor water safety and sanitation is particularly prevalent in LMICs and accounts for a disproportionately high burden of diarrheal illness through transmission of microbes between people and between people and their environments. The same applies to AMR contagion, which is aggravated due to the inability of current water treatment techniques, including chlorination and UV radiation, to effectively control AMR. This is because antimicrobial resistance genes are able to survive and pass into treated effluents, thus reinforcing the reservoir of antibiotic resistance genes in treated water (Lood et al. 2017).

There is no organized or functional system for AMR surveillance specific to the environmental sector, specifically water, soil, and air (Wuijts et al. 2017). Governments that are assessing investments on a cost-benefit basis should incorporate the public health benefits including AMR containment, as part of the expected returns from improving access to clean water and sanitation (O'Neill 2016).

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Vaccination

Vaccination is known to prevent disease transmission and engenders protection against infection by building herd immunity in humans and animals, though people and farmers may lack willingness to adopt vaccination practices for many reasons, including cost.

Vaccination of humans and livestock can prevent infections and lower demand for antimicrobials (World Bank 2017a). Higher vaccination rates against viruses can be an effective way to limit AMR through also reducing the need for antibiotics and subsequent selection pressure for the development of resistance.

The effectiveness of bacterial as well as viral vaccines in reducing the need and use of antibiotics in animal agriculture has been documented (Murphy et al. 2017). Vaccines are usually considered as part of alternative products, which can help minimize the need for antibiotics along with microbial-derived products, non-nutritive phytochemicals, immune-related products, chemicals, enzymes, and innovative drugs (Hoelzer et al. 2019). However, vaccines optimally fulfill their potential when used as part of an overall program of infection prevention and control as described above. Much of the first line treatments by farmers or veterinarians is empirical, based on experience and in response to syndromic indications (OIE 2015). Reduction of syndromic indications through better targeted, potentially multivalent vaccines has the potential to reduce the need for use of antibiotics (#KKIG 17).

What are the priority vaccines that could be developed for reduction of antimicrobials? What are their projected effects on reducing consumption of antimicrobials? **— #KKIG 17**

Vaccine-preventable diseases cause approximately 15 percent of disability-adjusted life years (DALYs) in Sub-Saharan Africa (Philips et al. 2017). Yet, vaccination rates are low in LMICs—for many reasons (Restrepo-Méndez 2016)—in contrast to others where vaccination programs are successful. For example, 90 percent of children in India are now being fully vaccinated as per the childhood immunization schedule (Harbarth et al. 2015). Delay in acceptance or refusal of vaccines despite their availability has been increasingly reported (see chapter 1).

Animal vaccination rates remain low with a trend to using antibiotics prophylactically instead, despite WHO guidelines that antimicrobials should not be used to prevent disease in healthy animals (WHO 2017a and d). Studies show farmers generally lack understanding and willingness to adopt vaccination practices, largely citing concerns about the costs, accessibility, and reliability of vaccines (Coyne et al. 2014). Finally, the need for cold chain—maintaining a product at a specified low-temperature range from production to consumption—often remains a limitation for vaccination in many countries.

The OIE has prioritized diseases in animals for which the availability of vaccines could reduce antimicrobial use, underscoring the potential of vaccines as alternatives to antimicrobials for controlling animal diseases. This also should guide research on vaccine development in pigs, poultry, farmed fish, cattle, sheep, and goats.

What measures can be taken to improve uptake and use of vaccines in specific contexts? **— #KKIG 18**

Husbandry and management

The rise of intensive systems of livestock production to reduce costs has led to misuse, including overuse, of antibiotics in livestock farming. In other words, antibiotics have been a short-cut solution to achieving high levels of productivity and profitability, while at the same time making meat cheaply available for a growing world population, albeit at a high cost in terms of AMR proliferation. But there is increasing evidence that continual improvement in animal husbandry—such as genetics, vaccines, nutrition, housing, biosecurity, animal management practices, and animal welfare—have now obviated the need for antibiotics for growth promotion and prophylaxis (Van Boekel et al. 2015).

In-depth surveys of farmers and veterinary professionals in HICs found that the key to good husbandry is highly skilled staff (Coyne et al. 2016; Coleman et al. 1998). Livestock kept under optimal farm environments with high-quality hygiene, biosecurity, and animal management practices require much lower antimicrobial use (Stevens et al. 2007) due to lower infection rates and reduced need for treatment (Postma et al. 2015), indicating the feasibility of preventive approaches to reducing the need for antimicrobial use.

A review performed for OECD (Laxminarayan et al. 2015) of the economic costs of banning antimicrobials for growth promotion use found that it is possible for pig and poultry producers to maintain production levels without antimicrobials through preventive management such as vaccination, segregation of animals by age, sanitary protocols, good ventilation systems, adjustment in feed rations, and physical external and internal biosecurity measures. Additional costs of production would be minor at around 1–2 percent in well-managed optimized livestock farms with up-to-date infrastructure. USDA concluded that because the efficacy of antibiotics in increasing farm-level productivity has decreased in the past 20 years, their removal would have limited effects on farm production and prices by less than 1 percent over time (Sneeringer et al. 2015). Hence the economic impacts of moving to preventive management in HICs are likely to be insignificant.

The same cannot be said for the situation in most LMICs, where hygiene and husbandry methods are less industrialized. In the absence of efforts to introduce good animal husbandry and management, antimicrobials are poised to become the major driver allowing the country to meet the projected livestock demand in these countries (Delgado et al. 2001). Demand for dairy, pig, and poultry products is set to grow fastest, with a concomitant increase in the use of antimicrobials for livestock of 66 percent by 2030.

What strategies can be developed to transition the livestock sector to become not only independent of antimicrobials as growth promoters but also less dependent on antimicrobials for prophylactic and metaphylactic use? **— #KKIG 19**

Power of consumer preference

Even in the absence of effective regulation and enforcement, the private sector livestock, processing, supply, and marketing industry can have a major influence on antimicrobial use on farms. Driven by consumer demand, supermarkets are starting to develop policies and enforce standards regarding antibiotic use by their meat suppliers. Most large food retailers already offer—although most often ill-defined and misleading—antibiotic-free, organic, and high-animal-welfare certified products. In the United States, this is still only a small market share at 5 percent of all meat marketed. But it is growing at 20 percent annually on average, with antibiotic-free poultry sales growing at 34 percent (DNV GL AS 2016), as factory-farming-produced meat demand declines.

Heightened consumer awareness also is increasingly affecting the sourcing policies of many major global fast-food companies, which are increasingly focused on antibiotic-free ingredients. For example, the McDonald's chain, which buys over 2 percent of global beef production, recently outlined its goals for antibiotic stewardship (McDonald's 2017). The company intends to reduce the need for antibiotics by ensuring its suppliers use appropriate farming practices, including the responsible use of antibiotics.

Several public interest nonprofit organizations working to eliminate the routine use of antibiotics in food animals now monitor the implementation of food industry commitments, some of which are more restrictive than required by government legislation, and publish annual findings (Friends of the Earth et al. 2018). There is encouraging evidence that strengthened consumer preferences, awareness, and transparency can influence the food industry in positive ways for better antibiotic stewardship.

How can we accelerate adoption of high farm and food industry antimicrobial stewardship through market forces and consumer preferences, awareness, and transparency? **— #KKIG 20**

CASE STUDY 5: **INTERVENTIONS INVOLVE MANY STEPS AND MANY ACTORS**

Denmark has a highly efficient meat production industry with significant export of meat products. Agricultural growth promoters (AGPs) have been used to increase production in this industry since the early 1950s (FAO and Ministry of Environment and Food of Denmark 2019). International concern about this practice was raised as early as 1969 in testimony from the Joint Committee on the Use of Antibiotics in Animal Husbandry and Medicine before the British Parliament (Swann Report 1969). In the 1990s, outbreaks of Salmonella infection brought local attention to food safety issues, including the potential for antibiotic use in animals to contribute to antimicrobial resistance (Kovács 2011), leading to scrutiny of AGP use in Denmark.

Following English and German studies on vancomycin-resistant enterococci in the 1990s, the Danish Veterinary Laboratory examined poultry samples and identified avoparcin—an antimicrobial closely related to vancomycin—as a potential driver of vancomycin resistance in the Danish food system (Aarestrup et al. 2000). Appealing to the food safety concerns of Danish citizens, use of avoparcin was banned as an AGP in Denmark in 1995 (FAO and Ministry of Environment and Food of Denmark 2019). In 1996, an FAO/WHO expert panel met to discuss the issue and, spurred further by the appearance of bovine spongiform encephalopathy in Britain that same year, the food production industry in Europe began to implement risk analysis principles and separated the responsibility for assessment from responsibility for management (EU Food Law) for a proactive approach to ensuring food safety. In 1997, the EU also banned its use. Scrutiny of the AGP virginiamycin followed shortly thereafter, with its use prohibited in Denmark in 1998 and the EU in 1999. Use of bacitracin, tylosin, and spiramycin were subsequently also banned in Denmark. Further, the Danish poultry industry voluntarily stopped use of all AGPs in broiler poultry by 1998, as did the swine industry in finishing pigs in 1998 and all swine by 2000. Supported with data collected by Danish and Swedish scientists and following the 1998 Copenhagen Recommendations—which outlined a framework for surveillance, monitoring, and good practice use of antimicrobials (Andersen and Hald 2017)—the use of all AGPs in the EU was phased out by 2006 (European Commission 2005).

Danish veterinarians shared the concerns of policy makers and industry and, in 1994, placed limits on the amounts and prices of antimicrobials that veterinarians could sell and restricted further antibiotic treatment to that obtained from a pharmacy by prescription only (FAO and Ministry of Environment and Food of Denmark 2019). In turn, farms were subjected to monthly veterinarian visits to maintain the health of animals without use of AGPs. This shift in income source—from sale of antimicrobials to increased advisory services—allowed livelihoods of veterinarians to be maintained while changing veterinarians' roles in the food production industry (Kovács 2011). In addition, in 2000 a database of all purchased and prescribed antimicrobials (the Danish Veterinary Medicines Statistics Program, or VetStat) increased accountability in the profession and provided data to determine the association between antimicrobial use and the appearance of antimicrobial resistance. VetStat data support the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP), which was launched in the mid-1990s as a collaboration among the veterinary, food, and human health sectors (FAO and Ministry of Environment and Food of Denmark 2019). Based on the "farm-to-fork" concept (Kovács 2011)—the keystone in responding to Salmonella outbreaks in the 1990s—and implicating all stakeholders in the supply chain, DANMAP tracks the use of antimicrobials and appearance of resistance in livestock.

Based on early DANMAP data, the European Food Safety Authority recognized Denmark as a country with a low incidence of antimicrobial resistance relative to other countries in the EU (Kovács 2011). Between 1994 and 2001, Denmark experienced a 54.2 percent decrease in antimicrobial use (Dibner 2005). A later analysis of antimicrobial consumption and swine productivity in Denmark from 1992 to 2008 indicated that, while consumption of AGPs decreased, productivity did not decline following the change in veterinary prescriptions and ban on AGPs (Kovács 2011). Other changes—such as improving farm environments, increasing the weaning age, and modifying the diets of animals—likely played a role in maintaining this productivity. The pork industry, specifically, expanded substantially—from 18.4 million hogs annually in 1992 to 28 million in 2010—during this period (Kovács 2011). Although antibiotics used for treatment did increase steadily from 1999 to 2007 due to

an increase in production, use was further curbed with implementation of a "yellow card" (a dynamic tool that limits acceptable antibiotic consumption) warning to farms found to be overusing antimicrobials (Andersen and Hald 2017). Denmark has continued to promote innovations to reduce antimicrobial consumption: in 2013, taxation of antimicrobials was scaled to promote use of narrow-spectrum over broad-spectrum drugs and an annual laboratory diagnosis was required for group treatment of animals (Andersen and Hald 2017).

Limiting use of antimicrobials is our third family of interventions. In this case study we looked at how Denmark managed to phase out antimicrobial growth promoters in the meat production industry. The Danish experience in reducing AGP use has been held as a model for other countries to emulate. It shows that multiple steps were needed with the involvement of multiple actors. The alliance between government and research partners was pivotal in this process. There is a long tradition of cooperation among stakeholders in the area of animal production. The Danish approach has included cooperation among organizations representing farmers and industry, veterinarians, government authorities, and universities. Policy decisions could be made based on data available in VetStat and DANMAP and then compared with those of other countries in the EU for evidence-based decisions. Another important success factor has been the cooperative model of Denmark's meat production industry, which enabled farmers to collectively decide to implement the precautionary principle and voluntarily ban AGPs. The role of civil society has been key as well; opposition from the pharmaceutical industry increased public awareness of the food safety risk debate in Denmark, and civil society's engagement created an opportunity for change. The support of veterinarians, including their acceptance of a shift in their practices and willingness to address economic incentives for the profession, led to a system that benefited both veterinarians and farmers and decreased the use of antimicrobials. Finally, the food chain approach, also known as "farm-to-fork," provided a comprehensive and broadly understandable approach to banning AGPs and reducing the use of antimicrobials to prevent the emergence of resistant bacteria in the food system. This experience blends interventions aiming at reducing the need for and use of antimicrobials.

LIMITING USE OF ANTIMICROBIALS (MITIGATION)

Economic incentives and disincentives

The market for antibiotics involves drug companies, wholesale suppliers, and distributers that have the profit incentive to maximize unit sales rather than act in the best interests of antibiotic stewardship. There is also a parallel market of counterfeit and substandard medical products, including antimicrobials. On the demand side, users of antimicrobials often pay high transaction costs to intermediaries in the medicine supply chain, and farmers may be unprotected from potential financial loss when phasing out the use of antibiotics. This section discusses interventions to alter the market dynamics of a "tragedy of the commons" scenario.

Farmers and food producers invariably operate under uncertainty and risk. Market interventions can be effective at improving access to antibiotics for treatment and mitigating the risk of income loss while phasing out AGPs. Even with improved husbandry practices, phasing out AGPs in livestock feed could affect the profitability of food production, especially in LMICs (Laxminarayan et al. 2015). Access programs and insurance schemes for farmers can promote appropriate antibiotic use while protecting farmers against market risks.

To help farmers manage this market risk, countries or regions could create pooled procurement programs to improve access to a sustainable supply of good-quality antimicrobials for therapeutic purposes, with reduced transaction costs. Demand planning and leveraging consumption data for these procurement programs also would lead to uninterrupted supply and the strengthening of distribution, which would boost efficiencies across the supply chain.

Another approach under consideration is for countries to develop insurance schemes to mitigate the risk of income loss among producers during the phaseout of antibiotics, or provide insurance against livestock diseases for farmers who don't use antibiotics. The EU ban on antimicrobials for growth promotion in 2006 may have resulted in an increased incidence of infectious diseases, based on the observation that the phaseout was associated with a short-term increase of disinfectants and therapeutic use of antibiotics in livestock (World Bank 2017a).

This type of intervention may be challenging for governments that don't have the institutional capacity to provide livestock insurance, but there could be opportunities to develop public-private partnerships such as those providing index-based insurance for pastoralists in Kenya to introduce husbandry interventions for improved household resilience under erratic rainfall conditions (Johnson et al. 2018).

What financial incentive schemes can be devised to reduce farmer risk in adopting good AM practices? **— #KKIG 21**

Precision use of antimicrobials

Better diagnostic tools are needed to prevent empirical prescribing, particularly in LMICs. Microscopy, culture, DNA or protein-based tests, and sensitivity testing can all help to identify individual pathogens so that a specific, targeted antibiotic treatment can be given. Lack of access, high cost, and lengthy wait times to obtain results of such diagnostic tests means antibiotics are often used empirically and "to be on the safe side." Empirical prescribing is particularly prevalent in LMICs, where diagnostic tools are even less available or less effective. It often includes the unnecessary combination of two or three individual antibiotics, each potentially contributing to the emergence of resistance. One challenge lies in producing tools that are cheap, portable, and provide a quick result. "Point of care testing" and "pen side testing" are still relatively rare—even in HIC settings—and it is likely to be some time before this translates to the LMIC setting. For example, in the UK GPs are faced with the dilemma of doing a sensitivity test, which would delay treatment and incur three times the cost of empirically prescribing immediate treatment (House of Commons 2018). We already know from experience with the introduction of rapid diagnostic tests for malaria, that these "simple and mobile" devices often require more infrastructure than they circumvent in order to be operationalized, and moreover that they still do not necessarily translate to improved health care and can have other unintended consequences (Beisel et al. 2016).

What are the priority diagnostic tools that could be developed to reduce use of antimicrobials? What is their projected effect of reducing antimicrobial consumption in different country contexts? **— #KKIG 22**

Education, awareness, and behavior of professionals

The importance of educating healthcare professionals has long been recognized (WHO 2013) and the organization recently developed a competency framework for health workers' education and training on antimicrobial resistance (WHO 2018e). The 2013 guidelines on transforming and scaling up health professionals' education and training emphasize the importance of linking education to population need and moving away from education that is segregated into silos (WHO 2013). As an issue that affects every member of the human race, everyone should be aware of AMR, its threat to humanity, and their individual role in avoiding the risks it poses to themselves and to others.

Despite AMR being recognized as one of the greatest global healthcare challenges of our time, coverage of the topic in medical education curricula is limited. The "We need you" communication campaign by OIE is probably the first global campaign dedicated to raising awareness of antimicrobial resistance in the animal health sector. The campaign, focused on the careful handling of antibiotics, was used to develop a toolkit for national veterinary services, policy makers, veterinarians, veterinary students, farmers, the pharmaceutical industry, wholesale and retail distributors, and animal feed manufacturers.

Knowledge and awareness

Educating healthcare professionals about AMR is a vital step in trying to tackle AMR, yet the focus of educational interventions to address AMR varies widely among countries in all income-level groups. For example, outcomes of effective education programs include a change in prescribing principles and behavior, incorporating AMR discussions into the consultation model, or automatically giving out leaflets with each antibiotic prescription.

Studies have shown that many healthcare professionals are lacking in knowledge and understanding of AMR and that gaps exist in the undergraduate healthcare curriculum (Pereira et al. 2017). For example, in an Ethiopian study of paramedical staff, very few had received any formal training on antibiotic prescribing and were lacking in knowledge of AMR (Tafa et al. 2017).

Some research suggests the need for greater emphasis in public messages for understanding how resistance is spreading, rather than an active focus on why and what can be done to reduce it. They recommend that educational interventions should focus on meaning and purpose (Tsai et al. 2017). The example of AMR is well suited to this school of thought, as knowing why we need to tackle AMR is key to sustainable implementation of interventions.

Van Katwyk et al. (2018) reviewed AMR education methods available globally and found that many organizations were working on educational resources for AMR control. They identified some areas for improvement, including increased student engagement, improved resource-sharing, and the need to recognize the importance of AMR learning in continuing medical education; those elements have been integrated into the WHO competency framework for health workers' education and training on AMR (WHO 2018e).

The importance of recognizing and acknowledging AMR in education cannot be underestimated. A recent survey showed that the problem of AMR was often externalized, being perceived to be "someone else's fault" (Zhuo et al. 2018). Other researchers have identified this attitude in other sectors; for example, veterinarians tend to "blame" the intensive farming industry for AMR and not their own practices (Hardefeldt et al. 2018). Incorporating shared responsibility and a "one health" approach into medical and veterinary curriculums, or including this in mandatory departmental induction alongside regular professional updating, would be a good starting point in most organizations.

Some interventions focusing on behavioral change and social norms have been successful, yet data on long-term follow-up and sustainability are not available.

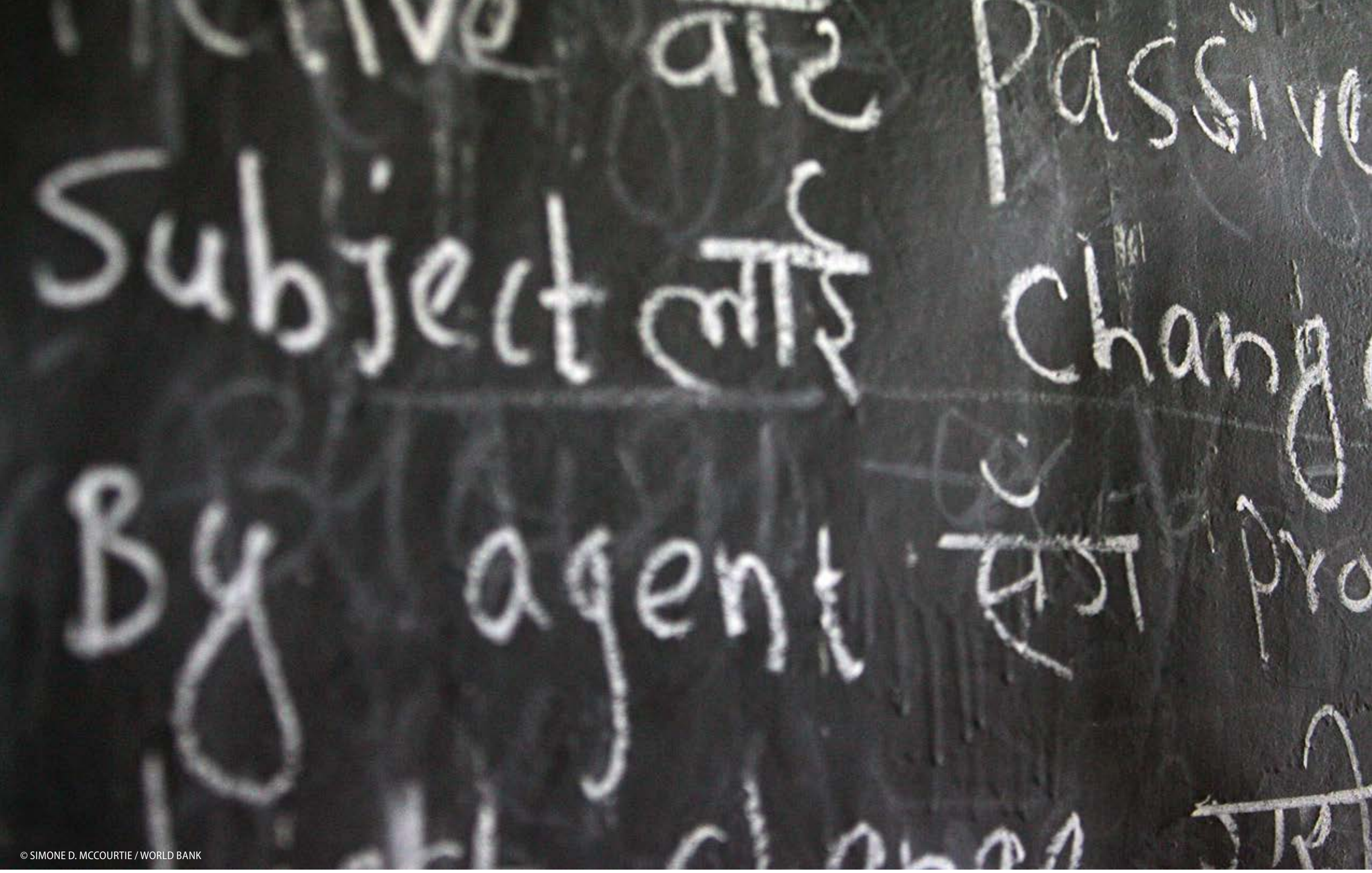
What is the long-term impact of interventions to change behaviors and social norms regarding antimicrobials? What interventions will engender sustainable change in behaviors and social norms regarding antimicrobials? **— #KKIG 23**

Behavior of professionals

The highest rates of antimicrobial prescribing occur in the community setting and thus are a priority area for AMR research. In 2014 in the UK, for example, 74 percent of antimicrobials were prescribed by GPs (Public Health England 2016).

Numerous elements of stewardship efforts have been associated with decreased levels of antimicrobial prescribing, including provider and/or patient education, provider feedback, formal guidelines, delayed prescribing, communication skills training of providers, drug restrictions, provider decision support systems, and financial incentives (Drekonja et al. 2015). However, more large-scale studies that assess the effect of outpatient antimicrobial stewardship on antimicrobial resistance are needed, in diverse contextual situations, to inform and prioritize interventions as a part of individual national action plans.

One UK study targeted the highest prescribing GP practices to try and alter prescribing rates. The study utilized "social norm" information, involved a high-profile figure to "champion" the initiative, and provided behavioral instruction, with the intended outcome to lower the rate of antimicrobial prescription by GPs (Hallsworth et al. 2016). Social norm feedback was effective in encouraging outliers to adjust their prescribing levels. However, other studies have found the effect to be short-lived (Cairns et al. 2013), so long-term follow-up of efficacy is needed. Punitive mechanisms may be effective but short-lived, whereas self-determined behavioral change may achieve better outcomes in the long term (Sikkens et al. 2017). The authors conclude that future antimicrobial stewardship efforts in hospitals should use behavioral theory to improve intervention effectiveness in various clinical settings.



Professional Culture

Cultures that influence prescribing appear to exist both within human healthcare and animal healthcare. A negative intrinsic hierarchy exists within the medical profession, leaving junior doctors reluctant to challenge their seniors and so inappropriate prescribing persists. Within the veterinary sector, financial pressures and client pressures also impact on prescribing decisions.

A negative cultural hierarchy appears to be ingrained in the medical profession and studies have reported that this culture has a strong influence on prescribing (Papoutsi et al. 2017).such interventions are often adopted without an adequate understanding of the challenges facing doctors-in-training as key prescribers.\nMethods: The review followed a realist, theory-driven approach to synthesizing qualitative, quantitative and mixed-methods literature. Consistent with realist review quality standards, articles retrieved from electronic databases were systematically screened and analysed to elicit explanations of antimicrobial prescribing behaviours. These explanations were consolidated into a programme theory drawing on social science and learning theory, and shaped though input from patients and practitioners.\nResults: By synthesizing data from 131 articles, the review highlights the complex social and professional dynamics underlying antimicrobial prescribing decisions of doctors-in-training. The analysis shows how doctors-in-training often operate within challenging contexts (hierarchical relationships, powerful prescribing norms, unclear roles and responsibilities, implicit expectations about knowledge levels, uncertainty about application of knowledge in practice Recently trained junior doctors, who may be more knowledgeable about AMR, have difficulty challenging clinical decisions of more senior doctors and consultants. Broom et al. (2016) studied the social context of the practice of antibiotic prescribing in Australian hospitals, finding that suboptimal antibiotic use is a real and pragmatic choice within a complex social context. Drivers of prescribing behavior were more about protecting patients, managing time pressures, gaining and achieving social capital, and expressing a benevolent identity, rather than focusing on the threat of antimicrobial resistance.

Prescribing cultures within the veterinary sector also have been linked to AMR. For example, multidrug use and subtherapeutic drug use are particularly strong drivers of AMR. Both of these practices are prevalent in agriculture (Silbergeld et al. 2017), where the high cost of diagnostic testing leads to empirical prescribing with few veterinarians following official guidelines (Hardefeldt et al. 2018). Veterinarians often feel pressure from farmers to overprescribe for several reasons (Coyne et al. 2014).

Therefore, in both animal and human health, cultural factors and their influence on prescribing behaviors need to be taken into consideration when implementing AMR interventions.

Prescribing guidelines exist in many LMICs, albeit in many instances they are not surveillance-based; yet even when they do exist, they are not always followed due to lack of resources, time pressure, and insufficient staff (Edelstein et al. 2017). Antimicrobial stewardship (AMS) programs aim to improve prescribing and advocate for following guidelines, but the success of AMS interventions remains a debated issue.

Official guidelines for antimicrobial stewardship

Many healthcare settings produce prescribing guidelines for advising clinicians about antibiotics that are appropriate for specific bacterial or viral infections. For example, the Royal College of general practitioners (GPs) has produced the TARGET (Treat Antibiotics Responsibly, Guidance, Education, Tools) toolkit, which includes links to tables with antibiotic guidelines.

The concept of antimicrobial stewardship (AMS) is defined as "a coherent set of actions that promote using antimicrobials in ways that ensure sustainable access to effective therapy for all who need them" (Dyar et al. 2017). Actions might include prescribers making accurate diagnoses, following guidelines, reviewing their prescriptions in a timely manner, formulary restrictions, and preauthorization of certain antimicrobials.

Some studies have shown that AMS guidelines have provided a significant contribution to combating AMR (Huttner et al. 2014), while other research findings challenge their effectiveness. Key barriers to effective AMS include a lack of effective strategies to implement AMS, particularly in the LMIC setting; poor response from governments to engage in AMS; lack of coordination of AMS across different sectors and specialties (Tiong et al. 2016); and economic viability (Ibrahim et al. 2018). A recent systematic review (Van Dijck et al. 2018) of AMS in LMIC settings concluded that most of the AMS interventions had a positive effect. However, general conclusions about their effectiveness could not be made, probably due to context-specific variables in certain settings.

Implementation of AMS among the veterinary and animal health sector also is challenging, with uptake of AMS programs being particularly low in the veterinary sector (Hardefeldt et al. 2018).

The general public—users of antimicrobials

Globally, the public has low levels of knowledge of AMR. Furthermore, they find the language and concepts behind AMR complex and difficult to grasp. Public health messages need to be carefully worded to appropriately emphasize the severity of the AMR situation. Reviews of public awareness campaigns mainly show whether people improve their knowledge—fear of AMR—rather than any other impact, such as unintended consequences of raising awareness or inadvertently getting people to move automatically to next-line antibiotics in fear that current drugs are not working.

Many studies and surveys have reported a lack of knowledge of both antibiotic use and AMR among the public. The European Commission (2016) carries out regular surveys to assess public awareness and knowledge of antimicrobials and AMR. The results from 2016 revealed that only 24 percent of participants answered all questions correctly, with only 43 percent and 56 percent being aware that antibiotics are ineffective against viruses and against colds and flu respectively.

A WHO (2015a) survey of 12 member states found that 57 percent of participants thought there was nothing an individual can do to help stop AMR, and 76 percent did not know why AMR occurs. Results were similar for both LMICs and HICs. People also exhibit concerning behaviors in their use of antibiotics, such as sharing of medicines among family members or storing leftover antibiotics for future use without medical advice (Barker et al. 2017).

In the United Kingdom (Wellcome Trust 2015), the public finds terms such as "superbugs" unhelpful and the concept

of AMR does not have much meaning to them. In Sweden, where the use of antibiotics has been reduced, research teams attributed success to well-designed public awareness and education campaigns. Finding language with impact and meaning in a particular setting is vital in getting the message understood, with a first challenge being to ensure the target audience understands the meaning of words.

Framing AMR in terms of crisis language as a threat to national security has been proposed (Kamradt-Scott et al. 2017). However, others suggest acting with caution, as a sense of crisis could lead to a fatalistic attitude (Lindland and Volmert 2017) since this could strengthen a sense of fatalism and disincentivize action. Careful consideration must be taken as to the best communication strategy and messaging for specific socioeconomic and cultural contexts.

The seminal works on AMR call for campaigns, yet there is a distinct lack of evidence for the effectiveness of AMR public health campaigns and there remains little research into the best way to go about implementing these campaigns. Different populations may require different interventions; nontraditional tools such as social media could be beneficial.

A major barrier to tackling AMR is public disconnect, lack of understanding, and indifference. Public health campaigns have been suggested as a key way to implement change by multiple high-profile agencies, including the IACG, WHO, and the O'Neill Report. However, there is a lack of evidence for these campaigns, and multiple studies report a lack of effectiveness (Kardaś-Słoma et al. 2013; McNulty et al. 2010). There is also little information and guidance from the seminal works on how to establish and manage public awareness campaigns. For an LMIC to start from scratch to organize an AMR public health campaign is extremely challenging, especially given the poor baseline starting point.

WHO published a paper in 2016 exploring public awareness campaigns designed to tackle AMR and included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both LMICs and HICs. The authors contacted 93 countries and received no response from 40 percent of them (Saam et al. 2016). Of those that did respond, only 25 percent had campaigns that ran all year, with the rest either temporary or seasonal (Saam et al. 2016). Those who responded to the survey reported that financial issues were a significant barrier to implementation, as well as lack of political support (Saam et al. 2016). Furthermore, there was a lack of program appraisals, with 60 percent of campaigns having no formal evaluation.

Today social media have an important and influential role and could be a potential platform for AMR interventions, but getting the framing right is essential. Research bodies conclude that Twitter is underused for AMR public health messages and could be a useful tool given the volume of users and enormity of the platform (Dyar et al. 2017). In contrast, however, a 2018 study linked the use of social media and print media with an increase in misuse of antimicrobials and misunderstandings about AMR (Groshek et al. 2018). It is vital to get an accurate message out using social media platforms. If public and veterinary health authorities and governments fail to deliver the correct AMR message, then user-generated social media could amplify and perpetuate misconceptions. Nevertheless, a study published in July 2018 described how social media for health-related purposes are expanding in LMIC settings and have potential as a tool to address AMR (Hagg et al. 2018).

Looking at the demographics of antimicrobial usage may help to frame communication interventions. Studies have shown that teenagers and adolescents are the highest users of antibiotics in Europe (Hawking et al. 2017). These studies also revealed a widespread lack of knowledge and understanding about antibiotics. An online educational tool has been developed in the UK (e-Bug) with favorable feedback from teachers and educators (Eley et al. 2018). This type of intervention is less applicable to LMICs, where internet access might be limited and alternative methods are needed. However, studies have shown that wireless access and electronic health (e-health) technologies and resources are increasing in LMICs, so this could potentially be expanded and implemented in the future (Clifford

2016). Although internet access is not essential, and hygiene, sanitation, infections, antimicrobials and resistance are concepts to be included early in curricula in all schools.

Changing the individual's behavior around antimicrobial use remains a key challenge.

Human behavior

Interventions discussed in this section are inextricably linked through the realization that AMR control ultimately depends entirely on changes in human behavior. There is currently little literature that addresses behavior change in relation to AMR that uses sound psychological theory (reviewed by Donald 2016). One recent study (Pinder et al. 2015) addresses the application of behavior change research with respect to reducing the use of antibiotics in the UK.

Some research groups describe human behavior as a significant obstacle and state that a "cultural change" is needed rather than education alone (Harbarth et al. 2015). AMR has been described as a tragedy of the commons (Baquero and Campos 2003; World Bank 2017), where the behavior to benefit an individual is taken at the expense of communal interests (Hollis and Maybarduk 2015). A key question to address is: Does the individual user view AMR differently than the public as a whole? Is it the case that, even with full knowledge and understanding of the societal implications, as individuals we are incapable of foregoing individual benefits in favor of the greater public good? How do we persuade the individual to take responsibility and change his or her behavior? This is also valid for health professionals: the 'just in case' antimicrobial prescription and the 'just once will not have any consequence' thoughts justify many instances of inappropriate consumption of antimicrobials.

In Sweden and other Scandinavian countries, where use of antibiotics has been successfully reduced, the importance of educating the public about the consequences for both society and the individual specifically were highlighted as important interacting factors (Wellcome Trust 2015).

Translation and application of findings such as these into other regions and societies is not easy and must be conditioned by prevailing social beliefs and norms, given that failure to change behavior will derail the best-laid technical plans. Understanding the drivers of human behavior in the context of AMR is a neglected area of research, yet is an essential prerequisite for designing and implementing impactful awareness-raising interventions. The "one health" approach is necessary, but insufficient without the inclusion of greater interdisciplinary contributions from the social sciences —such as ethnography, anthropology, sociology, and psychology (Harbarth et al. 2015)—if real culture change is to be achieved.

KEY KNOWLEDGE AND IMPLEMENTATION GAPS

Chapter 3

Key knowledge and implementation gaps

The aim of this chapter is to organize key knowledge and implementation gaps (#KKIGs) that were identified in the previous chapters. The cross-disciplinary narrative that emerges from our analysis carries two intertwined findings: (1) that AMR needs to be reframed as a development issue; and (2) that AMR-sensitive interventions are needed in LMICs to address the underlying weaknesses driving emergence and spread of AMR. The focus is the critical knowledge needed—and how to harness this knowledge—to support countries, particularly LMICs, in addressing AMR. Much of the action on AMR to date has focused on misuse of antimicrobials, but a country's AMR risk profile is also determined by context. Building on this understanding, we propose a typology for countries to better understand risk and susceptibility to AMR, as well as research needs.

MAPPING KNOWLEDGE GAPS IN A RESEARCH LANDSCAPE

As mentioned in the introduction to this report, there is a rapidly growing body of evidence on AMR, supported by a similarly growing number of research projects. In this study, however, we have identified a number of gaps in terms of knowledge and implementation. Those gaps (KKIGs) have been identified in chapters one and two. They are presented in a synopsis table (Table 1) with their area of relevance. Nine gaps relate to the contemporary narrative on AMR and to the current state of thinking; four relate to our capacity to establish an enabling environment for AMR control, which entails agenda setting, regulation and legislation, and surveillance; seven pertain to reducing the need for antimicrobial use (which can be referred to as adaptation), including hygiene, infection prevention and control, water and sanitation, vaccination, animal husbandry, and consumer preference; and three deal with limiting use of antimicrobials (i.e., mitigation), which includes economic incentives and disincentives, precision use of antimicrobials, as well as education, awareness, and behavior of professionals.

Describing comprehensively the entire landscape of AMR research is a daunting challenge given the high number of initiatives planned, undertaken, or having recently been completed. The IACG recognized the need to better understand the current efforts and enhance collaboration, and called for a coordinated global mapping of research and development and funding activities to address AMR (IACG 2019 b).

One approach is to analyze the breadth of research funded by public, private, and philanthropic donors. This was undertaken by the Joint Programming Initiative for AMR (JPIAMR), which mapped the scale and scope of 1,939 research investments across its membership, collecting information from 22 countries, in addition to information supplied by the EU commission and the Wellcome Trust (JPIAMR 2017), recording a total investment of $2 billion equivalent in AMR research [excluding the animal health sector]. This inventory can reasonably be considered as a reflection of the current engagement to address the threat of AMR through research and development. The mapping, however, has some limitations. The number of participating countries and the geographical area covered is one of them. Similar to AMR-sensitive and AMR-specific interventions, a number of research initiatives also may not have been tagged as AMR research, although the outcomes of some of these projects may contribute to the AMR agenda. Finally, only research projects were captured by JPIAMR, in order to ensure comparable and consistent information being collated. So surveillance sys-

TABLE 1

Twenty-three key knowledge and implementation gaps (#KKIGs) and their area of relevance

The contemporary narrative, enabling environment for AMR control, adaptation, and mitigation

CONTEMPORARY NARRATIVE

1	What is the significance of a specific resistance determinant? How to translate this in terms of risk of absence of treatment options or drug obsolescence? How can this help to focus on priority resistance determinants? (p. 3)
2	What areas of the AMR problem would behavioral and social sciences be most effective and impactful? How should AMR research and implementation activities best incorporate the social sciences to add value and improve progress? What proportion of overall AMR control effort should be devoted to social science research? (p. 4)
3	What is the current level of consumption (use) of antimicrobials in humans and animals? How can this be reliably quantified in practice? How this can be used to set targets and monitor progress on reducing the use of antimicrobials? (p. 5)
4	How to adequately capture the issue of access, especially in the context of acute and chronic poverty? What strategies can be developed to simultaneously address the double burden of access and excess? (p. 6)
5	What would be the most cost-efficient relative distribution of AMR related investments across countries and regions and between intervention types (research, implementation, AMR-specific, AMR sensitive etc.)? How could this help prioritize where and how funding should be used for greatest global benefit? (p. 6)
6	What are the multiple applications of antimicrobials –including disposal practices- and their contextual drivers in anthropogenic activities? How to assess their relevance to the AMR threat? (p. 10)
7	What factors contribute to the spread of AMR? How can their importance be assessed, in locally and regionally specific contexts (e.g. urban vs rural; rich vs poor, community vs hospital)? (p. 11)
8	How changes in drivers of spread, such as the lack of adequate sanitation infrastructure, inappropriate waste management, low expenditure on health per capita, low public share of total health expenditure, weak governance, and corruption, might impact AMR? (p. 12)
9	How can 'prudent and responsible' be better defined? What factors determine individuals' adoption of the "prudent and responsible" principle? (p. 18)

ENABLING ENVIRONMENT

10	How to accelerate and increase the level of implementation of NAPs? (p. 24)
11	What are the specific contributions of SDGs and other relevant agendas to AMR? How can these be quantified (cobenefits) in different contexts? (p. 26)
12	What are the essential characteristics of an enabling environment for AMR control? How countries should prioritize efforts towards establishing an enabling environment within their contexts? (p. 28)
13	What are the critical data and data models for meaningful surveillance and monitoring of priority AMR determinants? How can they be incorporated into facility and population surveillance, monitoring and reporting systems? (p. 29)

ADAPTATION

14	What are the major obstacles in implementing effective hygiene, infection prevention and control in specific contexts? How to overcome them? (p. 32)
15	What are the major obstacles in implementing good agriculture practices, biosecurity and food safety in specific contexts? How to overcome them? (p. 33)
16	What are the major obstacles in accessing clean water and sanitation? How to overcome them? (p. 33)
17	What are the priority vaccines that could be developed for reduction of antimicrobials? What are their projected effects on reducing consumption of antimicrobials? (p. 34)
18	What measures can be taken to improve uptake and use of vaccines in specific contexts? (p. 35)
19	What strategies can be developed to transition the livestock sector to become not only independent of antimicrobials as growth promoters but also less dependent on antimicrobials for prophylactic and metaphylactic use? (p. 35)
20	How to accelerate adoption of high farm and food industry antimicrobial stewardship through market forces and consumer preferences, awareness, and transparency? (p. 36)

MITIGATION

21	What financial incentive schemes can be devised to reduce farmer risk in adopting good AM practices? (p. 39)
22	What are the priority diagnostic tools that could be developed to reduce use of antimicrobials? What is their projected effect of reducing antimicrobial consumption in different country contexts? (p. 39)
23	What is the long-term impact of interventions to change behaviors and social norms regarding antimicrobials? What interventions will engender sustainable change in behaviors and social norms regarding antimicrobials? (p. 40)

tems—increasingly core programs receiving institutional funding—were not captured (Kelly et al. 2015).

Another angle taken to draw this AMR research landscape is bibliometric. As noted earlier, this has become a dense area of publication, with a significant increase in peer-reviewed articles over the past five years (11,158 articles published in 2017). We have used PubMed as a most prominent publicly accessible database to search the scientific literature and allocated 51,138 records—from 2014 to date—to the six JPIAMR priority areas (Kelly et al. 2015). This also has limitations. First and foremost, the records are peer-reviewed scientific papers published in English, hence ignoring grey literature and the significant number of articles published in other languages.

We believe that combining bibliometric and funding data may help to elaborate AMR research activity to a reasonable extent. The six proposed research areas are presented in Table 2, along with the share of funding, percentage of publications, and relevant key knowledge and implementation gaps. It shows that the big share of the funding has been allocated to the area of therapeutics, followed by diagnostics and interventions (Table 2). In contrast, in terms of publications, diagnostics take the lion's share, followed by intervention and surveillance. Most of the key knowledge and implementation gaps that were identified in the course of our analysis relate to interventions.

According to the JPIAMR records, 76.2 percent of investment-supported research projects focused on antibiotic resistance, followed by 20.6 percent on anti-parasitic and 3.2 percent on anti-fungal resistance research. In this report, we have also focused on AMR primarily as resistance to antibiotics. There are, however, rising concerns about resistance to antiviral, antifungal, and anti-parasitic drugs—far beyond resistance to antibiotics and the rise of resistant bacterial infections. The overwhelming attention to antibiotic resistance may not reflect the reality of resistance of microorganisms to the broader spectrum of antimicrobials. In the absence of any systematic and standardized collection of data and information on resistance, attention remains focused on what is already known, can easily be known, and leaving some potentially important areas unknown. This is true for resistance to different types of antimicrobials, and also true for different types of resistance to antibiotics. For example, a central focus has been on newly emerging resistance, last resort drugs, and our ability to treat critically ill patients at larger hospitals. It should be considered whether an improved understanding of drivers for resistance to front-line drugs and efficient first-time treatment would not be much more financially efficient and have a bigger impact overall.

The paucity and low reliability of information about the geographical distribution of AMR over time and trends in prevalence and incidence in human and animal populations makes reliable assessments of the health burden attributable to AMR difficult (Hay et al. 2018). This is a critical knowledge gap (captured by #KKIGs 1 and 13) that continues to weaken the evidence on which to steer research and policy agendas to combat AMR on the basis of sound evidence. It points at surveillance of resistance as an area that requires attention. We have also identified the lack of data and information on the use of antimicrobials (#KKIG 3) to be a significant problem. It is not only about antimicrobial consumption (use) by humans and information on animal species use, but our analysis also shows that antimicrobials have become infrastructures of modernity. Their widespread use in almost every anthropogenic activity calls for a systematic inventory of antimicrobial use (#KKIGs 3, 6), including inconspicuous uses of antimicrobials, to assess them in terms of risk.

Considering multiple applications of antimicrobials and their disposal practices (#KKIG 6), the current focus on antibiotics, and their misuse in humans and livestock could be far too narrow. It has often been compared to "searching at night around lampposts." This does not allow for the AMR community to comprehend the full realm of the issue and address it along its multiple dimensions (#KKIGs 2, 3, 6, 7, and 8).

AMR is a catchall term that encompasses a broad range of resistance determinants, emergence, and spread mechanisms. Discussions about AMR often oversimplify this biological complexity. As a matter of fact, if AMR is a global threat, not all resistance determinants equally threaten public health and development. It is prudent to set priorities of highly relevant pathogen/resistance combinations for which the community needs to pay particular attention, globally or locally.

Disparate data sources from public and private sectors are often not collated at the national and international levels and contain little information on individual patients

TABLE 2

Six priority areas for AMR research defined by JPIAMR

Along with the percentage of funding (2017, n= 1939), percentage of publications (2014–2019, n= 51138) and relevant key knowledge and implementation gaps (#KKIGs)

Sources: Kelly et al. 2015; JPIAMR 2017; PubMed (accessed on April 28, 2019).

Priority areas	Definition	Funding	Publications	#KKIG
Therapeutics	Improvement of current antibiotics and treatment regimens, development of new antibiotics and therapeutic alternatives to antibiotics.	**57.6**	**16.4**	**1**
Diagnostic	Improvement of diagnostics and the development of novel rapid diagnostics to stimulate better use of current antibiotics and support the development and use of new antibiotics and alternatives to antibiotics.	**13.1**	**52.5**	**1; 17; 18; 22**
Interventions	Study of preventive and control interventions that focus on improved antibiotic stewardship, compliance and prevention of transmission of AMR and to determine and improve their efficacy.	**11.3**	**38.7**	**2; 4; 5; 7; 9; 10; 11; 12; 14; 15; 16; 19; 20; 21; 23**
Transmission	Comprehensive, multi-disciplinary understanding of the transmission mechanisms by which AMR can spread between bacterial populations and between different animal and human reservoirs and to translate this knowledge into the development of evidence-based strategies to minimize the spread of resistance.	**7.5**	**5.4**	**7; 8**
Surveillance	Establishment of an international, standardized surveillance program for AMR and antibiotic use in human, and agricultural settings.	**6.7**	**25.8**	**3; 6; 13**
Environment	Assessment of the contribution of pollution of the environment with antibiotics, antibiotic residues and resistant bacteria on the spread of AMR and the development of strategies to minimize environmental contamination by antibiotics and resistant bacteria.	**3.8**	**10.5**	**6; 7; 8; 19**

and their outcomes. Furthermore, there are fundamental issues of selection bias in terms of who is tested for AMR and whether or not that information is entered into facility-based laboratory data systems (#KKIGs 1 and 13). Additionally, systematic efforts are yet to be made to quantify antimicrobial drug utilization patterns by animal species, which would yield important data to address AMR (#KKIG 3). Protocols for diagnostic methods and data collection need to follow international standards where available to allow an accurate depiction of the true health burden of AMR.

These problems are exacerbated in low- and middle-income countries, where there is often inadequate surveillance, minimal laboratory capacity, and limited access to essential antimicrobials (#KKIG 13). Surveillance and monitoring for antimicrobial use and resistance is one of the five strategic priorities of the Global Action Plan developed by WHO in collaboration with OIE and FAO and adopted by the OIE and FAO member countries. It has also been identified by the IACG as a priority (IACG 2018b; 2019a and b). Surveillance is an area that apparently receives low attention, in terms of research funding (6.7 percent, according to JPIAMR 2017), although the area appears more prominent (25.8 percent) in terms of publications. There are areas where knowledge in relation to surveillance needs to be adapted and implemented, the methodology standardized, and the results utilized for the management of infections in the context of AMR and AMS.

The majority of research funding remains directed toward the area of therapeutics (JPIAMR 2017). This can be partially explained by the volume of research initiatives, but also by its overall cost compared to other types of research area. During the course of this study, we described the traditional approach to combatting AMR by producing new antimicrobials. Despite large investments observed in therapeutics, the discovery pipeline is almost empty and the void in new antimicrobials still persists. According to The Pew Charitable Trusts (2019), as of September 2017, approximately 48 new antibiotics with the potential to treat serious bacterial infections were in clinical development. The success rate for clinical drug development remains low and historical data show that, generally, only one in five products that enter human testing (phase 1 clinical trials) will be eventually approved for patients. There seems to be a problem to a viable path for new drugs, no matter how valuable they are to society. An illustration of this is the 2019 bankruptcy of Achaogen and its flagship plazomicin (Zemdri), a novel intravenous aminoglycoside antibiotic with activity against carbapenem-resistant Enterbacteriaceae. This calls for new models to stabilize the market for antimicrobials and stimulate private sector innovation without exposing public funders to all the risk.

No new antibiotic class has been discovered since the 1970s. Currently, candidate antibiotics for further development display limited innovation. New antimicrobial drugs without preexisting cross-resistance are in very short supply, despite being still urgently needed, especially for certain infections and geographical areas. Although new antibiotics are urgently needed, they will neither stop nor curb AMR.

Resistance itself does not necessarily mean drug obsolescence; in many instances, drugs continue to be used despite resistance being known to occur. Hence, the significance of a specific resistance determinant or resistance/pathogen combination needs to be better understood, as well as how that translates in terms of risk under specific contexts (#KKIG 1). Not all resistance determinants have the same significance. This knowledge gap connects with the need to be more systematic on the epidemiology of resistance determinants, and the broadly recognized need for better surveillance and monitoring (#KKIG 13) in line with the principles of evidence for action (and improvement of prescription guidelines, for example, or better targeting of drug discovery).

The area of therapeutics covers the improvement of current antibiotics and treatment regimens, the development of new antibiotics, and also therapeutic alternatives to antibiotics. This knowledge area does not explicitly show up in our analysis, not because it is unimportant, but because of our focus on the underlying causes of the AMR crisis and the drivers of resistance emergence and spread (#KKIGs 2, 6, 7, and 8). Therapeutic alternatives to antibiotics are needed in relation to the low rate of drug discovery and absence of new classes of drugs. Additional research areas, such as that of bacteriophages and the detailed study of resistance mechanisms to find out new ways to fight resistance deserve our attention and financing efforts.

Similarly, our analysis emphasizes the need to better understand how vaccines contribute to reducing the use of antimicrobials (#KKIG 17), and certainly how to increase vaccine acceptance and uptake (#KKIG 18). These are important areas of research to address the existing knowledge and implementation gaps, but they should not overshadow the continuous need for new and improved vaccines.

Drug discovery has a crucial role to play in maintaining our ability to successfully treat infections. However, the drug discovery approach to AMR has essentially resulted in an arms race between new products and constantly evolving resistant microbes—a race we are losing and will be unable to win in the absence of a clear understanding of the fundamental drivers of resistance emergence and spread (#KKIGs 2, 7, and 8). Addressing these underlying causes of the AMR crisis is therefore of central importance. Underpinning this, we highlight the need to better understand antimicrobials as socio-technical objects, and propose a conceptual model around the way we think and use antimicrobials. This critically connects to our knowledge regarding consumption and use (#KKIG 3) and the high value of a comprehensive disaggregated inventory of antimicrobial use in the different sectors to better describe and understand the existing tensions around antimicrobials—that is, the way we think and use them and external drivers.

Surprisingly, transmission receives relatively little attention in terms of research funding, which is in contrast with our analysis and several key knowledge gaps identified in relation to transmission, spread and contamination (#KKIGs 7, 8). Transmission of AMR is not a unique issue, of course, because in essence it is about transmission of infectious diseases, some of which may potentially be drug resistant. Also, indirect mechanisms such as the transmission of MGE-mediated resistance (thus, interspecies resistance) play an important role and enmesh AMR concepts. Research projects allocated by JPIAMR to this category typically aim at understanding the transmission mechanisms by which resistance determinants can spread between bacterial populations and between different (animal, human, plant and environmental) reservoirs. Both levels of the transmission question are important, and the knowledge generated from this research should be translated into evidence-based strategies to minimize the spread of resistance. Our analysis shows that the focus has mainly been on use of antimicrobials as a major driver for emergence. We have shown that this may be true under certain circumstances and specific contexts. However, there is more than use as a driver for AMR; the question of spread and related risk factors needs to be more systematically addressed. Gaining a better understanding of these risk factors is essential because in many situations, they represent the most significant contribution to rising AMR and the prevalence and incidence of drug-resistant infections.

This is closely associated with another knowledge gap related to the environment (3.8 percent of the funding, according to JPIAMR). This requires more attention, with a focus on pollution of the environment with antimicrobials, their residues, and resistant microorganisms (#KKIG 6). This is an area of research critical to gain better knowledge about the spread of AMR and the development of strategies to minimize its evolution, contamination, and transmission in the environment, particularly through AMR-sensitive interventions (#KKIG 8).

The area of diagnostics—with projects aiming at the improvement or the development of diagnostics for better use of current antibiotics—is relatively well funded. It also overlaps with therapeutics (see area definitions in Table 1), as some of these projects also support the development and use of new antibiotics and alternatives to antibiotics. We have identified the need for improved and novel diagnostic tools to prevent empirical prescribing, particularly in LMICs (#KKIG 22).

Overall, there is a major "know–do" gap. While a substantial and growing body of evidence exists on AMR and drug-resistant infections, the challenge of using this knowledge in policy and practice remains formidable. Efforts to address AMR are compromised by the low level of implementation, the fragmentation of interventions, their sequencing in time and geography, and their deployment in difficult environments for AMR control measures (#KKIG 10). Knowledge exists, yet people do not seem to know what to do, how to do it, or how to bring it to scale. Typical examples of implementation gaps exist in the areas of hygiene, food safety, water, and sanitation. (#KKIGs 14, 15, and 16). This calls for a major research effort in addressing the gap between knowledge and actions in real-world settings and the practicalities of achieving national and global AMR goals. Implementation research involves the creation and application of knowledge to improve the practical implementation of interventions through policies, programs, and practices. This type of research builds on partnerships among community members, implementers, researchers, and policy makers, with a strong focus on practical approaches to action on the ground to enhance

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equity, efficiency, scale-up, and sustainability. Research projects focusing on interventions represent—so far—only 11.3 percent of the funding (JPIAMR 2017). They focus on preventive and control interventions for improved antibiotic stewardship (AMS), compliance and prevention of transmission of AMR, and to determine and improve their efficacy. We have identified a number of related gaps, such as the availability of data on long-term follow-up and sustainability of successful interventions focusing on behavioral change and social norms (#KKIGs 2, 9, and 23), or key components of AMS and what makes an AMS program successful, which can be seen as a combination of both knowledge and implementation gaps.

One major implementation gap is in transitioning the livestock sector to become less dependent on antimicrobials—not only as growth promoters, but also in their prophylactic and metaphylactic use. This is an important part of the resilience agenda we have identified (#KKIG 19, 20).

Intervention research was clearly being overlooked by research funders and the research community, yet it is crucial. We need to understand much more fully what constitutes an enabling environment in which interventions are able to deliver on AMR (#KKIG 12) and better identify enablers and barriers in context.

Public and philanthropic funding for research on AMR is increasing, making substantial research funds available, including to social scientists (Roope et al. 2019). Still this has not yet become visible in terms of publications or portfolio analysis. Social sciences, however, have much to contribute to the question of drug-resistant infections and can open avenues to bridge the knowledge-to-action gap. There are several areas where we have identified gaps related to human behavior (#KKIG 2, 9, 23), which should be further investigated to better understand the interactions between norms and behaviors in the conceptual model proposed in chapter 1 (#KKIG 2). One question, in particular, is to understand consumer awareness and preferences, and how can this influence the food industry in positive ways for better antibiotic stewardship (#KKIG 20).

Modeling the potential impact of AMR-specific interventions has been performed, but this has been done for a limited number of mainstream interventions and mostly in the context of high-income countries. There should be efforts to model the impact of interventions in low-resource settings of LMICs (#KKIG 11). One of the most pressing challenges, also faced by global AMR surveillance and monitoring, is in the generation, sharing, systematic analysis, and dissemination of data (#KKIG 13).

The discipline economics could make valuable contributions. Economic analyses successfully inform recommendations to countries by way of cost-benefit analyses (Roope et al. 2019). Among the many questions economists could help answer is how to improve livestock owners' access to programs and insurance schemes that promote appropriate antibiotic use while protecting farmers against market risks (#KKIG 21).

Similar to AMR-sensitive interventions, a number of research initiatives may not be recognized as AMR-related research, although the outcomes of these projects may contribute to the AMR agenda. It will be important to put an "AMR lens" for research funding.

CASE STUDY 6: **WHEN AMR IS AN INCONSPICUOUS ISSUE**

Ghana, like many other LMICs, is rapidly urbanizing, with a 3.6 percent annual rate of urban increase from 2015 to 2018 and over 56 percent of its population of almost 30 million now living in urban areas (UN Statistics Division 2019). With this intensification of people, the demand for fresh fruits and vegetables is also increasing, and urban and peri-urban smallholder agriculture is developing to meet this demand. Urban and peri-urban farms are highly dependent on the informal use of wastewater to irrigate fields, presenting the risk that food products will be contaminated with bacteria—some of which are resistant to antibiotics.

Although Accra, the capital of Ghana, is equipped with water treatment facilities, many of these are nonfunctional (KNUST 2016). A 2016 report showed that fecal bacterial contaminants were present in water sources in Accra as well as sampled vegetables (Amoah et al. 2006), suggesting the application of contaminated water to fields. Bacteria harboring resistance determinants can also be transferred through wastewater to irrigated soils (FAO 2018).

Ghana is a pioneer country in the fight against AMR. Several ministry-based units, agencies, and development partners are working to address AMR, but participation by the animal health and environmental sectors to date has been limited. A situational analysis conducted in 2017 (Yevutsey et al. 2017) showed that, in the human health sector, antibiotics are commonly prescribed and often dispensed by unauthorized personnel. Furthermore, in the animal health sector, there are no national standards or guidelines on antibiotic use. In one study, bacterial isolates from hospitals across Ghana were surveyed and found to have a high prevalence of resistance (up to 78.7 percent in *Streptococcus* species other than *S. pneumoniae*) across the country (Newman et al. 2011). This unregulated use of antibiotics by both humans and animals can contribute to the emergence of resistant bacteria that may be found in fecal matter and wastewater. Without decontamination of wastewater, such antimicrobial-resistant bacteria can enter soils and agricultural products grown in them.

Wastewater management is a pervasive challenge related to urbanization. Ghana faces significant need on this front, with household-level access to basic sanitation facilities at approximately 14 percent across the country in 2015 (WHO/UNICEF Joint Monitoring Program 2019). In addition to such technical challenges, urbanization also brings societal change: although fresh salads are not part of the traditional Ghanaian diet, they are now common in fast food establishments. In Accra alone, an estimated 200,000 people consume salads daily (Amoah et al. 2007). Examining external drivers of AMR, such as urbanization and changing food habits, is essential to addressing risks in both the human and animal health sectors.

Expanded testing, including AMR monitoring and surveillance of water and waste effluent by the Environmental Protection Agency (EPA), has been identified as a critical need for AMR risk reduction and food safety in Ghana. To address such needs, the Ghana National Action Plan on Antimicrobial Resistance Use and Resistance was approved in December 2017. This plan

identified points of entry for AMR risk reduction in various ministries and other agencies, with key stakeholders forming the AMR Policy Platform. Although contributions to the plan came from the Ministries of Health, Food and Agriculture, Environment, Science, Technology, and Innovation, and Fisheries and Aquaculture Development, and the plan was designed with an explicit "one health" approach, most of the responsibility for implementation still falls to human health-focused agencies. Significant expansion of this plan to the animal health and environmental sectors will likely require external funding, as well as commitment by urban farmers and the diverse agencies and actors responsible for human, animal, and environmental health.

For example, the Ghana EPA is an entity under the Ministry of Environment, Science, Technology, and Innovation that sets environmental standards and conducts environmental surveillance. This surveillance includes monitoring of effluent from health facilities, aquaculture enterprises, and farms, but is currently limited to detection of *Escherichia coli* bacteria. In the next five years, EPA plans to expand testing to include antimicrobial-resistant microorganisms and antimicrobial residues. To protect food safety, implementation of this routine monitoring will need to be followed with enforcement of regulations that limit the release of contaminated water into agricultural fields.

This case study illustrates the need to think about AMR even outside the antimicrobial system. It shows that besides emergence, spread is a component of AMR to consider. Seen from the point of view of our conceptual model (the way we think and use antimicrobials, and externalities), the case study emphasizes the existence of drivers outside the human health sector. For example, rapid urbanization and changes in food systems that are needed to meet growing demand must be examined; and governance, underscoring the importance of a holistic approach, must advocate for a comprehensive framework. Finally, this case study is an example of how AMR-sensitive interventions, such as water treatment and sanitation programs, can become game changers in the fight against AMR.

TAILORING A RESEARCH AGENDA TO COUNTRY NEEDS

In the first chapter of this report, we reframed AMR as a sustainable development challenge, acknowledging that, in many cases, antimicrobials have become substitutes for imperfect infrastructures and failing systems, which not only drives the emergence but also the spread of AMR. It is also an issue that cannot be solved with technical solutions only. In the second chapter, we reviewed our most common interventions, showing that much of the action on AMR to date has focused on use of antimicrobials and on AMR-specific interventions.

In this chapter we have seen that key knowledge and implementation gaps do not necessarily match the current focus of the research community, be it in terms of funding or publications. Too little is allocated to surveillance and interventions, and far too little is allocated to environment and transmission. Little consideration is usually given to local contexts, and most of the time a "best practice" approach continues to prevail. Building on this understanding, we propose a framework to guide countries and donors in tailoring a research agenda to address critical AMR knowledge and implementation gaps.

Our analysis emphasizes the importance of context. By considering exposure to risk factors, i.e., antimicrobial use (low vs high) and expected influence of drivers for spread (low vs high), four types of countries can be identified, with different levels of risks, essentially driven by differences in likelihood. Table 3 summarizes the four situations for countries, which have different expected levels of risk related to AMR in terms of emergence and spread.

Defining risk related to AMR would be more accurate than using AMR levels (usually expressed in percentage of samples) that do not equally translate into risk, defined as a combination of probability of occurrence for a specific hazard (likelihood) and consequences (impact). Risk should therefore be assessed for different types of resistance determinants (i.e., hazards). Both likelihood and impact may vary between countries and local conditions. By defining an acceptable level of risk (ALOR), countries would be able to set targets—moving from an input-based approach (reduce quantities of anti-

TABLE 3

Four types of countries based on levels of antimicrobial use and exposure to contextual risk factors for AMR

	Type A	Type B	Type C	Type D
Level of antimicrobial use	Low	High	High	Low
Exposure to other contextual risk factors	High	High	Low	Low
Expected level of AMR risk	Medium	High	Medium	Low

microbial use) to an outcome-based approach (reduce the risk posed by specific types of resistance in specific communities).

Type A countries correspond to countries where use of antimicrobials could be low, but exposure to contextual risk factors for spread is high, resulting in a medium level of risk. Low public investment in health and high out-of-pocket costs, particularly relative to income per capita, may considerably limit access to and availability of antimicrobials in the general population. Antimicrobial use in animals may be limited as livestock industries remain relatively traditional, with limited adoption of intensive or industrial practices. However, substandard medicinal products are thriving in informal markets. Issues of poor sanitation, unsafe waste management, weak governance, and corruption are more likely to be present and may exacerbate the severity of spread of resistance determinants, even though antimicrobial use would be still limited in volume.

In type B countries, use of antimicrobials (both in absolute and per capita terms) is increasing sharply driven by better access, increasing revenues, or [counterintuitively] improved education. Meanwhile, risk factors contributing to high levels of spread remain significant, hence contributing to the AMR risk. For example, growing populations and improved incomes are increasing demand for animal products, and with intensification of the livestock sector, the quantities of antimicrobials used in livestock production are expected to rise steadily (Van Boekel et al. 2015; World Bank 2017a). Global consumption of antibiotics in agriculture is expected to increase by 67 percent from 2010 to 2030, mainly in transitioning economies.

Type C countries correspond to countries where the demand for and use of antimicrobials remain high; however, factors affecting the spread of resistance (contagion) have improved with expected effect in reducing the contribution of spread to the high level of risk related to AMR. Stronger systems and better infrastructures—in terms of water management, improved sanitation, and access to quality health services, among others—make these countries less susceptible to increased levels of AMR. Beyond the point of inflection of the curve (Figure 5), this type of country is starting to win the battle against AMR. There may be inertia, however, between efforts and effect on the ground; as resilience increases, risk will be only slowly reducing.

Type D countries have managed to bring both risk factors and antimicrobial use under control. Large public investments in health and education, optimal financial protection against out-of-pocket healthcare costs, strong governance, and improved sanitation and waste management have facilitated the development of systems that are less reliant on antimicrobials and also provide little opportunity for spread. In addition, normative change to address behavioral drivers of the non-therapeutic use of antimicrobials—either through information campaigns or more stringent regulatory actions such as bans on the use of antimicrobials in livestock production—are likely to have been implemented successfully. Overall, these countries are still to face health and economic risks from AMR, but efforts to minimize the volume of antimicrobial demand and the risk of contagion bring the risk to a lower level compared to the other types of countries (A, B and C). However, only some of the type D countries have effectively brought their risk below an acceptable level and in a sustainable manner.

The four types of countries described in Table 2 are also displayed in Figure 5. The theoretical risk curve proposed here is based on levels of "AMR risk" (as driven by use and additional contextual risk factors) as a function of "resilience and preparedness" (driven by commitment to an

AMR agenda, economic development, resilience to AMR shocks). It shifts our way of thinking about AMR and sheds light on relationships that are not yet well understood. There are substantial data gaps, as expressed earlier in this report; nevertheless, this theoretical curve is intended to describe the risk profile of countries and articulate how to integrate contextual factors in the design of research to address specific knowledge and implementation gaps.

While necessary, and despite some countries demonstrating progress, current efforts to curb antimicrobial use are not sufficient to fight AMR on a global scale. Radically reducing the misuse of antimicrobials is a crucial and necessary step toward controlling AMR. However, this will not be sufficient in isolation, given the vast interactions between risk factors and antimicrobial use in ultimately determining the emergence and spread of AMR.

Figure 5 emphasizes type B and C countries as those requiring the most pressing attention. It should be noted that context is treated as country specific but in reality, within the same country, areas exist belonging to different types (e.g., cities, peri-urban slums and rural areas may differ significantly).

Where countries can understand their risk profile with regard to AMR (Type A to D), it may be easier to build AMR research and intervention (implementation research) agendas at lower cost and potentially high reward. A situation analysis of countries would help determine this risk profile based on antimicrobial use and other factors related to spread. Depending on the outcome of the analysis, different sets of interventions—either AMR-specific and/or AMR-sensitive—could be identified for prioritization.

An outcome of national action plans and situation analysis is the identification of key bottlenecks, at the national or subnational levels. Interventions as well as research should be prioritized based on their likely impact on bottlenecks and capacity to reach targets. A major contribution of situation analysis is to provide realistic assumptions enabling better appraisal of the "likely" impacts, by better identifying enablers and barriers.

The success of interventions will depend on the existence of an enabling environment and include consideration of norms and behaviors, as well as governance or externalities. Assessing the feasibility of interventions and their likely impact in light of this framework will be important to avoid the recurrent failures of the "good/best practice" approach. For countries to make progress on AMR to beat superbugs, it is important that AMR knowledge be translated into national context to bridge implementation gaps.

In the context of limited resources for development activities, AMR-sensitive interventions can be designed through tailoring and refining existing and planned interventions. Low-, lower-middle-, and upper-middle-income countries are already making significant investments in a range of development activities. There is a critical need to better understand the cobenefits of AMR-sensitive interventions (#KKIG 11).

AMR cobenefits can be defined as the benefits of policies and programs that are implemented for various reasons at the same time—including AMR. The concept of cobenefit acknowledges that most interventions also can have AMR impacts. The total flow of development assistance includes funds for the building of roads, ports, and other urban developments, as well as interventions to build health systems and improve water and sanitation efforts. Harnessing AMR-sensitive interventions does not mean business as usual. It is not enough to reinforce health systems, improve water and sanitation, urban planning etc. These activities should be considered for the impact they stand to have on AMR, hence generating scope to translate a host of development research into AMR-sensitive research.

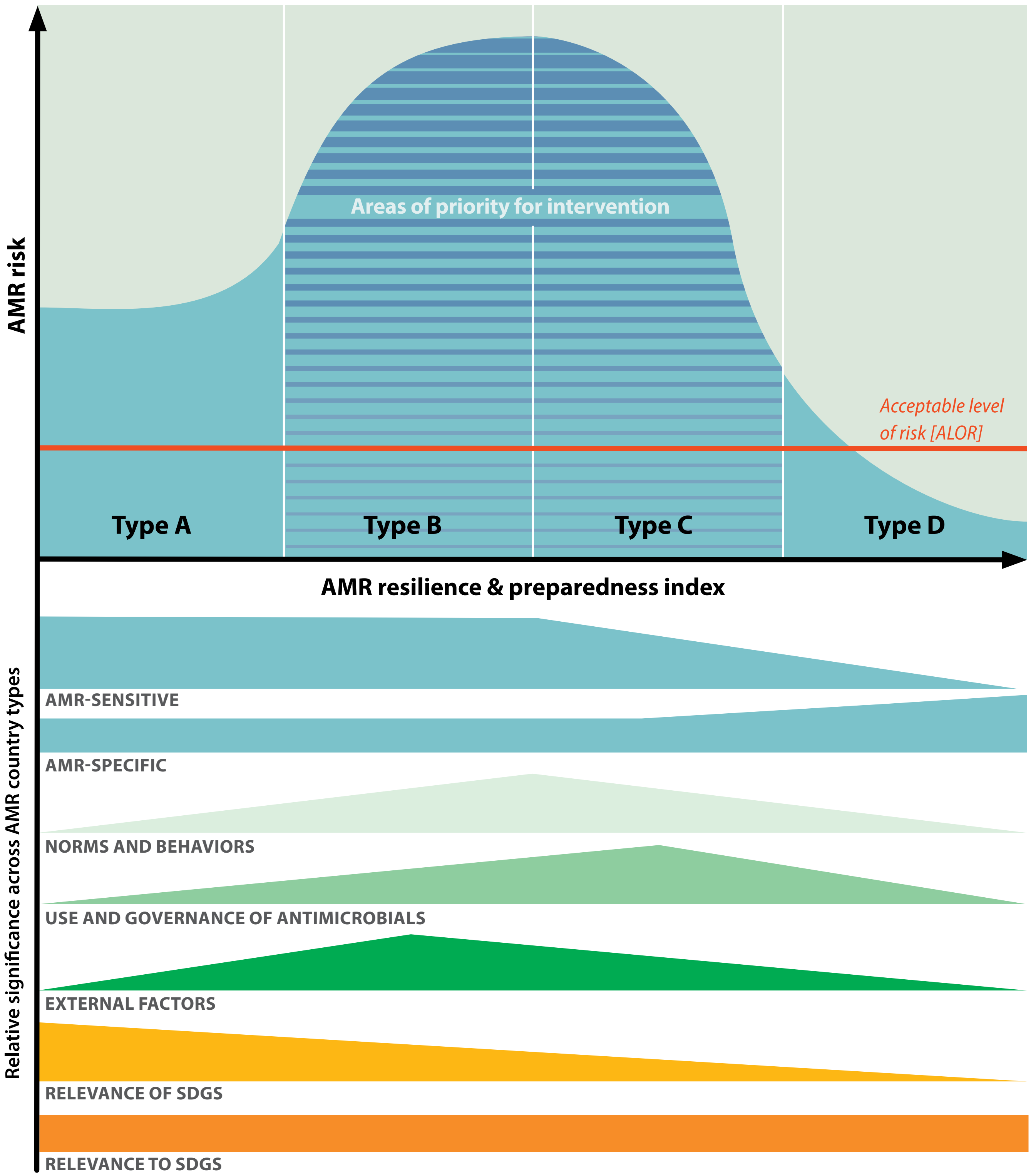
A focus on an AMR-sensitive agenda does not mean that AMR-specific research and interventions are not relevant. AMR-specific actions are always needed—including in Type A countries for their capacity to materialize the AMR national agenda and energize actors on the ground. Focusing exclusively on AMR-sensitive interventions would not provide the catalytic effect of AMR-specific interventions.

Rigorous planning and tailoring of interventions are vital to ensure that investments in research address the drivers of resistance. Reviewing the situation in relation to sanitation, public health, governance, education, and other relevant areas to ensure the research agenda is designed to provide a sound evidence base to minimize the risk of emergence and spread needs to become a top priority if countries intend to win the fight against AMR (Table 4). Not every research project will be able to have an impact on AMR, but careful

FIGURE 5

Theoretical risk curve representing four types of countries (A to D)

AMR-sensitive interventions are critical to countries in type A and B, and to a lesser extend to C and D. AMR-specific interventions are always needed for their catalytic role in NAPs. Research agenda addressing knowledge and implementation gaps should pay attention to dimensions related to norms and behaviors, governance of antimicrobials and external factors. While relevance of AMR to SDGs remains across the board, the relevance of SDGs for AMR tends to decrease from A to D.



analysis and tailoring of the national portfolio can play a significant role. In some instances, it will be more pertinent to continue focusing on AMR-specific interventions, such as infection control programs. In other environments, a focus on ensuring that other investments can be made AMR-sensitive needs to be highlighted. In all environments, however, it is a blend of AMR-specific and AMR-sensitive interventions that will be feasible, affordable, and highly impactful, ensuring that we all can share in a healthy future.

TABLE 4

Country risk profiles (A to D) and attributes for research and intervention agendas

	Type A	Type B	Type C	Type D
Status of AMR policies and programs (enabling environment)	AMR agenda focused on access to quality health services and quality of medicinal products, strengthening of basic public and animal health systems, education on hygiene and infection prevention	AMR agenda focused on responsible and prudent use of antimicrobials, further basic health system strengthening and capacity building, piloting new programs, establishing baselines through surveillance and monitoring, continued efforts in education on hygiene and infection prevention	Building strong political and societal consensus on addressing AMR, scaling up of pilot programs, monitoring and surveillance, complete policy and regulation reforms, mass awareness campaigns	Mature public and animal health systems, regular light-touch AMR interventions and programs, continuous adjustments needed to respond to new risks, maintained awareness, continued surveillance
Status of AMU and AMR (risk and resilience)	Low use of antimicrobials, lack of access to quality medicinal products, basic systems and services failed	Increasing use of antimicrobials with increasing revenues and consumption, underperforming systems and services, AMR slowly emerging as an issue in civil society	Systems still struggling to manage the rise of antimicrobial demand and use, AMR on the rise and high on the civil society agenda, outcomes of surveillance and monitoring raise public concern over AMR	Achievements in reducing use of antimicrobials, AMR remains a concern, but citizen trust restored in the system, established capacity to detect emergence of new resistance determinant
Importance of AMR-sensitive interventions	High	High	Medium	Low
Relevance of the SDGs	High	High	Medium	Low

CASE STUDY 7: **THE PIVOT OF COBENEFITS**

Madagascar is one of the 193 countries that signed a UN Resolution calling for a coherent global action to address the AMR issue and recognizing that failure to address AMR will undermine sustainable food production and jeopardize global sustainable development. Since then, the country has prepared and adopted a national action plan on AMR (Repoblikan'i Madagasikara 2018). It is strongly aligned to the Global Action Plan, articulating activities around five strategic objectives, which include improving awareness and understanding of antimicrobial resistance, strengthening knowledge through surveillance and research, reducing the incidence of infection, optimizing the use of antimicrobial agents, and promoting support to research and alternative solutions. This plan has been developed through a strong multisectoral partnership and endorsed by four line ministries of the presidency (health, agriculture, fisheries, and environment). The cost of the plan is slightly below $14 million for a five-year period.

As for many countries, the challenge comes with implementation of such a plan. Madagascar's progress toward the goal of ending extreme poverty in a sustainable manner is challenged on many fronts (World Bank 2015). The World Bank systematic country diagnostic concludes that poor governance, which partially finds its origin in poor dynamics among the economic elite and political instability, affects the ability of the state to collect revenues and prevents the state from undertaking investments to support a structural transformation of the economy and from providing sufficient basic services to develop the country's human capital.

Regarding plague—a public health issue with high relevance for AMR—Madagascar shows results. On average, 400 cases of bubonic plague are reported yearly, and the disease is most prevalent in the rural areas, especially the central highlands. Plague season runs from August to April. The response to the 2017 plague outbreak in Madagascar was large and effective. In total, 2,348 cases and 202 deaths were attributed to the epidemic (WHO 2017 f). The epidemic was curtailed largely by contact tracing and free antibiotic treatment supported, in part, by $1.5 million in WHO emergency funds. However, international responses quickly fade, a cycle of panic and neglect (International Working Group on Financing Preparedness 2017). In the aftermath of the epidemic response, Madagascar faces many ongoing challenges to public health, including endemic tuberculosis and a rise in AMR (Gay 2017). As noted by Bonds et al. (2018), there may not be the needed pivot to stabilize the economy, maintain essential healthcare capacity and risk awareness campaigns that were established during the epidemic, and develop long-term investments in the health, agriculture, and environment sectors. In July 2018—after the epidemic—Madagascar's Ministry of Health organized an After Action Review (AAR) using WHO methodology, identifying 23 priority actions to improve preparedness and response. From 19 August 19, 2018, to April 21, 2019, a new plague season occurred, with a lower number of 257 isolated cases reported. This progress shows national ability to shift from epidemic response to long-term management, and the capacity to confront the challenges of multisectoral coordination on complex problems.

Within the 2018 World Bank (IBRD) portfolio, $385 million was committed to investments in health, agriculture, environment, and other sectors. Although no project is currently explicitly dedicated to limiting AMR, there are opportunities to make components of existing and planned projects AMR-sensitive. A similar approach was recently taken by the country to address climate change effects on public health (Bouley et al. 2018). Access to basic education, health, water, sanitation, and nutrition services is critical. A few examples of such projects within the Bank's portfolio illustrate where AMR cobenefits could be identified and exploited.

Nutrition and health programs have high potential for AMR cobenefits. The objective of the Multiphasic Programmatic Approach on Improving Nutrition Outcomes (2017–23) is to reduce stunting by providing reproductive and maternal and child healthcare services and implementing nutrition interventions in specific regions of the country. More specifically, objectives include (a) scaling up a standardized platform of primary care facilities and community-based services to which selected services can be added/scaled to address the needs of specific populations, regions, or priorities; (b) modernizing the training of primary care and community workers, using technology; (c) providing information

technology (IT) solutions to improve data-based program management and quality service delivery; and (d) strengthening capacity in regions and districts to effectively manage delivery of the reproductive, maternal, and child health and nutrition (RMCHN) interventions minimum package. Each of these objectives could provide a platform to increase awareness on appropriate use of antibiotics, change in prescribing practices, and contribute to mitigation and reduction of AMR emergence.

Multisector programs are fertile ground for AMR cobenefits: The Sustainable Landscape Management project (2017–22) seeks to increase access to irrigation services, strengthen natural resources management by landholders, and facilitate emergency response. Designed with a proof-of-concept approach, this project brings together the Ministries of the Presidency for Agriculture and Livestock; Water, Sanitation, and Hygiene; and Environment, Ecology and Forests, offering a potential platform to introduce AMR surveillance and monitoring across relevant sectors other than public health. In particular, AMR-sensitive packages might be added under the data collection and decision support tools component and the capacity building component, allowing line ministries to better understand and appreciate the potential contributions of their sector to the emergence and spread of antimicrobial resistance and to build the necessary skills to promote ongoing AMR monitoring and surveillance in their sectors.

In this case study, we illustrate how development projects can be made "AMR aware" and increase their AMR-sensitive potential (cobenefits) by adjusting interventions, with only marginal costs. This potential does not come entirely for free; incorporating AMR-sensitive interventions is not business as usual. It requires some marginal costs to give an AMR-sensitive design to project components and make this transformation possible. This also requires a thorough portfolio analysis with an "AMR lens." In this case study, we have imagined, based on evidence presented throughout this report, how AMR might be tackled by "piggy-backing" AMR sensitive actions on other development investments to create AMR cobenefits at little additional cost. Most development partners share this ability to leverage ongoing investments, laying a strong base for AMR-specific interventions. By reviewing development activities and identifying underlying cobenefits, countries would be in a much better position to tailor their AMR research questions and design appropriate research agendas.

Conclusion

We have known since the very beginning of the antimicrobial era that using these drugs would fuel a natural selection process, an accelerated Darwinian evolution no less, that inevitably produces drug-resistant microorganisms. Yet, we have collectively ignored the risks and have been "playing with fire" for the past half century.

Our capacity to effectively treat infectious diseases is a global public good, which is now seriously at risk. AMR is already a big problem—plaguing and claiming the lives of hundreds of thousands—and could potentially become a much bigger problem if we fail in our collective action to preserve this public good.

Failure, however, would unlikely come from lack of knowledge. Much is known about AMR, and even if significant gaps remain, in many cases they are about implementation. We know what needs to be done, but we are not doing it—or we do not know how to do it. This report puts emphasis on implementation research; an integrated concept that links research and practice to accelerate the development and delivery of successful interventions. It involves the generation and application of knowledge to improve the implementation of policies, programs, and practices.

Such policies, programs, and practices do not relate only to the areas of health and agriculture. Looking at the many uses of antimicrobials across sectors and looking at AMR in terms of emergence and spread, we propose to re-frame AMR as a development issue.

Antimicrobials have become infrastructures of modernity, and it is indeed the gradual failure of these infrastructures that now make antimicrobials—and AMR—visible to societal attention. It is now clear that technical solutions on their own will not be enough to curtail AMR; it will also be necessary to unravel the many complex social tensions around antimicrobials. We propose to conceptually organize these tensions as (a) norms and behaviors (the way we think antimicrobials), as socio-technical objects; (b) use and governance (the way we use antimicrobials); and (c) external trends influencing the system. This conceptual model provides a powerful framework to identify enablers and blockers.

From a practical point of view, three broad categories of intervention can be employed to tackle AMR. They aim at establishing an enabling environment for AMR control, reducing the need for antimicrobial use (adaptation), and limiting use of antimicrobials (mitigation). A review of the most common interventions shows that we are not sure how they can best deliver in specific contexts at the country or community level. More work is needed on translating knowledge into effective action. In addition, a broad array of interventions, which are not specifically aimed at AMR, could nevertheless have an impact and reap cobenefits. The focus of research attention should also be broadened to encompass this field: we do not fully know how to identify AMR-sensitive interventions, how to assess the potential cobenefits they bring, or measure the associated marginal costs to make those interventions most impactful on AMR.

In terms of knowledge and implementation, twenty-three gaps have been identified in the course of this work. Nine relate to the contemporary narrative on AMR and the current state of thinking; something we referred to as taking a new look at an old challenge. The AMR conversation has largely been carried out within a circle of technical professionals and experts focused on the science of AMR, and there is a need to re-frame the discourse on AMR. The remaining gaps relate to our approach so far. They are about what has been tried and what has been done to establish an enabling environment, reduce the need for (adaptation), and limiting the use of antimicrobials (mitigation). These key knowledge and implementation gaps are not so much a research agenda but more likely pointers for the community. They highlight the relevance of implementation research.

The seven case studies included in this study have brought us successively to Vietnam, Senegal, India, Thailand, Denmark, Ghana, and Madagascar. The choice of countries is unavoidably arbitrary; many more cases could have been built for the purpose of this study. These case studies illustrate how contextualization will be paramount to success in the collective effort to curtail AMR. Using best practices at the wrong time in the wrong place will not help in moving the needle. Each case study highlights how context is critical to identify enablers and blockers.

Although each and every country, or community, is unique, a typology of countries and communities can be defined based on the risk posed by AMR in terms of emergence and spread. Such a typology allows the identification of the critical action areas for different country types, with different blends of AMR-specific and AMR-sensitive interventions, different relevance of SDGs and targets, and a different relative importance to focus on use. It can also help us in becoming more conscious of how our investments for development can affect AMR and in using available financing more astutely. By applying a more rigorous and imaginative AMR lens to all investments, and by designing these interventions to maximize their potential impact on AMR, humanity and our children all stand to gain from a healthier future.

Better understanding the gaps in our collective knowledge of antimicrobial resistance, and the limitations of our capacity to implement this knowledge is critical to success in action. However, it is by no means an excuse for inaction. Action is needed now, and there is more than enough knowledge for evidence-based policies, programs, and practices aiming at curbing AMR.

A primer on AMR

Key facts about antimicrobial resistance (AMR)

- AMR threatens the effective treatment of infectious diseases caused by bacteria, viruses, parasites, and fungi.
- Although exact numbers are difficult to ascertain, it is estimated that currently 700,000 deaths are annually attributable to drug-resistant infections. If unabated, this number could increase to 10 million deaths annually by 2050, more than deaths currently attributed to cancer.
- AMR has been alarmingly rising for certain diseases, including gonorrhea, malaria, and tuberculosis. It is a threat not only to global public health but also to the global economy and socioeconomic development.
- Unchecked, AMR could cause large economic losses, in excess of $1 trillion annually after 2030, comparable to the 2008–09 global financial crisis. Low-income countries would experience larger drops in economic growth and the impacts of AMR on gross domestic product (GDP) would be felt for a long period.
- AMR requires immediate action across all government sectors and society. There may be gaps existing in knowledge, but there is sufficient existing knowledge for action.
- Investing in AMR containment efforts, and more specifically in AMR-sensitive interventions, has a potentially high return, particularly in low- and middle-income countries.

Antimicrobial resistance

Antimicrobial resistance (AMR) happens when microbes (bacteria, fungi, viruses, and parasites) change in response to exposure to antimicrobials, by mutating or by "horizontal" acquisition of resistance genes from already resistant microbes or from mobile genetic elements (MGE) freed in the environment. AMR is the resistance of microbes to antimicrobials. When microbes are resistant, the drugs do not work to kill or control them. As a result of AMR, treatments become ineffective and infections may become lethal or persist, increasing the risk of further spread. Pathogens can also be resistant to several antimicrobials. Multidrug resistance (MDR) is a property of a pathogen that is resistant to two or more antimicrobial agents in three or more antimicrobial classes. The term extensive drug resistance (XDR) is also used, defined as resistance to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories). Pan drug resistance (PDR) is defined as resistance to all agents in all antimicrobial categories. Those microbes developing resistance to multiple drugs are sometimes referred to as "superbugs." An infection caused by a superbug is harder to treat because fewer effective drugs are available. In some extreme cases, treatment may not even exist. It is important to remember that when a species (e.g., *Escherichia coli*) is resistant to an antibiotic (e.g., amoxicillin), this does not mean that all *E. coli* individuals are resistant. Resistance appears in few individuals and can gradually expand; this is the bases that support the responsible and prudent use of antimicrobials as a way to curb AMR.

Emergence and spread of antimicrobial resistance

Evolution of microbes able to survive and reproduce in different environments has been occurring as part of Darwinian natural selection ever since their first appearance on earth millions of years ago. AMR is a naturally occurring phenomenon, resulting from various mechanisms such as mutations and transfer of genetic material between different microbes. Any use of antimicrobials can result in the development of AMR. The more antimicrobials are used, the more likely microorganisms will develop resistance. Misuse of antimicrobials—including using an incorrect dose or administering an antimicrobial at the wrong frequency or for an insufficient or excessive duration—speeds up the emergence of AMR. What is new is that, with the advent of modern antimicrobials in the 1940s, greater selection pressure has increasingly been applied and microbes have responded accordingly due to their massive and rapid reproductive capability. Even the most appropriate, prudent use of antibiotics and other antimicrobials to treat infections will inevitably promote emergence of resistant microbes, although an appropriate use have more chances to effectively kill all involved microbes and, thus, no individual will have the ability to share its resistance to another. Alexander Fleming issued a warning about this in his Nobel Prize acceptance speech, which has gone unheeded for the past half century.

Examples of misuse include when people take antibiotics without medical oversight during viral infections like colds and flu, and when antibiotics are given as growth promoters in animals or used routinely prophylactically in healthy animals because of suboptimal husbandry practices.

Spread of microbes resistant to antimicrobials can happen between people but also between people, animals, plants, and the environment (in water, soil and air). Poor hygiene and infection control, inadequate sanitary conditions, and inappropriate food handling all contribute to the spread of AMR.

In this report, the use of antimicrobials together with imperfect infrastructures and failing systems are considered as main drivers of the emergence and spread of AMR.

A major public health concern and a development problem

AMR increasingly threatens the ability to treat common infectious diseases in humans, resulting in prolonged illness, increased cost of treatment, and disability and death. Without effective antimicrobials for prevention and treatment of infections, the risks associated with medical procedures such as major surgery and complications of chronic disease conditions increase significantly. But in this AMR scenario, even a usually uncomplicated infection such as an otitis in a young child could be fatal. AMR also increases the cost of health care with more and longer treatments, lengthier stays in hospitals, and more intensive care required.

In this report, we re-frame AMR as a development problem. Addressing AMR is necessary to attain many of the sustainable development goals (SDGs), and it is likewise true that making progress on several SDGs and their specific targets also will contribute to tackling AMR. AMR is framed as a development problem, but it clearly affects both LMICs and HICs.

A quintessential "one health" issue

Antimicrobial resistance is a complex problem that affects all of society and is driven by many interconnected factors related to people, animals, plants, and ecosystems. Single, isolated interventions will have limited impact, if any. "One Health" is defined as a collaborative approach for strengthening systems to prevent, prepare, detect, respond to, and recover from primarily infectious diseases and related issues such as antimicrobial resistance that threatens human, animal, and environmental health collectively. Coordinated One Health action is required to minimize the emergence and spread of antimicrobial resistance.

A problem in communities and a global issue

AMR is primarily a problem in communities where it emerges and spreads. While resistance determinants emerge locally, they can spread globally. No single country is isolated from what happens in other countries regarding the emergence and spread of AMR. Increased connectivity driven by globalization—such as trade, transport, and tourism—makes the spread of AMR from one part of the world to another even more likely by the sheer scale of movements of people, animals, plants, and commodities. The international community, well aware of this potential, has initiated actions to raise awareness and propose steps for dealing with AMR. In 2016, 193 countries signed a UN Resolution calling for coherent global action to address the issue and recognizing that failure to address AMR will undermine sustainable food production and jeopardize global sustainable development.

A worrying present and a gloomy future

Patients infected with drug-resistant bacteria are at increased risk of poor clinical outcomes and even death. They incur higher health-care costs compared to patients infected with the susceptible strains of the same bacteria.

For example, resistance to carbapenem treatment in *Klebsiella pneumoniae*, a common intestinal bacteria that can cause life-threatening infections, has spread globally. This pathogen is a major cause of hospital-acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients, which in some countries renders treatment ineffective in more than half of affected patients.

Similarly, resistance of *Escherichia coli* to fluoroquinolone (one of the most widely used medicines for the treatment of urinary tract infections) is very widespread and there are many countries where this treatment is now ineffective in more than half of patients.

Treatment failure to the last resort medicine for gonorrhea (third generation cephalosporin antibiotics) is increasing in an alarming number of countries, and is rapidly spreading in urban settings, leading WHO to update the treatment guidelines for gonorrhea due to widespread high levels of resistance.

Treatment guidelines for chlamydial infections and syphilis have also been updated due to growing resistance. Another example is resistance to colistin—a last resort treatment that has recently been detected in several countries and regions—making infections caused by resistant *Enterobacteriaceae* untreatable.

Resistance of bacteria causing tuberculosis is also an increasing concern, with high incidence of multidrug-resistant tuberculosis (MDR-TB), a form of tuberculosis that is resistant to the two most powerful anti-tuberculosis drugs (isoniazid and rifampin), as is the rise of extensively drug-resistant tuberculosis (XDR-TB), a form of tuberculosis that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Resistance is also increasingly emerging and spreading in malaria, HIV, influenza, and candidiosis, as well as many other common infectious diseases.

A global agenda

WHO's Global Action Plan on AMR (2015) created a broad and comprehensive high-level policy agenda for the global AMR prevention and containment effort. Countries participate in global and regional coordination of AMR efforts and commit to national implementation. Regional and global coordination mechanisms are important to enable sharing of knowledge across a variety of national situations and can help countries learn from each other, share ideas and experiences, compare progress, and accelerate national efforts.

Global coordinating bodies are responsible for advancing compliance to the WHO International Health Regulations (IHR), the OIE International Standards, the WHO List of Critically Important Antimicrobials in human medicine, and the OIE List of Antimicrobial Agents of Veterinary Importance. Under the IHR, 196 countries have committed to work together to prevent, detect, report, and manage public health emergencies, such as infectious diseases outbreaks. It is important that countries designate institutions to be responsible and accountable for following up on the evaluation results so that IHR can accelerate AMR action and focus global support together with the Global Action Plan and country-specific NAPs. Global coordinating bodies also are responsible for building collaborative research networks so that funding allocations can be optimized to meet globally relevant AMR priorities.

A challenge is to incorporate and weigh the unique contexts of each country, which is where national planning mechanisms can play an important role. Such plans are effective mechanisms for countries to translate the global policy agenda to fit their respective context.

The ad hoc Interagency Coordination Group

In 2016, the United Nations Secretary-General established an ad hoc Interagency Coordination Group on Antimicrobial Resistance (IACG) to improve coordination between international organizations and to ensure effective global action against this threat to global health security. The IACG was co-chaired by the UN Deputy Secretary-General and the Director General of WHO. Its members included representatives of the Tripartite (World Health Organization, Food and Agriculture Organization of the United Nations, and World Organisation for Animal Health) plus representatives of relevant UN agencies, and other international organizations, including the World Bank. Alongside members from UN agencies, there were 15 independent experts, including three co-conveners. The diversity of expertise and countries represented in this group reflected the One Health and global nature of AMR and the multidisciplinary approach that is required to tackle it. The group seek to increase collaboration and mobilization of all forces to address the AMR issue. It has been mandated to (a) review progress globally since September

2016, providing oversight and using its convening power to advocate for concrete action to address AMR; (b) provide practical guidance for approaches needed to ensure sustained effective global action to address AMR, grounded in an understanding of varied country situations; and (c) recommend governance model(s) for future improved coordination and accountability to ensure continued political momentum and sufficient action is taken. The IACG delivered its report to the UN Secretary General (SG), who incorporated the 14 IACG recommendations into his report to the member states.

The link to investment

The World Bank recognizes AMR as an important development issue, with the potential to disproportionately and significantly affect low- and middle- income countries. AMR poses a major risk in our ability to help reduce extreme poverty and promote shared prosperity. The Bank's 2017 report—*Drug Resistant Infections: A Threat to our Economic Future*—assessed the global economic impact of AMR, identifying the urgent need to harness development finance for this important challenge.

A range of activities is underway to engage the Bank and advance this issue with a focus on concessional funding, global knowledge generation and dissemination, and advocacy. The Bank has a track record in implementing "one health" principles and it supports country efforts to tackle AMR by systematically including it in relevant investments. The Bank conceptualizes the AMR issue in terms of activities that are AMR-specific (those with the primary purpose—in objective and design—to reduce AMR) and AMR-sensitive (those whose primary purpose is not AMR control, but which can be designed and delivered in such a way that they contribute cobenefits in addressing AMR). The Bank can play a significant role by putting an AMR lens on existing and planned investments and blending of AMR-specific and a broad range of AMR-sensitive interventions across multiple sectors, together with partners. Not only do AMR-sensitive investments have the potential to reap high returns, but they are particularly effective in the context of scarce resources for development activities. The total flow of development assistance includes funds for the building of roads, ports, and other urban developments, as well as interventions to build health systems and improve water and sanitation efforts. Using available financing more astutely and being more conscious of how existing and future investments affect AMR is a powerful way to design AMR-sensitive interventions and curb resistance.

Abbreviations and acronyms

AMR	antimicrobial resistance
AMU	antimicrobial use
AMS	antimicrobial stewardship
ARG	antimicrobial resistant gene
ASU	antibiotic smart use
DALY	disability-adjusted life year
DDD	defined daily doses
EEA	European Economic Area
FAO	Food and Agriculture Organization of the United Nations
GDP	gross domestic product
GLASS	Global Antimicrobial Resistance Surveillance System
GP	general practitioner
HIC	high-income countries
HIV-AIDS	Human Immunodeficiency Virus – Acquired immunodeficiency syndrome
IACG	Inter Agency Coordination Group
IHR	international health regulations
IPC	infection prevention and control
LMIC	low- and middle-income country
MDR	multidrug resistance
MGE	mobile genetic element
MRSA	methicillin-resistant *Staphylococcus aureus*
NAP	national action plan
NGO	nongovernmental organization
NGS	next generation sequencing
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
OTC	over the counter
SDGs	sustainable development goals (of the UN 2030 Global Agenda)
SF	substandard and falsified (medicinal products)
UEMOA	Union Economique et Monétaire Ouest Africaine
UN	United Nations
UNGA	United Nations General Assembly
VMP	veterinary medicinal product
WASH	Water, Sanitation and Hygiene
WHO	World Health Organization
WTO	World Trade Organization
XDR	extensive drug resistance

Note: All dollar amounts are U.S. dollars unless otherwise indicated. All tons are metric tons.

Glossary of selected terms

We recognize that several of the following terms may have different meanings. This glossary provides contextual definitions for the purpose of this report. These definitions have been adapted from a variety of sources.

Antimicrobial Antimicrobial is a general term for the drugs, chemicals, or other substances that either kill, inactivate, or slow the growth of microbes, including bacteria, viruses, fungi, and protozoa. An antibiotic is a type of antimicrobial developed to treat bacterial infections.

Antimicrobial resistance Antimicrobial resistance (AMR) is the ability of microbes to grow in the presence of substances specifically designed to kill, inactivate, or slow their growth. It is the result of microbes changing in ways that reduce or eliminate the effectiveness of drugs, chemicals, or other agents used to cure or prevent infections they cause.

AMR sensitive AMR-sensitive interventions contribute indirectly to combating AMR. Their primary purpose is not AMR control; they can be designed and delivered to maximize their impact on AMR (see also cobenefit). Improving access to clean water and sanitation, thereby reducing the spread of infections, is an example of an AMR-sensitive intervention.

AMR specific AMR-specific interventions have as their main purpose the reduction of AMR; for example, promulgating and enforcing regulations to ensure people can only obtain antimicrobial medicines with a valid prescription.

Cobenefit The benefits of policies and interventions that are designed and implemented to address important rationales (e.g., related to objectives of development, sustainability, and equity) can also have AMR impacts.

Defined daily dose The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults. It does not necessarily reflect the therapeutic doses for individual patients, which take individual characteristics into account (e.g., age, weight, population differences, type and severity of infection). Drug utilization data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use.

Drivers Drivers are issues, which may act as facilitators or modifiers of the emergence and spread of AMR.

First-line antimicrobials First line antimicrobials are usually narrow spectrum antimicrobials that are empirically recommended for common infections in community and healthcare settings.

Implementation research Implementation research is an integrated concept that links research and practice to accelerate the development and delivery of interventions. It involves the generation and application of knowledge to improve the implementation of policies, programs, and practices.

Metaphylaxis Metaphylaxis is the treatment of a group of animals after the diagnosis of an infection has been established in some individuals from the group, with the aim of preventing the spread of the infectious agent to animals considered at risk.

Monitoring Monitoring is the intermittent performance and analysis of routine measurements and observations, aimed at detecting changes in the environment or health status of a population. See also surveillance.

Multidrug resistance Multidrug resistance (MDR) is a property of a pathogen that is resistant to three or more antimicrobial agents in three or more antimicrobial classes. Researchers have also proposed the term extensive drug resistance (XDR), defined as resistance to all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories). Pan drug resistance (PDR) is defined as resistance to all agents in all antimicrobial classes.

One Health One Health is a collaborative approach for strengthening systems to prevent, prepare, detect, respond to, and recover from primarily infectious diseases and related issues such as antimicrobial resistance that threaten human, animal, and environmental health collectively.

Pathogens Pathogens are microbes that induce infectious disease patterns in their human, animal, or plant hosts, usually as a way to spread and advance their own reproduction.

Prophylaxis Prophylaxis is the treatment of an animal or a group of animals before clinical signs of infectious disease are observed in order to prevent the occurrence of disease or infection.

Resistance determinant Resistance determinant is a catch-all term that includes the mechanisms that give a microbe the ability to resist the effects of one or more drugs, usually an antimicrobial resistant gene (ARG) or a mobile genetic element (MGE) carrying the gene/s.

Resistome The resistome is the complete set of antibiotic resistance genes and their precursors in both pathogenic and non-pathogenic bacteria. This is composed of four different types of genes: resistance genes found on pathogenic bacteria; resistance genes found on antibiotic producers; cryptic resistance genes; and precursor genes.

Risk Risk means the likelihood of the occurrence of a resistance determinant and the likely magnitude of its biological and economic consequences or effect on sustainable development.

Stewardship Stewardship is a coherent set of actions that promote using antimicrobials in ways that ensure their efficacy and sustainability for all who need them. Actions might include, for example, prescribers making accurate diagnoses, following guidelines, reviewing their prescriptions in a timely manner, formulary restrictions, and preauthorization of certain antimicrobials.

Subtherapeutic use Subtherapeutic use refers to levels of antimicrobials below the ones required to cure infections. In countries where it is still permitted, antibiotics may be given to animals on an ongoing basis at subtherapeutic doses for growth promotion.

Superbug Microbes developing resistance to multiple drugs are sometimes referred to as "superbugs." An infection caused by a superbug is harder to treat because fewer effective drugs are available; in some extreme cases, treatment may not exist.

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

Therapeutic use Therapeutic use is the curative treatment of a person, a sick animal or plant, or a group of animals or crops, following the diagnosis of infection and/or clinical disease in those individuals

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Antimicrobials have saved hundreds of millions of lives and substantially contributed to development and economic growth. However, they are now losing their power because of the microorganisms' acquired capacity to withstand the drugs designed to kill them, to inactivate or slow their growth: antimicrobial resistance (AMR).

Unchecked, AMR could severely reduce global economic output and hobble human and sustainable development progress in the decades ahead. AMR is a development issue.

The report shows that we are facing a major gap between "knowing" and "doing." Abundant knowledge exists about many aspects of AMR, yet people do not seem to know what to do, or how to do it. This calls for major efforts to be made in the field of implementation research to bridge knowledge and actions in real-world settings.

AMR-sensitive interventions can be designed and delivered in such a way that they contribute cobenefits in addressing AMR. In building roads, ports and other urban developments, as well as through interventions to build health systems, improve animal husbandry, or improve water and sanitation, there are opportunities to maximize impact on AMR.

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