1 *Introduction*

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Over the last decade, there have been several major reports on different aspects of antimicrobial resistance (AMR) (Mossialos et al., 2010; Davies, 2013; Davies, Grant & Catchpole, 2013; O'Neill, 2016a; Renwick, Simpkin & Mossialos, 2016; OECD, 2018; Renwick & Mossialos, 2018). The purpose of compiling this book was to bring together in one place the evidence and thinking from developed countries on the different facets of the complex problem of tackling AMR for academics and policy-makers. What is the evidence on the rise of AMR and its health and economic impact? How can it be most effectively addressed in the community and in hospitals? What role is played by antimicrobial use in the food and livestock sector and what can be done about it? How can the discovery of new antibiotics be reinvigorated to replace those rendered ineffective by resistance? What needs to be done to develop new diagnostic tests so that infections can be speedily identified or ruled out and unnecessary antibiotic use avoided? Can more use be made of vaccines to tackle AMR? How have civil society movements contributed to policy development in the fight against AMR?

In this book we refer to antimicrobial resistance but for the most part the argument relates specifically to antibiotics. Antibiotics are medicines used to prevent and treat *bacterial infections*. While it has been shown that some resistant forms of bacteria predate the use of antibiotics in modern medicine, the focus of this book is antibiotic resistance which occurs when bacteria change in response to the use of these medicines. Antimicrobial resistance is a broader term, encompassing resistance to drugs to treat infections caused by other microbes as well, such as parasites (e.g. malaria), viruses (e.g. HIV) and fungi (e.g. Candida). In this book we normally refer to antibiotics unless otherwise indicated but we retain the abbreviation AMR because it is in common use. Antimicrobial resistance is a biological mechanism whereby a microorganism evolves over time to develop the ability to become resistant to antimicrobial therapies such as antibiotics. The discovery of antibiotics has been one

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of the most significant developments for humanity over the last 70 years – a breakthrough in the treatment of communicable diseases which has also facilitated developments in other areas of medicine such as surgery, obstetrics and oncology (Holmes et al., 2016; Teillant et al., 2015). The development of AMR is intrinsic to the use of antibiotics but its growth and spread is exacerbated by their overuse and misuse. This risk has been known for a long time. Sir Alexander Fleming, the discoverer of penicillin, noted this in an interview as early as 1945:

> In such cases, the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted (New York Times, 1945).

The widespread dissemination of antibiotics in the succeeding decades only increases the relevance of his words today. Following the discovery of penicillin in 1928, many classes of antibiotics followed; a period many describe as the "golden era" of antibiotic discovery. Despite this initial expansion, in the last 30 years there has been a dearth of novel antibiotics discovered (Freire-Moran et al., 2011; Spellberg et al., 2004).

Globally, the prevalence rate of resistant bacteria has been steadily increasing. Currently, in many countries rates of resistance are particularly high in Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*; for example, in Europe (Figure 1.1).

Increased use of a major last-line antibiotic group – carbapenems – to treat these resistant infections is creating higher selection pressure resulting in more cases of carbapenem-resistant bacteria. The increased prevalence of carbapenem-resistant bacteria is a growing problem for clinicians since there are fewer alternative treatments remaining apart from, for example, colistin. However, plasmid-mediated colistin-resistant genes have now been identified in China and 30 other countries around the globe (Yin et al., 2017; Center for Infectious Disease and Research Policy, 2017). The growing rates of AMR combined with an insufficient pipeline for antibiotic discovery has yielded concerns that we may be rapidly approaching a "post-antibiotic" era (World Health Organization, 2017b).

As a result, global recognition of the threat posed by AMR has grown, with the World Health Organization (WHO) publishing the

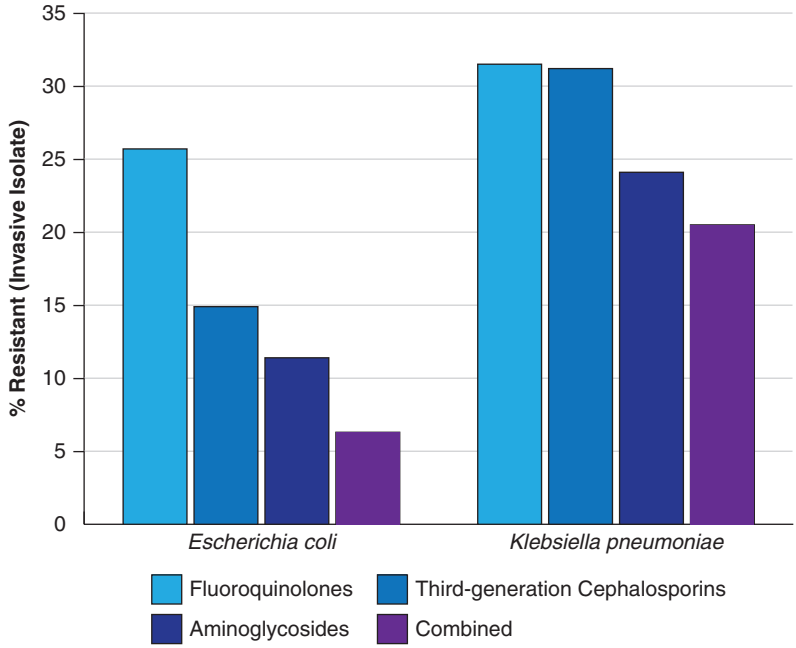

Figure 1.1 Percentage of invasive isolates tested resistant to selected antibiotics for *Escherichia coli* and *Klebsiella pneumoniae* reported from European countries in 2017

Notes: Fluoroquinolones, third-generation cephalosporins and aminoglycosides are antibiotic groups. Combined resistance refers to resistance to all three antibiotic groups. Resistance rates in this graph are the population weighted mean calculated using data reported from European Union (EU)/European Economic Area (EEA) countries.

Source: ECDC, 2018.

Global Action Plan on AMR in 2015, followed by the UN General Assembly issuing a declaration in 2016, with heads of state pledging their commitment to international cooperation to combat AMR.

In 2017, the WHO published a list of priority pathogens which outlines the antibiotic-resistant bacteria that pose the greatest threat to global public health (World Health Organization, 2017c). This list aims to guide antibiotic research and development (R&D) based on medical need as opposed to the economic factors that have traditionally directed antibiotic investment. At the top of this list, categorized as "critical",

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are the Gram-negative, carbapenem-resistant strains of *Acinetobacter baumannii, Pseudomonas aeruginosa*, and the Enterobacteriaceae family. In 2013, the US Centers for Disease Control and Prevention (CDC) published a US-focused urgent threats list for antibiotic resistance, which highlighted many of the same pathogens (US Centers for Disease Control and Prevention, 2013). To follow up, the WHO published an in-depth analysis of the global development pipeline for antibacterial agents (World Health Organization, 2017d). Based on optimistic clinical trial attrition rates, the report estimates that the entire pipeline could be expected to yield 10 new approvals. However, it concludes that these potential new treatments will add little to the already existing arsenal and will not be sufficient to tackle the impending AMR threat.

This recent escalation in global collective action to tackle AMR is therefore an important step, although both international and national level policy-makers must grasp this opportunity to develop national action plans which are adequately financed to address the economic and policy challenges which prevent coordinated and effective measures to contain AMR. International action is also required to incentivize the development of new antibiotics as well as other interventions (such as vaccines or diagnostics, or water and sanitation) which will be necessary to avoid the threat of a "post-antibiotic" era.

AMR in low- and middle-income countries

This book primarily focuses on evidence from high-income countries. However, it is still necessary to highlight the issue of growing AMR in low- and middle-income countries (LMICs), as AMR does not respect borders, and countries need to coordinate their actions with the rest of the global community. A review of AMR policies in LMICs has been published by the Center for Disease Dynamics, Economics & Policy (Gelband & Delahoy, 2014). In LMICs, such as India, the problem of AMR has reached critical levels (Gandra & Joshi, 2017) (Figure 1.2).

The spread of AMR is exacerbated in countries where it is common practice to buy antibiotics over the counter. The proportion of non-prescription human antibiotic use in countries outside northern Europe and North America, where the problem of AMR is greater, has been estimated at between 19% and 100% (Morgan et al., 2011). Hence, there is an increasing need to monitor this level of inappropriate antibiotic consumption and address factors common in those countries such as

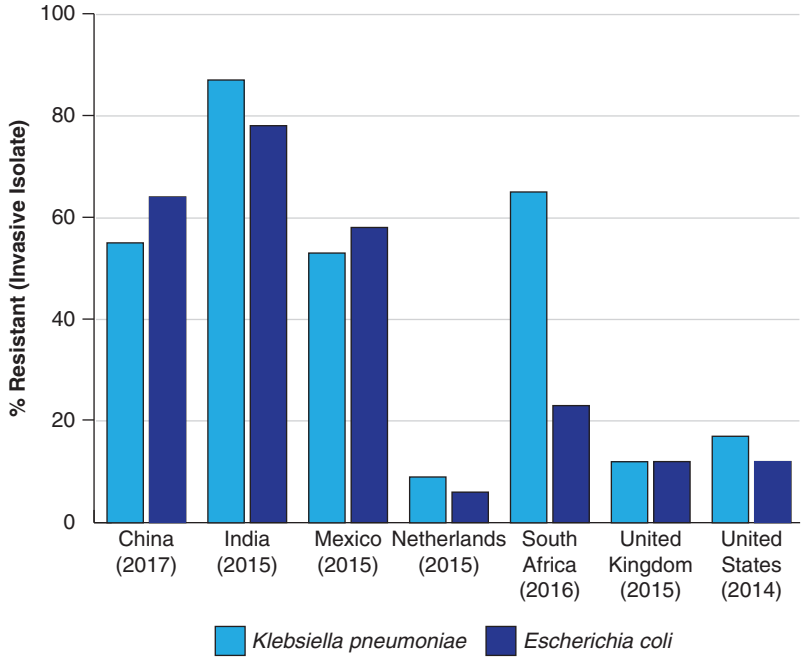

Figure 1.2 Cross country comparison of patterns of *Escherichia coli* and *Klebsiella pneumoniae* resistant to third-generation cephalosporins

Note: Years shown in brackets indicate date of most recent available data.

Source: Center for Disease Dynamics, Economics & Policy, 2018.

the misuse of antibiotics by health professionals, unskilled practitioners and laypersons; poor drug quality; unhygienic conditions accounting for spread of resistant bacteria; and inadequate surveillance (Okeke, Lamikanra & Edelman, 1999; Harbarth, 2008). Awareness of the long-term societal impact of AMR needs to be raised through global health campaigns.

Data from the ResistanceMap repository and the World Bank have proven a strong inverse association between prevalence of AMR in countries and average per capita income (Alvarez-Uria, Gandra & Laxminarayan, 2016). This is not surprising given the increasing antibiotic consumption in LMICs; in particular large emerging economies such as Brazil, Russia, India, China and South Africa (Laxminarayan, Van Boeckel & Teillant, 2015).

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Many LMICs have weaker health care systems, which are associated with several factors that limit their ability to tackle AMR. These include a lack of effective infection prevention and control (IPC) practices, the affordability of second- or third-line antimicrobials, and a lack of regulation or enforcement surrounding the production of low-quality/counterfeit antimicrobials and in respect of prescribing. In addition, increasing levels of environmental contamination, a lack of reliable surveillance data and increased antibiotic use in agriculture are some of the key factors contributing to the emergence and transmission of AMR in LMICs (Laxminarayan et al., 2016).

Furthermore, there is a tension between reducing antibiotic consumption in LMICs while also ensuring appropriate access to medicines. Many LMICs have a high burden of communicable diseases, and inadequate access to effective antimicrobials, which contributes to higher mortality rates. Therefore, stewardship policies in LMICs must pay particular attention to facilitating appropriate access to effective antimicrobials alongside conservation (Laxminarayan et al., 2016).

There have been some attempts to address the problems driving AMR in LMICs. Global initiatives involving the deployment of quick and cheap rapid diagnostic tests for diagnosis of malaria, and the Affordable Medicines Facility for malaria, to incentivize the use of artemisinin to replace the use of inexpensive chloroquine treatments to which widespread resistance had developed, can be regarded as examples of success stories for tackling antimalarial resistance in LMICs (Gelband & Laxminarayan, 2015). Similarly, the Global Antibiotic Resistance Partnership aims to tackle AMR related to bacterial infections in LMICs from a national and subnational perspective. There remains an increased need for LMICs to expand their technical expertise in relation to surveillance of AMR to guide policy. There is also a need for both increased political commitment and a legal framework to guard against irresponsible antibiotic use taking a One Health perspective.

Health and economic impact of AMR

Due to AMR's intricate transmission and acquisition routes in the community and hospitals settings, it is challenging to estimate its overall aggregate burden on society. Smaller scale studies have been conducted for specific resistant bacteria types (e.g. resistant Enterobacteriaceae) within individual institutions in different countries (Stewardson

et al., 2016). A number of non-comparative descriptive studies have also highlighted the issues surrounding the associated opportunity cost of AMR. However, research addressing the impact of AMR on society and the economy in terms of labour markets, trade, or tourism is limited.

Researchers investigating the health, economic, and societal burden of AMR are faced with limited data availability, resulting in uncertainty about the long-term cost and clinical efficacy outcomes for interventions (e.g. antibiotic stewardship programmes (ASPs)) currently in place to tackle AMR.

An independent AMR review commissioned by the government of the United Kingdom (O'Neill, 2016b) carried out a number of modelling studies in an attempt to estimate the burden of AMR. In the extreme scenario, where current infection rates were doubled and resistance reached 100% in all countries, it was estimated that by 2050 the deaths associated with AMR could reach 700 million with an associated cost of $14 billion (KPMG, 2014). Furthermore, the total loss of the working-age population was estimated to range from 11 to 444 million by 2050 (Taylor et al., 2014). Following the AMR review, the World Bank estimated that in a high-impact scenario, the global annual gross domestic product loss by 2030 could be around $3.4 trillion and $6.1 trillion by 2050 (Adeyi et al., 2017).

These initial modelling studies provide a bleak projection of the long-term impact of AMR on society if no action is taken. However, realistic estimates of the impact of AMR are necessary to target interventions where they are most needed. There still remains a gap in knowledge in relation to country- and setting-specific combined estimates, exploring the overall impact of these resistant strains on humans in terms of: mortality, morbidity, length of hospital stays, ineffective treatment, reduced efficacy of prophylaxis, productivity loss, or caregiver burden.

Tackling AMR in the community

Antibiotic prescribing is generally higher in the community than in hospitals. In England, about 74% of antibiotic prescriptions are in general practice compared to 11% in hospital inpatients (Public Health England, 2016). Thus, the potential for the development of resistant bacteria can occur in the community as well as hospitals. The common reasons for antibiotic prescriptions in the community include respiratory, urinary, skin, or tooth infections, with respiratory tract infections

accounting for the largest share (Goossens et al., 2005; Gulliford et al., 2014; Shapiro et al., 2014).

Recent efforts to curb unnecessary antibiotic prescribing in both community and hospital settings that are explored in this book include implementation of stewardship programmes and public health campaigns. The prescribing roles of nurses and pharmacists have been cited as increasingly important due to their better compliance with protocols and prescribing guidelines (Charani et al., 2013; Wickens et al., 2013). The role of individual stakeholders and their behaviour in consulting, prescribing, dispensing, and consumption of antibiotics are seen as increasingly important in tackling AMR. A number of behaviour change interventions in the community have been trialled focusing on clinicians, patients and clinicians, and the public (Tonkin-Crine et al., 2017).

From the community or primary care perspective, recent studies have reported the clinical effectiveness in terms of reduced prescribing when interventions incorporated shared decision-making with patients (Coxeter et al., 2015), point-of-care testing (Aabenhus, Costa & Vaz-Carneiro, 2014), and delayed prescribing measures (Spurling et al., 2017). In high-income countries, these interventions appear to be effective across countries with differing health care systems but the evidence concerning effective interventions in the very different circumstances of LMICs is very limited. Social, economic, cultural and environmental factors may mean different approaches are required. In addition, most studies focus on the short-term impact of interventions and there is little evidence concerning which interventions have the greatest long-term impact.

Tackling AMR in the hospital sector

Hospitals and long-term care facilities act as reservoirs for pathogenic bacteria causing hospital-acquired infections (HAIs). Cross-transmission of pathogens between patients and health care workers via hand contact or from the hospital environment (e.g. surfaces), as well as during invasive procedures (e.g. surgery or insertion of devices), have been found to increase this risk of transmission in hospitals. These variable mechanisms of transmission highlight the need for effective IPC measures combined with stewardship programmes (Holmes et al., 2016; O'Neill, 2016b). Effective leadership and incorporation of "champions" to lead

good prescribing and IPC practices, along with promotion of a positive organizational culture, have been cited as ways to tackle HAIs (Zingg et al., 2015). However, the resource constraints and overcrowding in hospitals (Clements et al., 2008) adversely affect policy compliance rates, especially in LMICs, giving rise to poor IPC measures, thus facilitating the development of resistant bacteria in hospitals (O'Neill, 2016b).

This book explores further the effectiveness and cost–effectiveness of strategies to combat AMR in the hospital sector. These strategies include IPC measures, such as contact precaution, isolation, screening, environment cleaning, and decolonization, the impact of surveillance, outbreak control measures, stewardship, and changing education curriculums at undergraduate level to influence behaviour change for nurses, pharmacists, and doctors (Pulcini & Gyssens, 2013). Recent systematic reviews and meta-analysis results have reported on the clinical effectiveness of these strategies in terms of reduction of resistant infections or prescribing (Baur et al., 2017; Karanika et al., 2016). Additional effectiveness of ASPs when combined with IPC measures have also been reported (Baur et al., 2017). However, cost–effectiveness analysis related to ASPs in hospitals is limited, but suggests ASPs may be cost-effective (Ibrahim et al., 2017).

Huge challenges remain in the effective implementation of IPC measures. Further studies are needed to estimate the excess financial costs of HAIs in order to estimate the financial scope for IPC measures and their cost–effectiveness. Too many of the current studies are of poor quality. Thus, it is recommended that action is taken to strengthen international collaboration in surveillance, that robust data are generated to provide useful information to decision-makers in hospitals and that the undergraduate curriculums of all health care professionals should include the principles of prudent prescribing.

Tackling antibiotic resistance in the food and livestock sector

The transmission of resistant microorganisms or genes may occur via direct contact between humans, or animals, or between them (including occupational, domestic or companion animal exposure). Indirect routes of transmission also exist related to travel and migration or the contamination of the food-chain from sources such as manure and soil, or due to unhygienic conditions (World Health Organization, 2017b).

In the livestock sector, antibiotic use extends beyond therapy to include use for metaphylactic, prophylactic, and growth promotion purposes. Antibiotics have often been used to boost productivity by counteracting the adverse consequences of poor and "intensive" farming conditions. A global study estimated that the volume of antimicrobials used in agriculture is expected to increase by 67% by 2030, principally as a result of increasing demand for food-producing animals and "intensive" farming in countries with growing populations, such as the USA, India, China and Brazil (Laxminarayan, Van Boeckel & Teillant, 2015).

This book explores strategies to combat AMR in the food and livestock sector such as changes to biosecurity measures to improve IPC, vaccination, husbandry practices and improved surveillance to detect emergence of infections. There are a number of economic evaluations which have reported on the effectiveness of these interventions, resulting in a reduction in antibiotic use within the livestock sector with limited repercussions on profitability (Gelaude et al., 2014; Postma et al., 2016).

The global use of antibiotics in animal production has been excessive and has resulted in selection for antibiotic resistance affecting both human and animal health. Even low doses, such as used for growth promotion, have an impact. In recent years there has been huge progress in some countries in reducing antibiotic use through improved animal management and the use of other interventions (such as vaccines or probiotics). Implementation of these measures more widely would increase this impact.

Fostering R&D of novel antibiotics and other technologies to prevent and treat infection

A number of economic, regulatory, and scientific barriers have resulted in reduced incentives to invest in new antibiotics research. Between 2007 and 2012, worldwide patent applications related to antibiotic research dropped by 34.8% (Marks & Clerk, 2015). The WHO's International Clinical Trials Registry Platform shows that there are only 182 active clinical trials that focus on bacterial infections other than tuberculosis, which is much less than 1% of the 67 000 clinical trials on noncommunicable diseases (O'Neill, 2015b).

From an economic standpoint, the return on investment in R&D on antibiotics is estimated to have, on average, a negative net present

value compared to investment in other treatments, such as oncology. Due to the current stewardship practices and the existing cheaper generic alternative antibiotics, a novel class of antibiotic will be for restricted use only, reducing its revenue potential and market value. Therefore, investing in R&D of this nature is not, for the most part, attractive to private sector drug developers (Renwick, Brogan & Mossialos, 2016).

Nevertheless, the recent recognition in political and international circles of the urgent need to address AMR has resulted in a number of new funding initiatives in the USA and Europe designed to improve the pipeline for the production of new antibiotics. These include investments by existing institutions, such as through the Joint Programming Initiative on Antimicrobial Resistance, the European Commission and the Innovative Medicines Initiative in the EU. In the USA the National Institutes of Health and the Biomedical Advanced Research and Development Authority are large funders of antibiotic R&D. Two new initiatives include the Global Antibiotic Research and Development Partnership (GARDP) and Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X).

While these initiatives and others have helped to boost funding on preclinical research, there remains a gap in financing the riskier and more expensive business of taking drug candidates through clinical trials. This particularly affects small and medium enterprises who are responsible for developing a large proportion of new drug candidates. Considering the widespread societal benefit associated with R&D for antibiotics, there is a need for innovative policy solutions to address this market failure. That is why consideration needs to be given to other forms of incentive such as those that offer extra rewards through the regulatory and intellectual property regimens. A combination of *pull* and *push* incentive strategies have been suggested to incentivize R&D either to boost the revenue earned from newly discovered antibiotics or to reduce the cost of R&D (Renwick, Simpkin & Mossialos, 2016). There has also been increasing support for the concept of *delinkage*; a policy tool whereby a company's return on R&D invested in a product is *delinked* from its volume-based sales (Outterson et al., 2016; O'Neill, 2015a).

Major recent reports have recommended the introduction of market entry rewards where a lump sum or phased payment would be made for the successful development of new antibiotics that meet pre-specified criteria. In its purest form, no revenue would be derived from sales so

there would be no incentive for firms to maximize the consumption of the antibiotic. A less expensive version of the reward would allow some revenue to be generated from sales. It is estimated that a reward of $1–2 billion would be necessary to encourage firms to invest in R&D for new antibiotic classes (O'Neill, 2015a; Renwick, Simpkin & Mossialos, 2016; DRIVE-AB, 2018).

The impact of such a scheme would be maximized if the funding and rules were harmonized between those countries with innovative potential in antibiotics and if it were administered by a single global body established for this purpose. A possible candidate is the Global Antimicrobial Resistance Collaboration Hub established on the initiative of the G20 in 2017 (G20 Leaders' Declaration, 2017).

Ensuring innovation for diagnostics for bacterial infection

A global AMR response will require diagnostics that are affordable and accessible, can be used at the point of care (POC), and can rapidly determine antibiotic susceptibility. These tests are urgently needed to reduce inappropriate use of antibiotics, guide patient management for improved outcomes and provide much needed AMR surveillance. For any diagnostic test to be effective in primary health care settings, it needs to be simple to perform, rapid, affordable and accurate. This means providing a result in less than 15–20 minutes in order to be able to guide more targeted use of antibiotics (Okeke et al., 2011).

Traditional diagnostic tests are designed to identify pathogens in specimens taken from the patient. However, the symptoms commonly encountered where antibiotic treatment is considered can be caused by many bacterial, viral or in some cases, fungal pathogens. It would be difficult to develop a test that can identify the cause or causes of all these symptoms. As a compromise, a simple rapid test that can be used to distinguish between bacterial and viral infections would potentially be useful to inform health care providers whether a prescription for antibiotics is warranted.

The key role of diagnostic tests includes identification of target patient populations resulting in 1) reduced inappropriate antibiotic use if there were rapid-POC susceptibility tests with high sensitivity and specificity, 2) improvement in AMR surveillance data collection and timely distribution of these data and 3) reduced cost of recruiting target patient populations in costly clinical drug trials.

While the importance of diagnostics in tackling AMR is recognized, developers currently face a number of technical, policy, regulatory, financial, and implementation barriers which hamper the diagnostic innovation which is urgently needed. The UK Longitude prize initiative and a *Target Product Profile* development for a diagnostic assay to identify bacterial versus non-bacterial infection types, are some of the first steps that are being taken to reduce some of these financial and technical barriers. In order to foster the development of diagnostics, the reform of regulatory systems is necessary. Regulatory science lags far behind technological innovation, and approval processes are often lengthy, costly and not transparent (Morel et al., 2016). Access to finance is a problem – in particular because public funders do not see investing in diagnostics as having a direct impact on health outcomes. Many countries do not have national policies on diagnostic use.

A new framework for health technology assessments (HTAs) for joint review of risks and benefits by regulators and policy-makers, programme managers and subject matter experts is urgently needed, not only to facilitate a faster and more balanced regulatory review but also to accelerate implementation and policy development. Regional harmonization of a new HTA framework would also reduce duplication in clinical performance studies, reducing delays and lowering costs so that the marketed product becomes more affordable, and hence accessible.

For AMR surveillance to be effective, it is critical to: 1) understand the science and technologies needed for immediate pathogen identification to provide disease risk assessments and support global health decisions, 2) build a comprehensive network of laboratories and POC testing sites to implement quality-assured POC diagnostic services with a good laboratory–clinic interface, 3) use implementation science to understand the political, cultural, economic and behavioural context for novel diagnostic technology introduction.

As cost and funding will continue to affect innovations in diagnostics, a sound business case needs to be made to incentivize and de-risk R&D, and to finance novel diagnostic solutions for AMR. Quantifying the risk of not having diagnostics to improve the specificity of syndromic management can also encourage investments. In addition, it is important to assess the contribution of a new generation of connected diagnostics to improve the efficiency of health care systems by simplifying patient pathways, guiding appropriate use of drugs and other resources and improving patient outcomes.

Vaccines and AMR

Alongside incentivizing R&D for novel antimicrobials, alternative options exist which could reduce the demand for existing antimicrobials and in turn decrease the selective pressure of resistance with the help of vaccinations and timely diagnostic tools (O'Neill, 2016a).

Since vaccination is a population-wide preventive measure, it could directly help in reducing the infected population, resulting in increased herd immunity, reduced the transmission of infections, and lowered antibiotic use (Lipsitch & Siber, 2016). For example, vaccinations against respiratory infections offer the potential to reduce substantially the number of inappropriate antibiotic prescriptions often given for a viral infection. These vaccinations could also reduce the number of secondary bacterial infections which are sometimes associated with influenza and respiratory syncytial viral infections. It has been estimated that if universal coverage of the pneumococcal conjugate vaccine was provided to the 75 countries that currently have less than 80% coverage of this vaccine, antibiotic treatment in infected children aged less than 5 years could be halved (Laxminarayan et al., 2016). As is the case with antibiotics, the value of vaccines in combating AMR is not captured in the financial calculus when private companies take decisions on investing in vaccine R&D.

Hitherto the value of vaccines in combating AMR has not adequately been taken into account. While there are difficulties in accurately assessing this value because of the multiple pathways by which vaccines could reduce AMR, and the absence of necessary epidemiological and economic data, it is important to incorporate it when making decisions on vaccine development priorities. Three sets of pathways need to be considered. The *health systems pathway* governs the impact of vaccines on antibiotic prescribing. The *epidemiological pathways* govern the impact of vaccines on AMR directly or via reduced prescribing. This is complicated by the fact that it is not well understood how reductions in antibiotic use translate (or not) into reductions in resistance. The *economic pathways* are about how to value reductions in AMR, once determined. This could involve complex modelling of the macroeconomic effects of AMR which would involve constructing counterfactual scenarios including, for example, the cost of developing new antibiotics, or of medical procedures becoming riskier, or even impossible.

The role of the civil society in fighting AMR

The global nature of AMR has given rise to worldwide collaboration initiatives and the need for a global collective action with the increased involvement of civil society. Civil society has been recognized by the United Nations as the third sector of society along with governments and businesses. It has played a vital role in raising awareness of the repercussions of AMR. At a global policy level, civil society has highlighted the importance of access to antibiotics (in terms of fairer prices for consumers and the public sector) and excess use of antibiotics (in terms of discouraging inappropriate or unnecessary promotion of antibiotics in LMICs by drug companies). Key contributions of civil society are the introduction of the Antibiotic Resistance Coalition and the formulation of the Antibiotic Resistance Declaration which has promoted the formulation of the Global Action Plan by WHO and the UN Political Declaration.

Just as civil society catalysed global attention over monopoly pricing of patented HIV/AIDS drugs, new civil society actors have been critical in highlighting the dearth of novel antibiotics in the R&D pipeline. Rekindling attention to AMR at WHO contributed to the policy momentum that brought the issue to the world stage. AMR, by its nature, demands an intersectoral response. Civil society organizations have successfully introduced the concept of delinkage into the policy vernacular and mobilized consumer pressure on major restaurant chains to source food animal products raised without routine use of antibiotics. This work is remarkable because of the complexity of the AMR issue, its intersectoral nature, and the fact that its victims do not readily identify themselves with this shared global health challenge. While the vision of ensuring a future free from the fear of untreatable infections is years away, the remarkable richness of the contributions that civil society has made to the policy discussions and debates over AMR offers a useful compass for future policy-making.

Conclusion: The need for global collective action

A comprehensive strategy utilizing a One Health approach targeting human, animal and environmental health is crucial to tackling AMR. To meet the five key objectives outlined within the WHO's Global

Action Plan, a multifaceted approach including antibiotic stewardship, improved global surveillance, better IPC, R&D of novel antimicrobials, diagnostic tools, and vaccines, combined with increased awareness of the threat of AMR is needed.

Individual countries can understand the need for *collective action*, whereby every country will benefit from cooperating to improve access, conservation and innovation. However, no single country is usually willing to contribute to this coordinated effort unless there are firm commitments by other countries to do the same. As a result, despite the success of individual countries in tackling domestic AMR levels (e.g. the Nordic countries and the Netherlands), there is a lack of effective internationally coordinated efforts to address the global nature of the problem. The way that global governance and global markets work can hinder or stall the search for solutions to tackling AMR on an international scale.

While there has been much discussion and proposed actions to address AMR from international organizations such as the WHO and the World Bank and in the recent declarations of the leaders of the G7 and G20, there has been little concrete progress to generate truly collective global action, although the Global Antimicrobial Resistance Collaboration Hub established in 2017 by the G20 could be an embryonic coordinating institution if supported sufficiently by a wide range of countries.

It has been argued that the national, regional and global interconnectedness of the drivers of AMR, the need to tackle simultaneously the three objectives of access, conservation and innovation, and the intersectoral actions required, make AMR a good candidate for an international legal treaty (Hoffman et al., 2015; Outterson et al., 2016). More recently a similar call has been made for an international legal agreement on AMR to be developed by a Global Steering Board and a High-Level AMR Commission (Rochford et al., 2018). However, collective action is often hampered by incentive mismatches and the competing interests of various stakeholders and institutions. A single global institution, supported by an international legal framework, could help to manage these competing interests and address the collective interest in overcoming the issues of governance, compliance, leadership and financing to achieve the shared common goal of reducing the health and economic burden of AMR.

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