GOVERNING ANTIMICROBIAL RESISTANCE: WICKEDNESS, COMPETING INTERPRETATIONS AND THE QUEST FOR GLOBAL NORMS

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CONTENTS

ABBREVIATIONS

ACT	Artemisinin Combination Therapy
AMR	Antimicrobial Resistance
BRICS	Brazil, Russia, India, China and South Africa
DRI	Drug Resistant Infections
FAO	United Nations Food and Agricultural Organization
G7	The Group of 7 nations
G20	The Group of 20 nations
HLCM	High Level Coordinating Mechanism
HIV/AIDS	Human Immunodeficiency virus/acquired immunodeficiency syndrome
IHR	International Health Regulations
IO	International Organization
OIE	World Organization for Animal Health
PHEIC	Public Health Emergency of International Concern
RDT	Rapid Diagnostic Tests
WHO	World Health Organization
WHO GAP	World Health Organization Global Action Plan

EXECUTIVE SUMMARY

AMR is undoubtedly one the most important issues challenging global public health. While the 1990s and first decade of this century was marked by inaction around AMR, more recently it has become a matter of high politics discussed that has emerged in a number of high profile settings. While AMR seems to have achieved some closure around the debates as to its seriousness, there is much less agreement around the types of strategies that it will demand in different settings.

Analysing the issue as a wicked problem and reviewing the various frames in which it has been proposed enables the reader to understand the need for action that responds to the complexity of the problem, the inability of many of the current frames to enable this to occur and finally the lack of consensus among global actors. The next step for global health actors is to set in place a series of processes through which the governments of high, middle and low income countries are involved in negotiating a set of normative instruments which will enable them to act on AMR in their national contexts and be responsive to improvements in the scientific understanding of resistance.

This paper argues that governing AMR at global level must entail action that insures that effective antimicrobials are available to all, that they be targeted effectively, and that wherever possible alternative ways of improving health and managing communicable diseases must be found and put in place. This means that governments and global health actors need to recognise that antimicrobial efficacy is a global public good that must be accessible and protected; and that norms need to reflect the importance of acting on structural and infrastructural constraints that shape unnecessary antibiotic use so that it is no longer necessary to use antibiotics to secure human health in the face of missing infrastructure, (when diarrheal infection resulting from poor sanitation is treated with antibiotics) missing commodities (antibiotics are often used because diagnostics have not been made available to ensure that medicine is targeted or if vaccine development has not been funded or scaled up) or missing expertise (when health care workers are not trained adequately to make safe decisions about medicine use).

Key Words
AMR, antibiotics, global health, governance, health security, normative instruments, One Health, SDGs, wicked problem, WHO

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Eleanor Hutchinson [*]

1. Introduction

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This paper argues that governing AMR at global level must entail action that insures that effective antimicrobials are available to all, that they be targeted effectively, and that wherever possible alternative ways of improving health and managing communicable diseases must be found and put in place. This means that governments and global health actors need to recognize that antimicrobial efficacy is a global public good that must be accessible and protected; and that norms need to reflect the importance of acting on structural and infrastructural constraints that shape unnecessary antibiotic use so that it is no longer necessary to use antibiotics to secure human health in the face of missing infrastructure, (when diarrheal infection resulting from poor sanitation is treated with antibiotics) missing commodities (antibiotics are often used because diagnostics have not been made available to ensure that medicine is targeted or if vaccine development has not been funded or scaled up) or missing expertise (when health care workers are not trained adequately to make safe decisions about medicine use).

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2. AMR as a wicked problem:
Indeterminacy and the lack of a definitive solution

The importance of formulating policy that is able to work with complexity, multi-dimensionality, multiple constituencies and radically different interpretations of problems is increasingly recognized (Roe, 2012). One way of beginning to deal with complexity has been through identifying and rendering visible the components of a particular group of policy problems labelled 'wicked' that emerge from increasing pluralism, appear impervious to resolution and result in the failure of traditional policy instruments (van Woezik et al., 2016). There are many formulations of the key characteristics of wickedness in the policy domain. In relation to AMR, the following are most important: the indeterminacy of the problem; the lack of a definitive solution; its irreversible nature; and it uniqueness as a problem (Xiang, 2013).

Antimicrobial or antibiotic resistance?

While many people feel that they know what AMR is, definitions of what resistance entails and the medicines that are involved are not fixed in either the policy or the scientific literature. This means that we are not always speaking to the same issue. The first critical distinction is whether we are considering AMR or antibiotic resistance. Many argue that AMR includes all antimicrobial medicines, including those that act on fungi, viruses and parasites. This means that they take in antiretroviral medicines, for example. Yet, this distinction does not always hold. The World Health Organisation's Global Action Plan (WHO GAP) (WHO, 2015), for example, considers AMR to combine antibiotics and other antimicrobial medicines that act like antibiotics. Similarly the meeting of the Berlin declaration of the G7 health ministers discussed AMR but focused their action on antibiotics and in particular the establishment of a Global Union for Antibiotics Research (GUARD) (G7, 2015). Others, while recognising the problem of antimicrobial resistance relates to a range of medicines, have crafted more detailed policy discussions and debates around the growth in resistance to antibiotics. The O'Neill reports that were published by the British Government, for example, recognised that all antimicrobials (including antibiotics, anti-retroviral, anti-parasitic, anti-viral and anti-fungal medicines) need to be protected but made clear that the most pressing problems relate to the lack of new medicines and growing resistance to and excessive use of antibiotics (The Review on Antimicrobial Resistance, 2016). Similarly, in research papers many authors begin by discussing the broader issue of antimicrobial resistance but then in their substantive work turn to consider a particular antibiotic or drug resistant bacterial as their case under discussion (Wernli et al., 2011).

The distinction matters and, as we will see in the next section on the interpretation of AMR in the policy literature, it matters to the way in which the problem is addressed. For example, while antibiotic use in agriculture is an important issue that can be addressed through a One Health approach, the relevance of a One Health approach to other antimicrobial medicines is less apparent and certainly less well discussed.

The complexity of the science of resistance

The complexity around the drivers of resistance also presents a considerable challenge. When AMR refers to the growth in resistance in bacteria, fungi, parasites and viruses, then the range of ways in which resistance is likely to occur and will need to be managed is extraordinarily broad. Even when we take the narrower understanding of antibiotic resistance, studies of the different forms of resistance within humans and animals show that some forms of resistance can be overcome simply by withdrawing the antibiotic for a time meaning that for the treatment of infection, a medicine may be rendered useful again upon reintroduction (Stokes and Gillings, 2011, Timbrook et al., 2016). Other forms of resistance, however, appear more permanent and raise the possibility that particular antibiotics could be rendered moribund (WHO, 2001).

What is appropriate or prudent use?

There is a growing consensus that the widespread use of antibiotics in agriculture as a growth promoter and as a prophylaxis to enabling intensive production is a misuse of a precious resource. In health, however, the concerns are more complex. The growth of resistance in human health occurs in the context of highly unequal access to antimicrobials (not just antibiotics but also malaria medication and antiretroviral medication). In the case of artemisinin combination therapy (ACT), which is used to treat malaria, considerable work has gone into improving the targeting of this medicine to enable those who need medicines to access them and scaling back the use of medicines for those who do not. The balance between access and excess has improved but there are still many people who do not have timely access to ACTs or the rapid diagnostic tests (RDTs) that are needed for successful targeting (Steketee et al 2017). It is important to note that improved targeting will not necessarily improve rates of AMR. For antibiotics in some low-income settings, for example, improving targeting may should lead to increased access and therefore an increase in antibiotic use. If resistance emerges from the use (not simply the misuse) of antibiotics, then it could be the case that equitable, prudent use of antibiotics may result in increasing resistance in settings in which antibiotics were not previously available. There is also a final complication in that the successful targeting of one antimicrobial will not necessarily improve the targeting of another. Recent experience with ACTs, for example, shows that the introduction of RDTs to assist practitioners to target malaria treatment more effectively coincided with the increased use of antibiotics as

practitioners swapped the prescription of one powerful medicine with another (Hopkins et al., 2017). Typical of a wicked problem, the potential for unintended consequences of policy action around AMR appear to be high (Hutchinson et al., 2017).

This is further complicated by a lack of consensus on what good use of microbial medicines constitutes in human health. While for antimicrobials that are used for a single disease (anti-retroviral medicines for HIV/AIDS, artemisinin combination therapy for malaria) there are global documents governing appropriate dosage, for others that are used as prophylaxis and treatment for different infections (antibiotics) standardization of treatment seems unlikely (Avorn, 2001). Moreover, what constitutes appropriate or prudent use and what constitutes rational use of antibiotics in particular will differ in relation to the availability and expertise of care providers, the local epidemiological and economic environment, accessibility to alternative medicines, the age and overall health of the patients, and the ways in which AMR has developed in a given setting. If the mechanisms put into place are to be effective then they need to be built around collective action that also allows for and responds to the different nature of AMR in different national settings, so that it can be flexible and adaptable.

The novelty of AMR as a problem for global health

Drug resistance infections are different to other infections and challenge the ways in which global health actors often talk about disease. Where calls for the eradication of different infectious diseases are increasing, this can never be successfully applied to AMR and the DRIs that they cause because, as Smith and Coast (2002) point out, from a scientific viewpoint, antimicrobial resistance emerges from the use of antimicrobials - not simply from its misuse (Smith and Coast, 2002). While work must be done to limit DRIs, for as long as antibiotics are in use, drug resistance infections will occur. This is an important distinction and means that AMR does not sit neatly within discourses of a "war on bugs", nor does it lend itself to having an elimination strategy (Wallinga et al., 2015).

Plurality of actors involved in the problem

While global health is seeing an increasing plurality of actors across many arenas, when the broadest definition of antimicrobial medicines is use and the various uses of antimicrobials across the globe are taken into account then the range of sectors, the plurality of actors involved in their use, and the considerable breadth of the organisations that make up what we might term the global antimicrobial regime comes into view (Hoffman et al., 2015a). There are three key global institutions that have been involved in the construction of global policy: the World Health Organization (WHO), the World Organization for Animal Health (OIE) and the Food and Agricultural Organization (FAO). If we take antimicrobial resistance in its broadest sense

(see above) then tackling it will require action in public and private sector actors involved in global health, multilateral groups (G7, G20, BRICS) and the governments who will need to oversee the construction and implementation of national level policy. Action will be needed among the producers and consumers of antimicrobials as medicines and the producers and consumers of antibiotics as farming and veterinary inputs across the world. It will require changes in the activities of both formal and informal health care providers and the people who seek care for themselves, their families and in some cases their livestock.

AMR as a super wicked problem

Littman's account of antibiotic resistance in high income settings describes additional core problems around antibiotic resistance that he argues makes it a super wicked problem. These are: that time is running out, central authorities needed to manage the issue are weak, that policy responses fail to recognize the effects that lack of action will have on the future (Littmann, 2014). In addition, and borrowing from the literature on climate change, Littmann also identifies AMR as a problem shot through with path dependencies that need to be addressed if AMR is to be successfully tackled. Path dependencies are particular historical constraints, policy options that made sense at a previous moment in time and that continue to shape current decisions despite the fact that they lead to unsustainable outcomes. For a problem to be sustainably managed, transformational action needs to occur to address the structures that underpin these dependencies. In agriculture, for example, this will likely mean transforming farming methods away from intensive forms that are only possible through the use of antibiotic prophylaxis. For human health, although antimicrobials will always be needed to manage infection, issues of path dependency mean that action will need to be taken to transform structures and infrastructures to reduce the reliance on antibiotics and that this will have to be as high a priority as creating new antibiotics. How will such an approach come into being? In high-income countries, Littmann argues that an improvement in vaccinations and better management of infections in hospitals offers an unspectacular but important beginning. In low-income however, it means that considerable investments (in infrastructure, in sanitation, clean water, housing) will be needed to reduce the need for antimicrobials and that this will have to be as integral a part of action on AMR as the search for better diagnostics and new antibiotics.

To conclude, AMR has a number of characteristics that enable it to be defined as wicked. and, according to the policy literature, understanding its wickedness is essential if we are to be able to act upon it. Multiple actors will be involved will need to be flexibility to react to different contexts in which AMR appears and critically to enable policy actors to take on board findings for scientific research. The next section presents and then interrogates the various interpretations of AMR that have appeared in policy discussions and in the literature and asks whether and how they enable the plurality actors and forms of complexity be understood and acted upon.

3. Discourses and interpretations of AMR in the policy literature

The complexity of the problem, the plurality of actors that need to be involved in global decision making, the range of medicines that AMR acts on and the complex pathways through which resistance emerges and may be managed means that there is no single, logical pathway through which policy prescriptions and governance mechanisms can be created to act upon AMR. Rather than considering collective action as a matter of linear progress running from problem identification to solution, it is useful to conceptualize AMR policy making as an assemblage of processes, regulations, targets and ambitions that come about through the interaction of different economic, social and scientific forces, and interests within particular political spaces (Müller, 2013).

Like other global health issues, AMR has been assembled into multiple competing discourses, with particular concerns raised by coalitions of actors who construct common interpretations of the problem (McInnes and Lee, 2016). Wernli et al (unpublished 2017) have identified what they refer to as five 'frames' through which AMR has been refracted: as a clinical concern, as an issue of sustainable development, as an innovation problem, as an issue of One Health, and as a health security issue. This paper is concerned with the ways recent interpretations of AMR have evolved from the One Health rubric to being considered a matter of health security and economic risk. It then goes on to consider the interpretations of AMR as a matter of humanitarianism that connects AMR to concerns about access to medicines and finally as a problem of (un)sustainable development to be managed through the SDGs. In each, we ask whether these constructions are broad enough to manage the plurality of actors involved, the complexity of the problem, to respond to new scientific knowledge and to manage path dependencies.

AMR as a health risk

One of the most dominant ways in which AMR has been interpreted as a global health risk has been through the One Health approach (Nguyen-Viet et al., 2016, Robinson et al., 2016, Harbarth et al., 2015). Drawn from an ecological model, the strength of this interpretation lies in its ability to bring scientific complexity and the interdependence of different fields of practice to the centre of debates about AMR. It tends to focus on antibiotics and for the most part attends to the relational nature of resistance, i.e. the dynamic interactions between people, animals and environments that co-produce antibiotic resistance and enable it to be spread across the globe.[1] The One Health approach encourages research and policy that focuses on the health risks that emerge through the

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1   The One Health approach appears much less useful for HIV/AIDS and its application to malaria also seems much more tenuous for example.

interdependence of different environments, analyses how they impact upon one another, and how these risks can be mitigated to curtail health problems that emerge. In many ways, the interpretation of AMR as a One Health problem has led it to be seen as a highly complex, wicked problem (Engelhardt, 2015) manifest in different ways in different spaces.

The One Health approach also emphasises the range of policy actors and the actions that need to be considered across different disciplines, institutions, political bodies and levels of government. Its success is reflected in the ways in which it is used by multiple authors seeking to influence debates and devise solutions (Laxminarayan et al., 2013). The recognition of the interdependence between animal and human health and agriculture has underpinned global action and drawn together the WHO, the FAO and the OIE. One Health occupies a central position in the WHO GAP on AMR but it is questionable whether it can be applied effectively to non-antibiotic antimicrobials (antiretrovirals and malaria medicines) and its power seems to lie in its ability to render visible the complexities of antibiotic use.

Attention to the global, national and local economies that underpin, and to some extent define, the emergence of health risks such as AMR is also often missing from One Health approaches to AMR (Engelhardt, 2015) (Robinson et al., 2016). Engelhardt (2015) argues that economic considerations might usefully be added to One Health Framework as a fourth arena for possible action on AMR. While the economy does not represent an environment in the same way as human bodies, animals and agricultural practices do, Engelhardt's contribution is useful to draw out the economic impact of AMR, both in the narrow fiscal sense, but also in respect of the broader macro-economic and social impacts that will result from efforts to deal with the problem.

AMR and health security

While the One Health approach develops the idea of interdependent risks and the externalities entailed in the use of antibiotics across agriculture, animal and human health, there have also been different interpretations of AMR as a health risk. This construction of AMR as a concern for health security emerged around 2000, when the United States (US) government published a report on infectious disease as a national threat (Noah and Fidas, 2000). In it, concerns about drug resistance incorporated different antimicrobials (including antiretrovirals and antibiotics) and was presented as a risk to the stability.

At global level, when the WHO published its first strategy to contain AMR, the notion of AMR as a health security matter was noted but was not an important element of the text (WHO, 2001). By 2013, however, the construction of antibiotic resistance as a matter of health security was much

more in evidence. A side event held that year by the UK and Swedish governments at the 66th World Health Assembly entitled "antibiotic resistance: a threat to global health security [2] and the case for action" reflects the ways in which these governments were using this narrative to push antibiotic resistance onto the global agenda. Statements and contributions reflecting this perspective were made by Germany, the Netherlands, Australia, India, China, Brazil, Philippians and Malaysia and when the WHO GAP was published two years later, the global health security discourses dominated. By 2016, this idea of AMR as a health security threat had become one of the most prominent ideas, with Sally Davis, the chief medical officer in the UK one of the chief proponents, arguing that a post-antibiotic era is close at hand and that AMR constitutes one of "the greatest future threat to our civilisation"(Department of Health (UK), 2016) . This health security narrative fits well with the One Health approach and the two are found together in the WHO GAP (WHO, 2015). While there is scope to discuss medicines beyond antibiotics, the health security agenda often raises clinical concerns about the uses and misuses of medicines, the need to create surveillance systems, and the need to change behaviour of the end users (patients and health care staff) and to develop new markets and new commodities (new antibiotics and diagnostics).

AMR as an economic threat

The final interpretation around the risk posed by AMR relates to its potential to undermine the global economy. This emerged most powerfully in the O'Neill reports commissioned by the British Government (The Review on Antimicrobial Resistance, 2016). The reports present AMR as an economic risk of such magnitude that it would likely wipe billions off the global economy. The presentation of AMR as both a health security and economic risk has been critical in raising its profile among policy makers and politicians.

The increased attention to the economics of AMR has also allowed arguments to emerge that present AMR as a form of market failure, and that point to the significant risk posed by the "dry pipeline" of antibiotic development (Morel and Mossialos, 2010) (Spellberg et al., 2012). The market in pharmaceuticals is described as having failed to provide new antibiotics to replace those that no longer work. New funding lines for innovation have been identified as critical in efforts to de-linking of research and development from profits, where research and innovations is funded through public funds rather being driven by the overriding profit-motive of the market place (Outterson et al., 2016).

Economic models of risk and risk taking have been applied to the consumers of antibiotics. Here, ideas that pit individuals against society such as the 'tragedy of the commons' have been applied

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2   It should be noted that the WHO has a different concept of global health security «global public health security is defined as the activities required, both proactive and reactive, to minimize vulnerability to acute public health events that endanger the collective health of populations living across geographical regions and international boundaries.» WHO 2007

to AMR. While these offer a powerful narrative of how risk can be manifest, they are unsophisticated in their understanding of the relationship of people to antimicrobial medicines (Baquero and Campos, 2003). This concept of the tragedy of the commons has been roundly criticised in the economic literature as relying upon a model of a rational actor who has access to a complete understanding of the problem at hand (Appell, 1993).

At the heart of the discourse on AMR as a security problem and as an economic risk are a series of dystopian images of a post-antibiotic future in which deaths from infectious disease become more commonplace and complex biomedical techniques can no longer be used (Wallinga, 2015). These dystopian framings however are very focused on high income settings and overall this framework does not fare well in its ability to provide an adequate response to AMR in the context of global income inequalities per se, and in particular with the fact that it is, at base, inequality and poverty that limit the access of the poor to medicines.

AMR and health humanitarianism

Humanitarian approaches to global health, pushed most strongly by Medicines Sans Frontières are often concerned with an overriding policy goal of increasing the access to medicines for the worlds most vulnerable people, makings sure that everyone can afford and are able to use life-saving medicines, including antibiotics and other antimicrobials. Unsurprisingly, therefore, concerns about AMR as a health security risk can be difficult to combine with humanitarian approaches to global health. The incompatibility of health security and health humanitarian issues is reflected in the WHO GAP AMR (2015), for example, where issues of increasing access to medicine appear in parenthesis the text alongside target reductions in the use of antibiotics.

There are, however, overlaps between conceptualisations of AMR as a health security risk and humanitarian interpretations of the problem. Concerns about resistance, and in particular resistance to antibiotics, have appeared in the discourse of humanitarian organisations, usually in the context of addressing particular diseases, such as multi drug resistant TB or sepsis, or when discussing AMR among particular groups of people who are more likely to suffer from resistant infections, such as war victims (Carrie Lee et al., 2014). Just as in the literature on health security, concerns about market failure around the development of antimicrobials and antibiotics feature prominently. Both health security and humanitarian approaches argue that the relationship between the cost contained in the development of medicines and the profits made through the sale of the medicines needs to be de-linked, hence, bringing these two agendas together. Moreover, the solutions that embedded within this humanitarian discourse are not as distinct as the narrative might suggestion. Health

humanitarians, and those more concerned with economic risks and health security all advocate for the use of commodities to manage AMR, with new medicines, point of care diagnostics (RDTs in particular) and access to vaccines (recently most visibly to protect against pneumonia) being prominent.

Like other approaches, there is little to address path dependency through which the need for anti-biotics can be curtailed among the world's most vulnerable people, for example, investments in water and sanitation, housing and improvements in nutrition. For this to occur, a broader concep-tualisation is required to draw together different elements from the One Health, health security, economic security and health humanitarian approaches, as also referred and committed to in the G7 Ise-Shima Vision for Global Health.

AMR as a matter of Sustainable Development

Writing in the Lancet, Das and Horton pick up on the concerns that have arisen in health humani-tarianism and the continued need to increase access to antibiotics in some settings. For them, simply seeing resistance as a health security matter represents too narrow a framing and they argue powerfully that it has emerged at the cost of concern for the world's most vulnerable people. Like others, they argue that antibiotics need to be approached as a precious, public good (Das and Horton, 2016). Usefully, rather than approach antibiotic resistance as an issue of health humani-tarianism, they seek to shift the problem out of this common held binary by placing AMR in the context of the SDGs and argue that this needs to be underpinned through a wider globally agreed goal of ensuring sustainable access to effective medicines.

Elsewhere, Javosky et al (2016) approaching AMR through the lens of the SDGs, identify the way in which the SDGs enable an "adaptive multi-pronged approach" to global issues, enabling action that operates across previously siloed arenas with the involvement of multiple stakeholders. If wicked problems are those that need multiple answers and multiple ways of acting upon them, then it seems likely that an approach that draws on and is underpinned by the SDGs would work well.

For the purposes of this paper, drawing on the SDGs is useful in that it can allow issues of risk to be combined with concerns of equality and the overriding goal of improving health outcomes in a sustainable manner. The commitment of to leave no one behind means that people - rather than medicines or microbes - will always be at the centre of the debate, and AMR cannot be acted upon if it increases inequality of access or health outcomes, or arguably if it does not increase the health outcomes of the worlds poorest and most vulnerable. Moreover, the SDGs have a fundamentally

transformative agenda that could enable a more holistic approach to AMR, with the creation of projects that deal with structural issues such as healthcare infrastructure, the expertise of health workers and the development and scale up of vaccines. While this is one of the least developed analyses of AMR in the literature, it seems likely that this also has the capacity to take in concerns around health system development, drawing out the complex adaptive systems thinking proposed by Tomson and Vlad (Tomson and Vlad 2014).

4.Architecture and Instruments

The Political Declaration of the High-Level Meeting of the General Assembly on AMR contained in Resolution A/RES/71/3 brings a number of elements found in the different frameworks to bear on the subject. AMR is presented as a risk that necessitates a One Health approach to tackle the appearance of resistance in multiple settings, manage market failure in the development of new antibiotics, act on the misuse of medicines by different sectors. AMR is also defined as a threat to the SDGs, which espouse the goals of health humanitarianism, and in particular access to medicines. The role of the WHO as the primary driver in designing the blue print for action on AMR at national level is recognised and the WHOs role as a leader of the global development and stewardship framework was reconfirmed alongside an acknowledgement of the important role that partnerships between governments, the private sector and civil society will play. The Declaration concludes with a paragraph requesting the establishment of an ad hoc interagency coordination group co-chaired by the Executive Office of the UN Secretary-General and the WHO. On 17 March 2017, the Secretary General has announced the official establishment of the Interagency Coordination Group on Antimicrobial Resistance, co-chaired by the UN Deputy Secretary-General and the Director General of the WHO.

Establishing antibiotic efficacy as a global public good

Prior to the 2016 meeting of the General Assembly, other proposals for new forms of global health architecture were developed. New funding mechanisms have been proposed in order to promote the development of commodities to manage AMR through research, the creation of new antibiotics, new combinations of old antibiotics, alternative treatments and diagnostics (Laxminarayan et al., 2013). Through this mechanism the need to access effective antibiotics could be addressed through new medicines, the better targeting of antibiotics could be achieved through new diagnostics, and the path dependencies of AMR could be addressed through the creation of new and alternative forms of treatment, including to vaccines that would reduce the burden of communicable diseases. Antibiotic efficacy could be acted upon as a global public good, to be protected and taken out of the usual mechanisms of pharmaceutical production in which the costs of the production of new medicines are connected to pricing and volumes of sales.

In response to these calls, a not for profit partnership, GARDP, was formed in 2016 to develop new antibiotic treatments with funding from the German, Dutch and UK Governments, the South African Medical Research Council and a number of humanitarian organisations including Medecins Sans

Frontières. It seeks to act on the interconnection between antibiotic resistance and access to medicines in low-income settings and has the following goals:

→ address global public health and specific needs of low- and middle-income countries;
→ target products that industry will likely not develop due to lack of profitability or other reasons;
→ pilot the use of alternative incentive models delinking cost of R&D from volume-based sales and prices of antibiotics, which support conservation of and access to new antibiotics; and
→ ensure that new antibiotics developed by GARDP are affordable to all in need.

(Drugs for Neglected Diseases Initiative, 2016)

In addition, public private partnerships similar to GAVI and the Global Fund have been presented as potential mechanisms through which the funding, development and procurement of new products could be managed, especially for low-income settings. Tomson and Vlad 2014, for example, argue that such a global antibiotic resistance governance coalition could be established to fund the research and development of technologies needed in the containment of antibiotic resistance (Tomson and Vlad, 2014).

As yet, however, there are no proposals for additional funding or increased capacity for organisations to manage AMR by investing in infrastructure in low-income settings.

An intergovernmental panel and high level coordinating mechanisms

Beyond the development of new commodities, forms of collective action have also been proposed to establish global norms, policy and action around AMR. Laxminarayan and colleagues consider that collective action could draw on the Intergovernmental panel on climate change but do not give further details of how or why this could and should be done (Laxminarayan et al., 2016a). Woolhouse and Farrar made a more concerted attempt to argue for an intergovernmental panel on climate change but while they point to the similarities of AMR and climate change (externalities and their global scale and effect) again their proposal is not developed past the desire to have a powerful group to marshal data and inform and encourage the development and implementation of evidence based policy (Woolhouse and Farrar, 2014).

In the build up to the high level meeting, many activists and researchers proposed or supported proposals for the creation of a high level coordinating mechanism (HLCM) modelled on the remit of UNAIDS as its was set out in 1996 (Laxminarayan et al., 2016a, Allergan et al., 2016, PLOS Medicine Editors, 2016). Again, this recognises that AMR goes well beyond the remit of a single international

organisation and instead requires the participation of multiple IOs, states and non-state actors. While membership would have to be negotiated, it has been proposed that this includes governments, international organisations, NGOs, civil society organisations, and possibly philanthro-capitalists and private industry (Laxminarayan et al., 2016a). Laxminarayan who have developed the most comprehensive proposal consider that the HLCM should have four core functions: advocacy, monitoring and evaluation, mobilisation of resources and coordination of multi-sector action, and the definition of resources, goals and metrics to hold governments accountable for progress (PLOS Medicine Editors, 2016). With the emphasis on multi-sector action, this high-level mechanism could also be mandated to establish meaningful links between antibiotic resistance and other SDGs (access to water and sanitation and access to housing, for example) and so act on path dependencies in a way that goes beyond the production and circulation of new commodities. Finally, while it has been conceived as a forum that acts on antibiotic resistance in particular, it also has the potential to provide linkages with other forms of antimicrobial resistance and so enable a more holistic approach to the sustainable use of antimicrobials per se to emerge.

In 2017, following a commitment made at the General Assembly meeting, an ad hoc inter-agency coordination group on AMR was established by the UN. Its objective is to provide "practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance, including options to improve coordination" (United Nations, 2017). It has a breadth of actors from across the United Nations and national level governments and civil society. Private industry and philanthrocapitalists are rightly not represented but of concern is the fact that there is no representation from governments of low-income countries in Africa or Asia.

HR/PHEIC

In on of the earlier papers on AMR and global action, Wernli and colleagues argued that AMR is a threat of such magnitude that it warrants the application of International Health Regulations (IHR) (Wernli et al., 2011). Again, relating AMR to antibiotic resistance rather than a broader category that took in different medicines, Wernli et al. use one carbapenem-resistant bacteria as an illustrative example and argue that its spread could provoke an emergency of international concern (PHEIC), notifiable to the WHO under the IHR notification requirement.

While Wernli et al.'s paper effectively heightening attention to AMR, their suggestion of the applicability of the IHR to AMR was quickly criticised as being based on a misinterpretation of the IHR and in particular of its lack of capacity to manage chronic rather than acute infectious outbreaks, and its inability to provide surveillance and oversight mechanisms (Kamradt-Scott, 2011). In this respect the IHR seem unlikely to be applicable to global efforts to tackle AMR, nor to the global

governance infrastructure that needs to be constructed to deal with the problem. Despite the fact that the health security agenda has been such a critical element in attempts to get AMR on to the agenda at the G7 and G20 meetings, the use of the IHR as a particular instrument to address AMR has not been debated at length in the literature or in international forums following this paper. While Hoffman and colleagues suggest that a new WHO regulation under article 21 could be a useful way of tackling AMR by binding access, conservation and innovation together (Hoffman et al., 2015b), in another Hoffman and colleagues point out the limitations of the IHR in tackling many health problems as governments lack capacity and have yet to report on their implementation status or intentions.

The Paris Declaration

As argued above, contributions to the literature on global governance instruments have been made by drawing on the global governance of climate change, in particular, the Paris Declaration on Climate Change and the Montreal Protocol (Anomaly, 2010, Laxminarayan et al., 2016b). These are considered to hold governments to account and allow for flexibility among countries at different stages of development. Drawing on one of the most successful global governance instruments it has been argued that the Montreal Protocol - a legally binding treaty to phase out chemicals that are harmful to the ozone layer - offers useful lessons for AMR (Anomaly, 2010). It seems that its attraction lies in its perceived ability to effect change, in part via a fund to support its implementation in low-income countries.

While the Montreal Protocol, and other examples of legally binding global mechanisms are important examples of the role that binding treaties can play in global governance, they cannot simply be replicated and expected to have the same effect. Differences in terms of the problem at hand are clear. Ozone gases, the subject of the Montreal Protocol are not the super wicked problem that we find with AMR: the changes in practice required for adherence to the Montreal Protocol were relatively straightforward; the substitution of one chemical for a relatively cheap alternative. No such solutions exist for AMR and it is unclear how such a legally binding instrument could be negotiated, given the issues of balancing excess use and access to antimicrobials, and the need to address path dependency. These issues of the incommensurability of the problem at hand also hold for proposal for an international framework convention, as has been created for tobacco (Anomaly 2010).

Given the complexity of AMR, especially once a One Health approach is taken and the interconnections between animal health and agricultural uses of antibiotics are taken into account, it seems that creating a legally binding global agreement would take many years to negotiate. Moreover,

even if we turn to focus again only on human health, then it is unclear how such a treaty could establish a collective pathway for action that was both effective and that would manage the shifting tension between access to, and excessive use of antimicrobials and the excessive use of antimicrobials as they each appears in different settings in the world. In countries where in which the overuse of antibiotics in the management of human health is the key problem in human health, then targets around the reduction of antimicrobial resistance could be effective without impacting negatively on health. In settings where access and the targeting of medicines remains the most significant health problem, that is where issues of incorrect use and access are both in play, then targets to reduce AMR could be problematic in one of two ways. Either such a treaty would recognise that the reduction of antibiotic resistance was not possible in settings in which access to medicines is the key problem, thus rendering it ineffective in governing AMR in these settings, or it could create a situation in which antibiotic use was more effectively governed but in which there was concurrently a negative impact on access to medicines for the poor.

The role for normative instruments

While there seems to be growing consensus around the understanding that AMR is a serious global problem that requires collective action, and there is increasing agreement that the use of antibiotics in agriculture needs to be substantially reformed, the significance of AMR for human health and the changes that need to occur in relation to human health are yet to take sufficient form to enable treaties to be negotiated. Moreover, scientific evidence on AMR is still relatively undeveloped and, given the scale of funding available for research in many settings, the next twenty years are likely to transform our understanding of the mechanisms through which resistance is formed and through which it can be managed.

With this in mind, normative instruments that can be drawn up with a range of actors involved, guidelines, regulations, codes of conduct continue to offer a much better option through which AMR can be governed at the global level. These forms of global policy offer much more flexibility and can be responsive to improvements in scientific knowledge, changes in country and regional contexts and the ability to incorporate successful change strategies into them. They are, therefore, likely to facilitate on-going response to the dynamic nature of the problem and put into play an on-going discourse between countries that could facilitate learning and change. Suggestions for reporting AMR could draw on the lessons learned for HIV AIDS global reporting mechanisms (Taylor et al., 2014b, Taylor et al., 2014a) which underline the fact that reporting mechanisms need to take into account not only the health security issues around infectious diseases but that they are also focused upon the vulnerability of the people most affected by the disease.

In sum, a review of the problem, its various frameworks, architecture and instruments suggests that the following is required:

a) Action needs to be underpinned by an understanding that antibiotic efficacy is a global public good that is crucial to human well-being. Antibiotics themselves could also be reformulated as global public goods, made accessible to all but in such a way that they are not over-prescribed. This would, however, be a second step following from the first (Moon et al., 2017).

b) As global norms around AMR develop, global governance strategies should move away from interpretation of AMR as health security issue and the call for binding treaties that seems to have gone hand in hand with this approach. Instead, normative instruments that provide flexibility, and support countries as they act on AMR, that can be updated as scientific evidence emerges about resistance and about the effectiveness of different interventions offer a much more effective means of enabling global action.

c) Finally, while there has been action at global level to enable the development of commodities that are needed to manage AMR, attention also needs to turn to the structural and infrastructural drivers of AMR to address path dependencies and reduce the reliance upon antimicrobials for human health.

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