Toward a Grand Bargain: The Incentives, Institutions and Necessary Components of an International Agreement on Antimicrobial Resistance

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EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is an increasing threat to global public health. Despite widespread recognition of the need for immediate collective action to combat resistance, national and international efforts to address AMR have been largely fragmented and uncoordinated. The creation of an international agreement on AMR has been proposed to spur the necessary global response needed. However, for this agreement to be reached, a grand bargain must be struck that fairly balances the burdens and benefits of collective action among state actors.

This report explores some of the issues that must be addressed for a grand bargain to be struck. First we analyze the actions necessary to address AMR and identify the key components of an international agreement on AMR. Next we proceed by proposing burden and benefit sharing principles that should inform an agreement’s development and present a sharing system that translates these principles into action. Lastly, we identify three complementary institutions and eight incentives that would promote stewardship and innovation.

We conclude that an international agreement on AMR must include components such as the harmonization of international standards and mechanisms, global surveillance of AMR, financial support and incentives, and sharing of knowledge and technical information to equitably encourage countries to participate in global collective action.

For an agreement to be acceptable, sustainable and effective, AMR’s burdens and benefits must be shared equitably. To this end, we identify four sharing principles that should inform an agreement’s development. These principles require that burdens be shared in proportion to incidence of AMR, in proportion to economic capacity, in proportion to actions taken to mitigate AMR, and in proportion to the harm imposed domestically by conservation measures. A multi-indicator based burden and benefit sharing system is proposed that could effectively translate these principles into action.

Our research found that development co-benefits and future burden mitigation are the main motivating factors for countries to invest in antimicrobial stewardship and innovation, while the greatest obstacles to participation are largely financial. The proposed incentives and institutions must therefore focus on the economic benefit a country can derive from taking part in the fight against AMR. The incentives proposed to encourage stewardship are categorized as those that reward responsible use of antimicrobials in humans and animals; those that reward contributing to data on AMR and antimicrobial use; and those that reward leadership in the transition away from use of antimicrobials in the agricultural industry. The incentive proposed to re-invigorate the research and development sector is a complex reward system for novel antibiotics and de-linkage of pharmaceutical profitability from sales volume.
INTRODUCTION

Antimicrobial resistance (AMR) is an increasing threat to global public health and annually accounts for an estimated 70,000 deaths worldwide. Based on current trends, AMR is likely to cause more than 10 million deaths annually by 2050. Comparatively, both cancer and diabetes currently account for an estimated 9.7 million deaths annually. AMR’s impacts are also predicted to be economically damaging, with attributed costs rising to 3.5 per cent of global gross domestic product (GDP), or up to $100 trillion by 2050.1

AMR develops when microorganisms, most commonly bacteria, viruses, parasites and fungi, evolve to become resistant to drugs to which they were previously susceptible. While a natural process, the development of resistance is accelerated by inappropriate overuse, misuse and abuse of antimicrobial drugs.2 As geographic borders among countries become less distinct due to increased global trade, societal changes and technological advances, the transport of infectious agents and their AMR genes has become increasingly prevalent and problematic.3 Compounding the problem is the fact that the rate at which antimicrobials are becoming ineffective is faster than that at which new replacement drugs are being developed.4

Despite widespread recognition of the need for immediate global collective action, national and international efforts to address AMR have largely been fragmented and insufficient.5 The complexity of the problem lies in the fact that three interdependent factors - access, innovation, and conservation- need to be simultaneous addressed.6 Firstly, access without innovation and conservation will likely increase the rate of resistance.6 Secondly, innovation without access and conservation is unjust and wasteful respectively. Finally, conservation by its very nature constrains access and undermines innovation.6 In addition, collective action is difficult to achieve because numerous disparities between countries, from economic capacity to rates of resistance, need to be considered and adequately balanced.

This report provides the necessary components of an international agreement that seeks to address these numerous factors. Given the inequalities between countries, this report and by extension the proposed international agreement will be centered on a burden and benefits sharing system. Based on the realization that the greatest obstacles to tackling AMR are often related to financial limitations, this report goes on to discuss a range of incentives and institutions that focus on offsetting financial loss and creating economic opportunities for commitments to AMR action.

TOWARD AN INTERNATIONAL AGREEMENT

Global health institutions, scholars, and policymakers have identified the need for an international AMR agreement to ensure that the problem is effectively addressed. Any global health challenge, including AMR, requires countries to engage in the following ways: (1) by providing leadership and stewardship; (2) by ensuring provision of global public goods; (3) by managing externalities; and (4) by providing direct country assistance.7 Mitigating AMR, however, also requires three unique goals to be simultaneously addressed: access to antimicrobials, innovation of new antimicrobials, and conservation of existing antimicrobials.3 The essential components of an international agreement must therefore address gaps in existing global collective action to fulfill these goals. Table 1 categorizes suggested actions found in literature according to the four engagements of the Global Health System and the three specific goals of AMR that they address.

Essential Components

Based on the categorization of the possible actions (Table 1), the four identified essential components for an international agreement on AMR are: (1) international standards; (2) surveillance, data collection and reporting; (3) financial support and incentives; and (4) knowledge sharing and technical assistance.

1. International Standards

The lack of international standards regarding universal access to antimicrobials, and the responsible use of antimicrobials in humans and livestock may explain the large discrepancies in AMR consumption between countries. Additionally, while the WHO and other international organizations have stressed the importance of uniform standards, given that each organization has specific mandates, there are gaps in the services that they provide.8 As part of the solution, uniform standards regarding the prescription of antimicrobials to humans are necessary. Because the agriculture industry currently accounts for 75% of all AMR consumption worldwide, standards on the use of AMR in agriculture will also play an important role in addressing resistance.3 For example, while there have been many calls to designate human-only classes of antimicrobials, there is yet to be an internationally recognized standard regarding this issue. A lack of standards makes it difficult to quantify the extent to which a country misuses antimicrobials, making it even more difficult to assign responsibility for the problem.4 Therefore, an international agreement on AMR should establish international standards to ensure affordability of antimicrobials while restricting use through guidelines on responsible consumption.

2. Surveillance

One of the major challenges to addressing AMR is the existing gap in surveillance information. Although the World Health Organization passed a resolution to urge member states to develop national surveillance systems to monitor AMR in 1988, little progress had been made until 2014. That year, the WHO released the first global report on AMR surveillance.2 Data from the report, however, is concerning as only 22 countries were able to report on all 9 bacterial species of international concern. Consequently, the problem of surveillance in AMR can be divided into two main issues: (1) there is a lack of collection and reporting of data related to AMR; and (2) even when the data is present, information is not recorded in real time or in a globally compatible format due to inadequate laboratory capacities.4,8,9 A self-reporting memo at the WHO Executive Board Meeting in 2014 further identified lack of laboratory capacity as a primary concern for global AMR surveillance: countries across all income categories confessed to struggling with the laboratory capacities stipulated by the International Health Regulations.

There is currently no information regarding the laboratory capacity for AMR surveillance for individual countries.9 A global
surveillance system is an important component of possible international agreement(s) as it will better frame the AMR problem and allow countries to properly address related issues. Evidence from recent successes in reducing child mortality from pneumonia and diarrhea suggests that streamlined surveillance data as a result of strengthened national institutions is key to adequately addressing global health problems.10

3. Financial Support and Incentives

Development co-benefits are a major motivator for countries to participate in global collective action. Evidence from climate change literature suggests that countries are more strongly motivated by development co-benefits such as job creation and economic growth than dysfunction co-benefits such as disease reduction and decreased mortality are among the least motivating factors.11 Given that development co-benefits are a major determinant of whether countries are willing and able to address AMR, financial support, funding and incentives to help low-income countries is an important component of an international agreement.9 Reviewing data on the efficacy of financial support for aiding global collective action, many scholars have suggested that a grand bargain in AMR has not been reached yet due to the inequitable distribution of its burdens and benefits.12 The section on Sharing Burdens and Benefits will further discuss this principle, and its implication on reaching a grand bargain.

Low-income countries with high rates of AMR are most likely to participate if they do not incur negative immediate economic impacts from addressing the problem. Similar to pollution discussions, these countries pose an important challenge to addressing AMR as they typically have larger populations and risk contributing disproportionately to global resistance.13 Production of antimicrobials that are relevant to these countries’ needs is vital to effectively address AMR. However, the prohibitive costs associated with their discovery and development are a barrier to innovation.14 In addition to the positive impacts on innovation, financial support for AMR initiatives can greatly improve responsible use of antimicrobials in humans and agriculture. As mentioned previously, the lack of laboratory capacities and professional training of healthcare workers worsens the AMR problem.14 Given that low-income countries cannot afford to improve their laboratories or train healthcare workers on AMR and prescription practices, financial support will greatly alleviate such situations and reduce AMR.

4. Knowledge Sharing and Technical Assistance

Literature suggests that the amount of scientific knowledge on AMR is growing rapidly. Knowledge sharing of this growing literature as well as technical assistance can assist countries to develop effective strategies to combat AMR.15 Given that countries have different levels of expertise when it comes to addressing the problem, this may help to achieve a more uniform level of global action. However, knowledge sharing efforts must address two challenges: (1) knowledge is constantly changing and being updated; and (2) knowledge is often fragmented and difficult to access.16 In fact, climate change literature suggests that low-income countries often suffer disproportionately because they do not have access to the most recent information.16 Given the sometimes immediate need for response in infectious disease control, the availability of accurate and up-to-date information is key to addressing global AMR. If information is not shared among countries, and if there is insufficient technical assistance to achieve this goal, there may be duplication of research, wasting both time and resources.17 More grievous, such a lack of knowledge sharing may result in avoidable deaths and create a greater public health burden for countries already struggling to contain outbreaks.

BURDEN AND BENEFIT SHARING

For an international agreement to be accepted, sustainable and effective, the burdens and benefits of both AMR itself and of addressing the problem must be shared equitably between
participants. Researchers have consistently found that a high level of global collective action is required to effectively address the threat of AMR. Because the incidence of AMR and its associated costs are not uniformly felt, however, not all states have the same capacity to act or motivation to address the issue. As seen in Figure 1, incidence of resistance varies considerably, even among developed countries. Therefore, while burdens and benefits remain disproportionate, it will likely be difficult for an agreement to receive widespread support. To address this limitation, AMR’s burdens and benefits must be shared proportionally so that a grand bargain can be struck that encourages participation. To this end, four burden and benefit sharing principles have been identified which should inform the development of an agreement. Based on these principles, a burden and benefit sharing system is proposed, which helps to translate these principles into action.

In addition to AMR’s direct burdens, actions taken to address the problem create burdens and benefits of their own. Logically, the benefits associated with addressing AMR are primarily a reduction of its potential direct burdens. Because direct burdens have been found to be unevenly distributed, it is clear that certain countries will benefit more from actions taken. Therefore, compensatory arrangements may need to be included in an agreement so that countries who are expected to benefit less from addressing AMR still have an incentive to participate.

It is true that actions taken to address AMR may impose additional burdens on certain countries. Antimicrobial conservation measures in particular have the potential to disproportionately burden the domestic industries of some countries. States whose agricultural sectors benefit from the non-therapeutic use of antimicrobials, for example, may experience reduced productivity if antimicrobial conservation initiatives were to be introduced. Similarly, measures taken to limit human antimicrobial consumption have the potential to impede projected growth in several countries’ pharmaceutical industries. Therefore, an international agreement must balance two potentially opposing objectives: maintaining sufficient fairness to receive the consent of all parties, while not placing unreasonable costs on participants who benefit

![Figure 1: Resistance trends of six high priority bacterial- antimicrobial resistance combinations in OECD countries. ∞Includes resistant and intermediate data. *Indicates some data missing.]()
from the inequalities of the status quo. The following four burden sharing principles may help to achieve this balance by informing the development of an agreement that is acceptable, sustainable and effective.

**Burden and Benefit Sharing Principles**

**Principle 1: Countries with higher rates of AMR should have a greater proportion of their burdens shared**

For an agreement to effectively address AMR at the international level, areas with high rates of AMR must be properly managed. Research has found that incidences of AMR are often concentrated in so called “hot-spots”. The existence of these hot-spots is thought to be caused by an array of interrelated factors which include income disparity, climatic influences and even medical tourism. These high-resistance areas contribute significantly to the global pool of resistant genes. Therefore, it has been held that managing these hot-spots is critical to controlling AMR globally. However, countries with high rates of resistance may be reluctant to divert limited resources away from more pressing needs in order to adequately address AMR. It is therefore suggested that countries with higher rates of AMR should have a greater proportion of their burden shared by the international community to increase the effectiveness of interventions, incentives and institutions.

An agreement that shares the burden in proportion to vulnerability may also provide participating countries with a form of insurance against future risk. While there is a general consensus that AMR’s impacts will increase in severity, it is difficult to accurately predict its spread given the unpredictability of bacterial evolution and the variety of factors that drive AMR’s development. As an example, bacteria that produce a powerful drug-resistant enzyme known as New Delhi metallo-betalactamase (NDM 1) were first identified in India in 2008. Within five years these bacteria were being reported in more than 40 countries, often in individuals with no links to the region where the strain was initially discovered. This demonstrates that there is no guarantee that the relatively low incidence of AMR that some countries experience will last. Therefore, countries may be more willing to enter and remain part of an agreement if they can be assured that the burden will be shared should they face disproportionate pressure from AMR in the future.

**Principle 2: Countries with greater economic capacity should be responsible for a proportionately larger share of burden**

Countries with the ability to shoulder greater costs should be responsible for a proportionately larger share of AMR’s direct burdens. While this may make an agreement less appealing to high-income countries, it is likely necessary for an agreement to be effective. Unfortunately, any use of antimicrobials, even if appropriate and conservative, contributes to the development of resistance. However, because poverty is a major factor in the development of resistance, AMR’s burdens currently affect developing economies disproportionately more than developed ones. Poverty encourages behavior that accelerates the development of resistance, such as the consumption of sub-standard, counterfeit or expired drugs and the sub-therapeutic dosing of antimicrobials. When combined with inadequate sanitation and poor access to health care facilities, these practices allow for AMR to thrive. It will be very difficult, given these practical realities and the immediate threat of the problem, for developing countries to effectively address AMR without some level of assistance. The sharing of burdens by countries with greater economic capacity, therefore, may be necessary for an agreement on AMR to be effective at the global level.

**Principle 3: Countries should benefit proportionately to mitigate actions taken**

An agreement is more likely to be acceptable and sustainable if countries can expect to benefit proportionately for taking greater steps towards addressing the problem. The benefits of addressing AMR derive from a reduction of its potential future
burdens. Since burdens are unevenly distributed, some countries will likely benefit disproportionately from actions taken to reduce or manage resistance. Altruistic purposes aside, countries have been found to be generally hesitant to accept international agreements and maintain contributions towards addressing a problem if their actions result in minimal domestic benefits. Therefore, sharing arrangements should be informed by a principle, which states that countries will receive assistance and reimbursements in proportion to the actions that they take towards addressing AMR.

Principle 4: Countries should not be disproportionately harmed by efforts to address AMR

For an agreement on AMR to be accepted and effective, burden sharing arrangements that help countries mitigate the expense of imposing greater limits on antimicrobial use will likely be necessary. Despite AMR's significant costs, certain countries benefit economically from the limited regulation of antimicrobial consumption in humans and livestock. In several low and middle-income countries, for example, the demand for animal protein has led both to economic growth and to the increased non-therapeutic use of antibiotics in the agricultural sector. In fact, the majority of global antibiotic consumption now occurs in an agricultural setting. The distribution of global agricultural use can be seen in Figure 2. This upward trend is expected to remain, with agricultural use projected to rise by 67% by 2030 in low and middle-income countries and nearly double in the BRICS countries (i.e., Brazil, Russia, China, India and South Africa).

As previously mentioned, countries may be hesitant to accept an agreement if it would necessitate antimicrobial conservation measures that could disproportionately harm their domestic industries. This could limit an agreement's effectiveness, given that participation by the BRICS and other countries with high consumption levels has been seen as imperative for addressing the problem and for promoting action by other developing states. Thus, burden sharing arrangements ought to be informed by the principle that states should not be unduly harmed by actions taken to address AMR.

Burden and Benefit Sharing System

To support an agreement that is acceptable, sustainable and effective, a multi-indicator-based burden and benefit sharing system is proposed that translates the four previously identified sharing principles into action. A review of existing international agreements suggests that such a system would likely be appropriate in the context of AMR. At its core, this system relies on a series of indicators that provide information about a country's ability to share burdens and benefits. These
indicators are used to calculate actor scores, which specify the proportion of contributions for which a country is responsible and the assistance to which they are entitled. An illustration of how this system operates is shown in Figure 3.

Such systems are most effective when there are numerous disparities between countries. With regard to AMR, multiple disparities are clearly present, including in relation to economic capacity and incidence of resistance. Furthermore, when compared to other sharing arrangements, multi-indicators-based systems are thought to be more promising for successful negotiations because there are more areas in which bargains can be struck. Therefore, the proposed system may not only be appropriate given the context, but may also contribute to an agreement’s acceptability.

The system relies on surveillance and reporting information collected by the Global AMR Surveillance Institute. This institution, which is described below in the section entitled “Incentives and Institutions”, would also be responsible for calculating the indicator values and actor scores of countries. However, it should be noted that for this system to be functionally equitable, appropriate weights for the indicator scores would have to be determined. This would require considerable economic calculation and is beyond the scope of this report.

Assignment of Contributions and Assistance Based on Actor Scores

The system determines the extent of contributions for which a country is responsible for or the level of assistance for which a country is eligible based on individually calculated actor scores. Contributions and assistance may either take the form of direct financial aid or the provision of technical assistance. Actor scores for contributions are primarily based on an economic capacity indicator. The score is then reduced through the subtraction of an AMR incidence indicator. A higher final value indicates that a country should be responsible for a greater proportion of contributions. Actor scores for assistance are formed by adding three individual indicators: the mitigation efforts indicator, the AMR incidence indicator, and the domestic harm indicator. A higher final value indicates that a country should be eligible for a proportionally larger share of assistance.

AMR Incidence Indicator

The AMR incidence indicator is a reflection of Principle 1, which requires that countries with higher rates of AMR should have a greater proportion of their burdens shared. This indicator’s value would represent the severity of AMR in a given country. It would be calculated based on health information provided by reporting and surveillance, such as resistant infection rates and AMR attributed mortality rates.

Economic Capacity Indicator

The economic capacity indicator is a reflection of Principle 2, which states that countries with greater economic capacity should be responsible for a proportionately larger share of burdens. This indicator’s value would represent a country’s ability to pay or contribute resource based solely on its economic status. It would be calculated based on readily available economic measurements, such as a country’s GDP.
Mitigation Efforts Indicator

The mitigation efforts indicator is a reflection of Principle 3, which maintains that countries should benefit proportionately to mitigation actions taken. This indicator’s value would represent the degree to which a country has taken efforts to address AMR domestically. It could be calculated based on the percent of GDP that a country spends on addressing the issue. Alternatively, it could be calculated based on a checklist of necessary actions that have been established by the proposed institutions. Countries who complete a higher number of these actions would see their mitigation efforts indicator increase.

Domestic Harm Indicator

The domestic harm indicator is a reflection of Principle 4, which states that countries should not be disproportionately harmed by efforts to address AMR. This indicator’s value would represent the extent of loss experienced by domestic industries that is attributed to AMR conservation measures. It would initially be calculated based on economic projections. As conservation measures are introduced, calculations would come to rely on surveillance and reporting data to ensure that an accurate representation of actual domestic harm is made.

INCENTIVES AND INSTITUTIONS

Despite widespread recognition of the need for global collective action, coordinated international efforts to address AMR have been limited. Motivation for countries to invest in antimicrobial innovation and stewardship lies primarily in development co-benefits and future burden mitigation. Therefore, one reason why countries may be hesitant to act is because addressing AMR imposes high up-front costs, with results that may not necessarily be realized in the immediate future. The existence of free-riders may also act as a disincentive for action if states perceive that their efforts are being negated by others’ actions. Therefore, incentives and institutions that support actions and minimize externalities are necessary for coordinated global action.

Recommended Institutions

AMR Surveillance Institution

The AMR Surveillance Institution will act as the authority for data collection, interpretation, and recommendations for stewardship of antimicrobials, including country-specific targets for inappropriate use reduction. To motivate countries to abide by best practices in stewardship, the institute’s reports will detail the trends in global AMR, including naming countries who fall below targets for reduction and those that have not implemented stewardship policies. The institute will also be responsible for calculating countries’ indicator values and actor scores. These scores will be shared with the Institute of Innovation to determine funding for research and development.

Institute for AMR in Agriculture

The Institute for AMR in Agriculture’s mandate will be to help agriculture industries transition away from the excessive use of antimicrobials. This institution will be tasked with creating and publishing a detailed economic analysis of the transition costs to lower antibiotic use in farming practices in different regions and countries. This will help inform countries of the appropriate targets for reduction and limits on use of antimicrobials in animal husbandry. It will also provide important information to food producers on the actual economic benefits and costs of antimicrobial use in the food production system.

Institute of Innovation

The Institute of Innovation will govern the Global Innovation Fund and determine where investment should be prioritized. It will receive information on countries’ mitigation efforts from the Global Surveillance Institute and will determine innovation
funding based on burden and benefit sharing principles.

**Incentives for the responsible use of antimicrobials in humans**

**Incentive 1: Increased Funding Toward Innovation for a Reduction in Inappropriate Prescription by Healthcare Professionals**

Reducing inappropriate use of antimicrobials is essential to reducing antimicrobial resistance. A study on the prevalence of inappropriate antibiotic prescription in ambulatory care visits in the United States demonstrated that 30% of prescriptions were likely inappropriate.41 The drivers of inappropriate use in human health are multifactorial: these include cultural perceptions of antimicrobials as confirmation of illness and vindication of being unwell, a lack of education of healthcare professionals and the public on the harmful effects of inappropriate use on population health, and aggressive marketing by pharmaceutical companies.42

It is recommended that countries that meet or exceed the targets for reducing inappropriate antimicrobial prescription, as determined by the AMR Surveillance Institute, will receive additional funds from the Institute of Innovation. The additional funding amount will be determined by the calculation of their mitigation efforts indicator. In addition to reduced funding, if poor stewardship remains a problem in a country that is not enacting proper conservation measures, the global community should agree to restrict access in the event that a novel antibiotic is discovered until it can be assured that the new drug would be used appropriately and with restraint.

**Incentive 2: “Ready-to-Go” Education and Training to Standardize Prescription Practices**

To reduce demand for antimicrobials a massive global awareness campaign targeted at health practitioners is proposed. This campaign would educate those with the authority to prescribe so as to control the unnecessary consumption of antimicrobials in humans. An incentive to participation would center on easing countries’ ability to initiate this campaign by creating “ready-to-go” material translated into the languages of the recipient country. This would help by removing the significant temporal and financial hurdles required to develop educational materials. Although not a necessary component for a grand bargain, high-income countries that are contributing large sums of money to develop new drugs will be reassured by a push for increased stewardship and health literacy in the countries that receive subsidized medication and technology. Improved stewardship efforts will lead to increased effectiveness of expensive interventions as well as improving public health and reducing the need for subsidized medication in the future. The AMR Surveillance Institution, whose mandate includes developing best practices in antibiotic prescription and stewardship, will create the educational material. This incentive will be uniformly provided to high and low income countries, as the cost for manufacturing the physical materials and airtime on television and radio will be borne by the countries themselves.

**Incentive 3: Prizes, Grants and Advanced Purchase Commitments for De-Linkage**

The pharmaceutical industry’s business model is based on market exclusivity of their products due to patenting laws. This model allows the patent holders to demand high prices until the period of exclusivity expires. Generic competitors are then allowed to enter the market and compete for sales. The flooding of the market creates a high-pressure race to sell a high volume of product before resistance accelerates. This unsustainable business model encourages aggressive marketing techniques and over-consumption of antimicrobials.43 Exacerbating the issue is the declining productivity of R&D and rising costs of commercialization that increase the pressure on companies to focus on strategies that increase the returns from the existing product portfolio.44 In achieving a global agreement on AMR, it is necessary that all countries agree to de-link sales volume from pharmaceutical
developers’ profitability. Doing so would require countries to mandate bans on direct advertising to medical professionals and require that agricultural producers obtain prescriptions in order to treat animals with antimicrobials.1

It is proposed that the Institute of Innovation provide financial incentives in the form of milestone prizes, academic grants, funding of clinical trials, market-entry rewards, and advanced purchase commitments to alleviate the drive to oversupply antimicrobials by generating a return on pharmaceutical developers’ investment that is independent from the market. The Global Innovation Fund will be administered utilizing the burden and benefit sharing principle that countries should benefit proportionately to mitigation actions taken. For example, a country that has proven to abide by stewardship standards will receive proportionately more funding for R&D, as determined by the AMR Surveillance Institute’s mitigation efforts indicator calculation.

Creating an incentive package that achieves de-linkage while also providing enough financial motivation to pharmaceutical companies is a linchpin to having an international agreement on AMR. The ideal incentive package for both of these goals would include several incentives that facilitate cooperation and synergy throughout the market, one or more R&D-linked push incentives and a significant pull incentive rewarding successful development.43 Of the models suggested in the literature, the WHO’s Global Consortium appears to be one of the most robust for stimulating antibiotic R&D. The model is comprised of five parts: (1) support at the drug discovery stage through milestone prizes and an open source platform, (2) push mechanisms in the form of grants for academics, small and large pharmaceutical firms to remove the risk of investing in R&D, (3) patent buyout prizes for proven novel antibiotics, (4) public funding of clinical trials and (5) advance purchase commitments with conditions to preserve the new antibiotics.45 The WHO model attempts to create a product-development partnership (PDP) across the entire pharmaceutical value chain. This structure shifts significant cost and risk to the public sector and would require global agreement to uphold the integrity of the program by requiring de-linkage of sales volume and pharmaceutical industry profitability.46

The de-linkage models that posit transferring intellectual property to the public domain would remove the obstacles in the implementation of such a de-linkage policy. However, this model would create a greater risk exposure for pharmaceutical companies that could lose substantial profit if the suggested IP reward commitments are reneged.43 An alternative to patent buyout would be a Market Entry Reward that would compensate for the revenue lost with de-linkage. Market Entry Rewards are financial awards for successful drugs that have been approved to enter the market and would be proportionate to the unmet medical need the drug addresses. Given the scope of this model, challenges such as obtaining adequate financing and creating an agreement with the pharmaceutical industry on IP rights may prove too vast to overcome.47

**Incentives for Surveillance**

**Incentive 4: Compilation of ‘Big Data’ on AMR, and Open Access Information**

Surveillance is a cornerstone of infectious disease management and must be prioritized in the fight against AMR. Surveillance is needed to detect resistant microorganisms, follow their spread among geographic areas and enable outbreaks to be investigated and treated quickly. Tracking use and misuse of antimicrobials with uniform and high quality data collection methods would allow the AMR Surveillance Institution to make policy recommendations and monitor the effectiveness of interventions countries have taken.48 The Global AMR Surveillance System (GLASS) developed and overseen by the WHO is the most comprehensive surveillance system in place, however members participate on a voluntary basis.1 Given the urgent need for data, participation in the program should be prioritized for global agreement on AMR to
ensure accountability and to inform health policy. Participation in this program will count positively in the determination of a country’s mitigation efforts indicator.

Having an external body analyze data and recommend policy changes will shift the burden away from participating countries. High-income countries benefit from funding surveillance in low-income countries, as the data generated would serve as an early warning sign of developments in AMR and forecast how it may spread to their own country. Generating ‘big data’ is incentivizing to countries of all income levels as the conclusions would inform policy decisions, economic investment and generally improve overall public health. Big data in AMR will be instrumental in informing decisions on the areas of research and innovation that should be prioritized by the Institute of Innovation. Low-income countries that do not have the infrastructure and data management capabilities to routinely collect, analyze and monitor AMR data will receive administrative assistance and financial support for implementation through allocations calculated by the burden sharing system.

Incentives to Reduce Antimicrobial use in Agriculture

Incentive 5: Leadership Rewards for Antibiotic-free Animal Husbandry

Countries who take proactive measures in legislation or policy creation that limit the use of antibiotics in animal husbandry will be rewarded with additional direct funding and technical support through the burden sharing system. By introducing national-level restrictions, a country will be credited with increasing their AMR mitigation efforts in the calculation of their mitigation efforts indicator. This will help to offset the loss of productivity due to conservation measures in the agriculture sector.

The AMR in Agriculture Institute, funded through pooled resources, will provide direct financial incentives to companies who show leadership in adhering to the raising of animals without antibiotics and improving hygiene standards to reduce spread of infection, independent of their country’s regulations. As part of this leadership reward, companies will be permitted to use a “raised without antibiotics” seal for products. An internationally accredited seal would be a motivating factor for companies who desire to market their food product as a better option for public health and influence consumer behaviour to value antibiotic-free products.

Incentives for Innovation

Incentive 6: Market Entry Rewards as Part of an Incentive Package

Large-scale intervention is necessary to reverse the long-term disinvestment from antibiotic research and development. Achieving a functioning pipeline will depend on aligning public and private incentives to invest in R&D with public health needs, drawing on the expertise and creativity of research teams in all countries. Clinical trials represent 80% of the cost of bringing a new antibiotic to market. The enormous cost of developing an antibiotic and the high risk of failure or inefficacy makes the market unattractive to pharmaceutical companies. Reducing the cost of clinical trials without compromising their quality of safety is a key target for addressing a stalled innovation pipeline and will require international cooperation.

Market Entry Rewards are proposed as an incentive to spur antimicrobial R&D as a modification to the WHO Global Consortium incentive package described in Incentive 2. A points system has been suggested to determine the quantification of the appropriate Market Entry Reward based on the drug’s level of unmet need, toxicity, efficacy and its ability to counter resistance. This reward would be calculated and administered by the Institute of Innovation. As a condition of receiving the reward, companies would be contractually
obligated to bar all financial incentives for clinicians who prescribe their product, to de-link the volume of sales and salesperson income, and would be required to offer the drug at affordable prices to low-income countries that lack access.

Low-income countries could participate in the research and development of new antimicrobials by conducting clinical trials and hosting laboratories as part of partnership agreements with high-income countries where pharmaceutical companies are based. High-income countries and the Institute of Innovation could provide technical assistance to the low-income countries on standards related to clinical trials. Low-income countries are traditionally underrepresented in research and would benefit economically from hosting. Pharmaceutical companies would benefit from decreased trial costs and reduced bureaucracy, an attractive incentive that could be a powerful force motivating global action on innovation.50

Incentive 7: Increase Funding and use of Vaccines as an Alternative to Antimicrobials

There is a growing appreciation for the role of vaccines in tackling AMR. Vaccines can reduce the prevalence of resistance by reducing the need for antimicrobial use and can reduce its impact by reducing the total number of cases. Vaccines can also help narrow the use of antimicrobials to a smaller number of pathogens. Some vaccines have had disproportionate effects on drug-resistant lineages within the targets species, a benefit that could be deliberately exploited in vaccine design.51 Vaccine programs have historically been proven to be very cost-effective with direct and societal benefit-cost ratios of 3.0 and 10.1.22 For this reason, alternatives to antimicrobials such as phage therapy, lysins, antibodies, probiotics, immune stimulation, peptides and gene editing should be a secondary focus of investment from governments and NGO’s.1 Vaccine R&D funding currently lags behind antibiotic research, representing only 3% of the global pharmaceutical market.1

Because vaccines tend to be a less profitable market, they require national-level purchasing commitments from governments and national health bodies to ensure that the R&D phase is financially viable. The challenges in vaccine development are similar to the challenges for POC diagnostic tools. Therefore, similar lump-sum rewards for new promising early-stage research should be implemented along with Market Entry Rewards for vaccines that are approved for entry to the markets. The rewards would be dispersed by the Global Innovation Fund based on its estimation of the usefulness of the vaccine.

Low-income countries that are unable to financially contribute to funding innovation could contribute by hosting laboratories and trials. These countries would be incentivized to participate in partnerships with high-income countries because of the injection of income and economic growth they would gain. This arrangement would allow companies to find an adequate study sample size to ensure the efficacy of their vaccine, and would reduce the financial risk for developers. In return for the funding of the vaccine programme, the health care providers of recipient countries would commit to providing high quality data to the AMR Surveillance Institution on the results of all trials and experiments.

Incentive 8: Market Entry Rewards to Develop and Fast-Track New Antibiotics

Rapid diagnostics tools are needed to reduce inappropriate prescription and consumption of antimicrobials, slow AMR growth and prolong the life of existing drugs.1 Prescription based on symptomatology, rather than on verifiable evidence, increases the use of incorrect antimicrobials. By funding point-of-care (POC) diagnostic tools, clinicians will have access to better instruments to help them quickly and accurately identify illness-causing pathogens and prescribe appropriate treatments.1

The incentive to motivate high-income countries to invest more in their own R&D sectors is that their investment would be counted as a mitigation effort in the calculation of their
mitigation efforts indicator, unleashing additional funding for research and creating a positive-feedback arrangement. Beyond this, there is inherent motivation for countries to invest in R&D: it creates employment opportunities domestically and may attract international scientific talent.

To incentivize the funding of R&D in POC diagnostic tools, a Global Market Entry Rewards system that pays lump-sum amounts for new intellectual property during the early stages of production should be implemented. The promise of these rewards would provide financial incentive to inventors by increasing likelihood of profitability and thereby, their motivation to pursue innovative ideas. The Institute of Innovation will create contractual commitments with manufacturers to ensure the purchase of these tools for low-income countries that lack the financial capability to do so independently.

Low-income countries that do not have the capacity to spend additional money on R&D investment could be incentivized to contribute to this goal by assisting in the trials of POC diagnostic tools. The tools would be provided to the countries free of charge, with the stipulation that all clinicians using the tools must collect data and report findings on their effectiveness to the manufacturing country and the scientific and medical data to the surveillance institution. Furthermore, hosting would contribute towards the country’s mitigation efforts indicators, which would result in them being eligible for a greater proportion of international assistance and funding.

Incentives to motivate countries to action should be based on their economic benefits. The suggested institutions to lead the fight against AMR are the Surveillance Institute, AMR in Agriculture Institute and the Institute of Innovation. These institutes will administer incentives that focus on appropriate use of antimicrobials in humans and animals. It will also provide incentives to increase investment in R&D for novel antibiotics and diagnostic tools. The amount of funding countries will receive will increase according to their AMR mitigation efforts. This approach favours positive and proactive actions that are rooted in the economic and political realities of a global community. By combining these incentives and institutions with the proposed burden and benefits sharing system, a grand bargain may be struck that would allow coordinated global action to effectively address the threat of antimicrobial resistance.

CONCLUSION

Global collective action is necessary to halt the approach of a post-antibiotic era. An international agreement on AMR must focus on harmonizing international standards to help ensure the responsible use of antimicrobials in humans and livestock. It must also prioritize surveillance and reporting so that timely and efficient health care policies can be created. Finally, an agreement must allow for financial support, technical assistance and knowledge to be shared among countries.

For an agreement to be accepted, effective and sustainable, AMR’s burden and benefit must be equitably shared between countries. To address this, a burden and benefit sharing system is proposed that seeks to balance disparities. The system, which operates in conjunction with the proposed institutions, allows for equitable sharing by calculating the proportion of contributions for which a country is responsible and the level of assistance to which they are entitled. This system’s design is informed by four principles, which require that burdens and benefits are shared based on an individual country’s economic capacity, the domestic AMR incidence, the extent of efforts that they have taken to address AMR, and the harm that conservation measures are predicted to impose domestically.
The essential components for an international agreement on AMR include harmonizing international standards and mechanisms, improving global surveillance of AMR, providing financial support and incentives, and sharing knowledge and technical information.

An acceptable, effective, and sustainable agreement should reflect four burden and benefit sharing principles: burdens should be shared in proportion to incidence of AMR, in proportion to economic capacity, in proportion to actions taken to mitigate AMR, and in proportion to the harm imposed domestically by conservation measures.

The creation of incentives and institutions must be informed by the sharing principles and must also function in tandem with burden and benefit sharing arrangements.

Obstacles to invest in innovation and stewardship are primarily financial, therefore incentives and institutions must focus on economic benefits acquired through participation.

The most important incentives are those that lead to a reduction of inappropriate use of antimicrobials and a creation of an attractive market for investing in research and development of new antimicrobials.
REFERENCES


APPENDIX

METHODS

An extended literature review was conducted to identify the most recommended actions to address global AMR. Identified actions were categorized according to the four engagements necessary to successfully address any global health issue as described by Jamieson (2013): (1) leadership & stewardship; (2) ensuring provision of global public goods; (3) management of externalities; (4) and direct country assistance. Actions were further sorted according to the relevant AMR goal that it aimed to achieve: access; innovation; and conservation. The goals of access, innovation and conservation was divided into specific goals to better analyze the relationship between the recommended actions and their desired results. These specific goals were compiled from existing action plans from the WHO and other organizations.

A review of these action plans identified four major gaps that explain the misalignment between recommended actions and current impacts. These gaps, or rather the proposed actions to address these gaps, acted as the basis for the essential components of an international agreement on AMR. A review of successful climate change agreements further explained the need for the four identified essential components in the report.

The common challenge in implementing the four essential components of the report was identified as the issue of burden and benefit sharing. Namely, a review of literature found four main challenges to striking a grand bargain in AMR related to burden and benefits sharing arrangements. These problems were addressed as guiding principles for ensuring global collective action. Based on the indicators identified in the Review on Antimicrobial Report (2016) and through a comprehensive review of existing agreements on climate change, refugee protection, and pandemic influenza preparedness, specific burden and benefit sharing arrangements were suggested to strike a grand bargain and achieve global collective action.

The burden and benefit sharing principles and arrangements also informed the decision for the specific incentives and institutions recommended in the report. The recommended incentives and institutions relied on the initial literature review on recommended actions to address individual goals of access, innovation and conservation. Given that actions needed to address access are included in the recommendation for innovation and conservation, the report proposed 8 specific incentives and 3 institutions to address AMR. In addition to existing institutions, all the recommended incentives were designed to be achieved by the recommended institutions.

PROVENANCE STATEMENT

The authors contributed equally to complete initial background research, design methods and finalize the report. The executive summary and conclusion were also written collaboratively. NA was responsible for compiling a literature review of recommended actions, writing the introduction and methods, and for identifying the necessary components of an international agreement (Toward an International Agreement). CT was responsible for categorizing the burden and benefit sharing principles, developing the sharing system, formatting the final report and collecting photos for the report. EB took the lead identifying the incentives and institutions necessary to motivate global collective action on AMR.