Using International Instruments to Address Antimicrobial Resistance

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The Global Health Law Clinic is an experiential learning opportunity for students to apply their previous studies to real-world global health practice. Students work in teams to provide a United Nations agency, government, or civil society partner with research, analysis and advice on addressing a pressing global health challenge facing them.

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The Global Strategy Lab, directed by Steven J. Hoffman, is an interdisciplinary research program based at the University of Ottawa’s Faculty of Law. The Lab brings cutting-edge science and scholarship to bear on how global institutions, instruments and initiatives are designed to better address transnational health threats and social inequalities.
EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is a global health concern that poses a serious threat to the control of infectious disease. A continuous increase in rates of AMR poses a challenge to the global community and impedes progress previously made in improving health outcomes. It has, for example, increased patient morbidity and mortality, limited options for treatment, and increased the length of hospital stays. The ultimate result is a costly burden on individuals and communities affected by microbial infections in both developed and developing countries.

This report examines how AMR can be addressed using international instruments, and the appropriate role of the World Health Organization (WHO) in this task. It is recommended that global collective action on AMR be achieved by implementing a Treaty under Article 19 and a Regulation under Article 21 of the WHO’s Constitution. This suite of international instruments can be used to address the greatest proportion of issues that currently impede AMR’s resolution and can mobilize the most effective action.

This report further establishes that the WHO has legal authority under its Constitution to create these international instruments to address AMR. Further, the WHO’s institutional experience and global influence will encourage international participation. Potential international instruments for AMR are compared against existing frameworks implemented by the WHO and the United Nations. This comparison highlights the benefits and challenges that should be considered in the adoption of an international instrument to address AMR.

Recommendations and conclusions were drawn from an extensive review of current research literature in the field of AMR, a gap analysis of the current and desired states of global AMR action, and a modified Pareto analysis to select the suite of international instruments.
BACKGROUND

Antimicrobial resistance (AMR) is a global public health concern that poses a grave threat to the control of infectious disease. The World Health Organization (WHO) has identified increasing rates of AMR in all regions of the globe. An estimated 3.6% of new TB cases and 20.2% of previously treated cases worldwide are thought to be multidrug-resistant TB, with much higher incidence rates in Eastern Europe and Central Asia. Resistance to the antimalarial drug Artemisinin was detected in Cambodia, Myanmar, Thailand, and Vietnam. The ever-increasing rates of AMR significantly challenge the progress made on health outcomes in manners including: increasing patient morbidity and mortality, limiting options for treatment, increasing the length of hospital stays and inflicting significant costs on society. In the European Union (EU), it is estimated that approximately 25,000 patients die each year as a direct consequence of multidrug-resistant infections, with an associated cost of 1.5 billion euros per year. In the United States, more than two million people fall ill every year with AMR infections, and 23,000 people die as a result. The economic cost of AMR for the American health care system is more than US$20 billion annually, and the societal value as a result of the loss of productivity is US$35 billion per year. If AMR is not addressed, it is estimated that 300 million additional people will die globally by 2050 and it is expected that the global economy will lose between US$60 and $100 trillion.

This report examines how international instruments can be used to combat AMR globally; how to mitigate the risks associated with the spread of AMR; and whether WHO is best suited to address this issue. The purpose of this report is to recommend an international instrument or a suite of international instruments best suited to combat AMR on a global level. This report identifies eleven primary problems to concerted global action on AMR. An international instrument is then paired to each of the eleven problems. A modified Pareto analysis then prioritizes the paired international instruments to maximize efficiency of effort and resources. Further, this report confirms that WHO is well situated to advance an international instrument on this issue. Based on this finding, this report recommends adopting two international instruments; the first, a WHO Treaty, and the second, a WHO Regulation.

GAP ANALYSIS AND INSTRUMENT RECOMMENDATION

It is widely acknowledged that resolving the global health threat that AMR poses requires concerted global action. Currently, a considerable number of States across the world have demonstrated an active willingness to solve AMR by undertaking diverse initiatives domestically to address this issue. Most of these initiatives are multi-sectorial in nature. For example, Canada’s Federal Action Plan on Antimicrobial Resistance and Use in Canada and the German Antimicrobial Resistance Strategy combine strategies on rational use of antimicrobial drugs, establishment of surveillance systems, and innovation of new medicines.

Despite the efforts of individual States, AMR continues to be influenced by cross-border trade, and international mobility of people and goods. The global character of AMR requires harmonized State action. An international instrument or...
suite of instruments will outline the solutions that, when implemented by all countries jointly, lead to unified action. The literature identifies a significant number of impediments to solving AMR. This report has identified and analyzed eleven of these primary problems.

These problems have been organized under the policy headings of Access, Conservation, and Innovation to reflect the body of literature from which they are drawn. Access measures allow the largest number of people to receive appropriate antimicrobials to combat disease. Conservation measures limit the inappropriate use of antimicrobials for the purpose of slowing the development of AMR. Innovation measures promote the development of new drugs for which bacteria, viruses, parasites and fungi are not yet resistant. Considerations for selection of the instruments include: jurisdictional reach of the instrument; limitations of the instrument; restrictions on content for the instrument; economic factors; and lessons learned from past implementation of similar international instruments. A description of the full range of international instruments considered for selection is presented in the Web Appendix.

**Access**

**Problem 1: Insufficient financial resources for health systems infrastructure in low-and-middle income countries**

Weak national health systems in low- and middle-income countries (LMICs) pose a significant threat to the spread of AMR. Since “[s]trong health systems are the backbone of reducing the global threat of [AMR],” LMICs must have the financial means to secure stronger laboratory and surveillance systems as well as infection prevention programs. Unfortunately, there is widespread consensus that existing financing resources dedicated to health care are insufficient, and as such, significant international resources must be acquired to support the poorest countries. Compounding this problem is corruption at the state level. Even in countries where more financial resources exist, corruption has sometimes led to the diversion of funds from intended health services.

Potential solution to Problem 1

- Development assistance
- Conditional grants
- Anti-corruption measures

To ensure financial resources are available to LMICs, sufficient and predictable development assistance should be leveraged to guarantee that there is adequate cooperation between countries, involving customs, suppliers, medical institutions and the police. This assistance would ideally support the goal of ensuring that LMICs are able to achieve minimum standards for “infection prevention, laboratory and surveillance systems.” Internationally, governments are the largest source of development assistance for health (DAH), accounting for approximately 70% of the total aid. However, private sources of funding including foundations, NGOs, and corporations, have grown in importance. As of 2010, private sources accounted for 15% of DAH and the largest single contributor was the Bill & Melinda Gates Foundation.

Conditional grants from the World Bank and International Monetary Fund (IMF), based on policy implementation, can also be leveraged to strengthen health systems infrastructure in LMICs. For example, the International Development Association (IDA) is the World Bank’s fund for the poorest countries. It provides assistance through grants and loans to support a range of development activities—one of which could be reinforcing health systems. However, strengthening health infrastructure for the purposes of laboratory surveillance systems, for example, may not realistically be a primary concern for some of the poorest countries which face more pressing issues like basic access to clean drinking water. Finally, financial resources, whether acquired through development assistance or otherwise, should be appropriately
disbursed free from corruption at the state level. Defined as “the abuse of entrusted power for private gain,”\textsuperscript{10} corruption diverts funds and lines pockets. Not surprisingly, less corrupt countries are more attractive investments for private investors and donors alike.\textsuperscript{11}

**Recommended International Instrument: Treaty**

A Treaty, per Article 19 of the WHO Constitution, is likely the most effective legal instrument to address the lack of financial resources for health systems infrastructure. The multifaceted character of health systems requires that the breadth of content allowable under the chosen international instrument be comprehensive; a Treaty is the only legal instrument that permits this expansive scope. This is necessary because there cannot be an assumption that all countries are operating a “functional health system.”\textsuperscript{12} A Treaty allows for the inclusion of a development assistance plan and conditional grants to support developing countries in the improvement of their health systems. A Treaty would address the effectiveness, predictability, and equity of these financing mechanisms. Resource-sharing among States through development assistance programs requires mutual reliance among countries and would therefore benefit from the formality of a Treaty. Similarly, conditional grants also fall within the scope of a Treaty and would benefit from the compliance mechanisms available through that instrument to ensure obligations between States and donors are honoured. The IHR were adopted without any concrete financing mechanisms. The adoption of a regulation under Article 21 of the WHO’s Constitution is therefore not recommended to address the financing of health systems. This is founded in the argument that “[s]ustained multilateral and bilateral partnerships are clearly needed for low-income countries to make progress with their capacity to detect and contain global health threats.”\textsuperscript{13} Notwithstanding this, formal funding mechanisms may also be required to enable LMICs to implement this Treaty if minimal health systems standards are a requirement.\textsuperscript{12, 14}

To address corruption, a Protocol could be adopted to supplement the umbrella AMR Treaty. Like the Protocol to Eliminate Illicit Trade in Tobacco Products (PEITTP) under the WHO Framework Convention on Tobacco Control (FCTC), an anti-corruption Protocol could provide additional guidance to States who choose to ratify both the umbrella Treaty and the Protocol. Specifically, a medicines-related anti-corruption Protocol could address measures to be taken to eliminate diversion of funds, counterfeit medicines, falsified prescriptions and substandard medicines. Parties to the Treaty are not obligated to become signatories and to ratify an accompanying Protocol.\textsuperscript{15} This can lead to limited acceptance among States; for example, although the FCTC has 180 parties to the agreement, only 54 States have signed the accompanying PEITTP, and of those, 15 have ratified it. The PEITTP requires 40 States to ratify the agreement before it can enter into force; therefore, the Protocol is not yet enforceable.\textsuperscript{15} As such, the weight given to an Anti-Corruption Protocol should reflect this hurdle.

**Problem 2: Insufficient funding for access to antimicrobials**

The increasing rate of AMR suggests that more antimicrobials are becoming ineffective. Due to the cost of drug development, effective antimicrobials are expensive.\textsuperscript{16} Developing countries with high rates of infectious disease are more vulnerable to AMR because a large number of people who are most in need of antimicrobials are without access. Furthermore, even where limiting access exists, appropriate drugs are not consistently available.
Funding is required for developed and developing countries to attain equal access to antimicrobials. Many developing countries suffer from high rates of infectious disease and are more affected by inequitable access to antimicrobials. For example, though Sub-Saharan Africa accounts for only 12% of the world's population, the region accounts for approximately 50% of all deaths from infectious disease.\(^{17}\)

Inadequate funding has led to subsidiary issues which exacerbate AMR. An example of this is the rise of drug counterfeiting in developing countries. In a study conducted by WHO between 1999 and 2002, counterfeit antibiotics accounted for 28% of drug counterfeiting and were the most counterfeited class of drugs worldwide.\(^{17}\) This was deemed a non-issue in Europe but was of high concern in Sub-Saharan Africa where infectious disease rates are high, and income is low.\(^{17}\)

The lack of funding for access to antimicrobials is a market failure and requires corrective action. This action could take place through international financial assistance that is organized and coordinated by a central body. An example of this is the Global Fund to Fight AIDS, Tuberculosis, and Malaria.\(^{18}\) Ensuring that there is funding for access to antimicrobials will also require joint prioritization from donors and recipient governments. Without prioritization, the creation of a centralized body is not possible or useful.

### Potential solution to Problem 2

- Creation of a centralized body to manage funding and ensure affordability in low- and middle-income countries
- Joint prioritization from donors and recipient governments for universal access to antimicrobials

### Recommended International Instrument: N/A

The problem of lack of funding for access has an exceptionally broad scope with different nuanced needs in each State. Existing research literature suggests that the scope of this issue is too broad to be wholly addressed in an international agreement. Additionally, its equity focus and redistribution consequences would also be nearly unprecedented in international law.\(^5\)

It is recommended that any instrument addressing AMR include a provision addressing the lack of funding for access to appropriate antimicrobials. An alternative method of addressing this issue is through policy advanced by non-State actors through development goals, codes of practice, global level facilitation to ensure affordability in LMICs, or the creation of a centralized body to manage and distribute funding. The Pandemic Influenza Preparedness (PIP) Framework uses a similar strategy where industry partners who benefit from the Framework are asked to contribute annually to the centralized body's operating costs. These funds are then allocated in part to developing countries to help strengthen their capacity.\(^{19}\)
A similar approach could be taken when addressing AMR. Efforts to lobby industry partners involved in the research and development of antimicrobials could be effective given that providing equitable access to the appropriate drugs stimulates market growth.

**Problem 3: Insufficient knowledge sharing**
Countries have limited access to one another’s logistical, financial, legal and administrative information related to AMR. Therefore, when an individual State implements an initiative to address AMR, other States are not necessarily aware of the results of the implementation. This impedes the coordination of State efforts. Lack of knowledge exchange regarding AMR prevents governments and policymakers from ensuring that the appropriate measures are taken to reduce AMR. To foster knowledge exchange, WHO has supported the establishment of “knowledge translation” platforms, such as the Evidence-Informed Policy Networks and the Alliance for Health Policy & Systems Research. Although these networks are focused on the research component, they are examples of functioning mechanisms for knowledge sharing.

**Recommended International Instrument: Regulation**
A WHO Regulation, per Article 21(a) of WHO’s Constitution, is the best international instrument to address insufficient knowledge sharing. This instrument has been known to “strengthen national disease prevention, surveillance, control and response systems” as well as “conduct studies and monitor progress,” which positions States to share knowledge. Procedures for knowledge sharing in the context of AMR fall well within the scope of subsection (a) of Article 21, granting authority to the Health Assembly to adopt regulations “to prevent the international spread of disease.” When knowledge is shared, States are better situated to implement measures that will slow the spread of microbes across borders. This is a procedure that is essential to solving AMR.

A Regulation ensures that States have the responsibility to report to a centralized body by providing domestic surveillance reports detailing the logistical, financial, legal and administrative status of AMR initiatives. It would be incumbent upon the centralized body to disseminate the information to Member States.

Since AMR is a well-known global health threat affecting all States, Member States may be more likely to voluntarily agree to share knowledge. Unlike the IHR where sharing information may negatively impact travel and trade to affected areas, a Regulation on AMR would be more favourable to collective response. Therefore, the Regulation’s provisions may not need to be as strict as in the case of the IHR.

**Conservation**

**Problem 4: Use of antimicrobials for growth promotion or routine prevention in animals**
The use of antimicrobials in animals for growth promotion and routine prevention contributes to the cross-species transmission of AMR from animals to humans, either
directly through contact with animals or indirectly through contaminated food.\textsuperscript{23,24} Studies of AMR in livestock show that farm animals carry a large load of resistant organisms.\textsuperscript{24} Research reveals that the amount of antimicrobials used for growth promotion and prophylactic disease prevention in food animals such as poultry, pork, and beef is greater than that used by the entire human population.\textsuperscript{24}

The increase in use of antimicrobials in the meat industry is attributed to the demands imposed by a growing human population and rising global income, which have increased meat consumption.\textsuperscript{24} This pressure on the meat industry has led to the non-therapeutic use of antimicrobials in large-scale intensive farming,\textsuperscript{24} where it is used primarily for growth promotion. It has been suggested that the use of such antimicrobials in growth promotion could be replaced by better livestock management including proper hygiene/sanitation, vaccination and nutrition.\textsuperscript{24} Research and development of alternatives to antimicrobial use in the food chain is required.\textsuperscript{23} Presently, the meat industry is not uniformly regulated regarding the use of antimicrobials in animals.\textsuperscript{23} There are countries and regions that have adopted voluntary measures (e.g., Canada and United States) and others that have adopted formal regulations (e.g., EU) for monitoring antimicrobial uses and resistance patterns.\textsuperscript{23,24} There are ongoing efforts by international organizations to target this problem. The WHO Advisory Group on Integrated Surveillance of Antimicrobial

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Potential solution to Problem 4 \\
\hline
\textbullet{} International instrument to introduce minimum national regulatory standards \\
\textbullet{} Development of quality assurance systems \\
\textbullet{} Creation of accountability mechanisms\textsuperscript{25} \\
\textbullet{} Implement harmonized global standards for AMR surveillance and monitoring systems in the food chain \\
\textbullet{} R&D alternatives to antimicrobials for use in animal husbandry\textsuperscript{23} \\
\textbullet{} Further investigation of current practices of antimicrobial use in animal production\textsuperscript{24} \\
\hline
\end{tabular}
\end{table}

Resistance tracks AMR in the food chain; the Codex Alimentarius Commission sets international standards for safe antimicrobial residue levels and feeding practices; and the WHO/FAO/OIE Collaboration provides recommendations for limiting the use of non-therapeutic antimicrobials in food animals.\textsuperscript{23}

International Instrument: Regulation

A Regulation under Article 21(d) of the WHO Constitution is the most appropriate mechanism to address the problem of the use of antimicrobials for growth promotion and non-therapeutic use in animals. The binding nature of an instrument to deal with this problem is paramount, although there may be low adoption of the instrument due to the commercial interests of the meat industry. For example, countries with large livestock industries may be reticent to voluntarily adopt it.
The problem of using antimicrobials for growth promotion and prophylaxis in animals falls within the scope of subsection (d) of Article 21 of the WHO Constitution. This section addresses “standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce.” The international commerce aspect of this problem plays an important role in the spread of AMR across borders because of the lack of harmonization of antimicrobial administration standards in livestock. A Regulation could provide for: minimum national regulatory standards, support for the development of assurance systems such as best practices and quality assurance for the prudent use of medications, and specifications for procurement of antimicrobials through a client-veterinarian relationship.

### Problem 5: Use of the same antimicrobials in agriculture, aquaculture and humans

The use of the same antimicrobials in agriculture, aquaculture and humans causes increased resistance to antimicrobials within human populations. There is evidence that animal use of antimicrobials has been linked to human health problems. There are 27 antimicrobial classes of drugs used in animals, only nine are used exclusively in animals.

Various domestic and international reports have recommended that certain antimicrobials be classified as “critically important” for human medicine and not be used for non-therapeutic purposes in animals. However, despite such recommendations, “growth promotion antibiotics account for the majority of use in animals”, and the top three antibiotics used in animals are critically needed by humans.

<table>
<thead>
<tr>
<th>Country</th>
<th>Measure</th>
<th>Description</th>
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<tbody>
<tr>
<td>France</td>
<td>Specialized strategies</td>
<td>Regulates antimicrobial prescription and availability for humans in hospitals, outpatient clinics and long-term care facilities.</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Disciplinary measures</td>
<td>Fines imposed by the Slovene National Health Insurance onto primary care providers who do not follow guidelines on AMR.</td>
</tr>
<tr>
<td>Denmark</td>
<td>Monitoring the consumption of medical products</td>
<td>Financial coverage of antimicrobials by the Danish government is low. Health care professionals collaborate to reduce infection, resistance, and optimize the use of antimicrobials.</td>
</tr>
<tr>
<td>Canada</td>
<td>Justifying prescription dispensation</td>
<td>Ensures that the governmental health insurance agency receives justification as to prescription dispensation of antimicrobials.</td>
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</table>

Table 1: Selected domestic measures to regulate antimicrobial prescription
Recommended International Instrument: Regulation
The best mechanism to address the use of the same antimicrobials in agriculture, aquaculture and humans is a Regulation under Article 21(a) of the WHO Constitution. The resistance developing in the agricultural and the aquaculture sectors impacts morbidity in humans. The Regulation should provide for: the research and development of alternatives to antimicrobial use in animal husbandry and aquaculture;\(^{23}\) and a restriction of antimicrobials categorized as critically important to human medicine to avoid AMR development in animals that would detrimentally affect humans. This would regulate and prevent the international spread of disease.

This problem may also be addressed under Article 21(d) of the WHO Constitution. Like the problem of antimicrobial use in animals for growth promotion and non-therapeutic, the use of the same antimicrobials in agriculture, aquaculture and humans have a facet of international trade, which puts it within the scope of this subsection. However, Member States may be discouraged from voluntarily adopting a mechanism if it would stunt economic growth in their domestic agricultural sectors.

Problem 6: Suboptimal regulation of antimicrobial prescription and availability for humans
Suboptimal regulation of antimicrobial prescription and availability for humans is a global issue affecting both developed and developing countries. Presently, there is a lack of harmonization among countries on this issue. For example, antimicrobials are available over the counter in some countries, while the same medicines require a prescription in others. Additionally, migration and movement across borders maintain a role in increasing the rate at which AMR spreads.

An important consideration is the disparity regarding consistency in prescription dispensation. There are also certain economic incentives for health care providers to prescribe particular antimicrobials over others. Suboptimal regulation of prescriptions has resulted in health care providers having a broad discretion regarding the prescription of appropriate antimicrobials. Some States have adopted domestic measures to regulate antimicrobial prescription, these include: specialized strategies, imposing disciplinary measures, monitoring consumption of antimicrobials and requiring justification of prescription dispensation. Selected domestic measures are shown in Table 1.

<table>
<thead>
<tr>
<th>Potential solution to Problem 5</th>
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<tbody>
<tr>
<td>› Research alternatives to antimicrobial use in animal husbandry and aquaculture(^{23})</td>
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<tr>
<td>› International instrument that restricts to human use antimicrobials categorized as critically important to human medicine</td>
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<th>Potential solution to Problem 6</th>
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<tr>
<td>› Creation of formularies for use in health care facilities(^{25})</td>
</tr>
<tr>
<td>› Introduction of appropriate and evidence-based treatment regimens to suit local needs focused on widespread and appropriate access(^{26})</td>
</tr>
<tr>
<td>› Implement stewardship programs(^{25})</td>
</tr>
<tr>
<td>› Provide incentives for health care providers to follow AMR guidelines</td>
</tr>
<tr>
<td>› Encourage non-comprehensive reimbursement policies to deter healthcare providers from over-prescribing antimicrobials</td>
</tr>
<tr>
<td>› Develop new strategies for rapid diagnosis</td>
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</tbody>
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the gatekeepers of medicines, yet they are not always familiar with the reality of AMR and the threat it poses.

Currently, passive and active educational measures are being used to address this issue in health care settings. Passive educational measures include the dissemination of informational materials both in-person and online. These can take the form of local antimicrobial guidelines as well as educational sessions. Active persuasive educational measures include clinical rounds at which cases are discussed, audits and feedback, as well as epidemic detailing. Health care providers have limited access to the latest information on the effective use of antimicrobials. This makes it increasingly difficult for them to follow accepted practice standards and guidelines. In many developing countries, community workers are the main providers of health care. Their level of education, knowledge-base and scope of practice therefore differs widely from that of health care professionals in developed countries. Furthermore, there is often a disparity between the education that is available to providers in LMICs compared to developed countries. Ongoing support in the form of new educational tools and practice development is required for health care professionals and community workers alike.

Recommended International Instrument: Treaty

The international instrument best suited to address the problem of suboptimal regulation of antimicrobial prescription and availability for humans is a Treaty, under Article 19 of the WHO Constitution. A Treaty is the most appropriate mechanism because it is binding on Member States and it has the jurisdictional breadth to support a broad range of provisions, some of which could have a financial component to ensure compliance.

Content for the Treaty could include: tracking of antimicrobial use, fostering accountability by monitoring health care professionals’ prescription dispensing patterns; encouraging evidence-based dispensing through global data collection of antimicrobial-resistant pathogens or genes; ensuring that there are sources of predictable financial commitments to support optimal regulation; implementing harmonized global standards in sampling methodology; and diagnostic protocols to develop rapid diagnosis techniques.

Problem 7: Lack of education on effective use of antimicrobials

Lack of education on effective use of antimicrobials contributes to the spread of AMR. This problem is two-fold. First, citizens are minimally educated on the consequences of antimicrobial resistance and what they can do to help slow its spread. Second, in many countries, health care providers are
Potential solution to Problem 7

- Create policies that mandate national public awareness campaigns
- Provide mandatory training for healthcare professionals and community workers
- Ensure health care providers have access to the appropriate level of education, based on the scope of their practice
- Provide educational programs designed to encourage the adoption of guidelines by health providers
- Involve health care providers in the development of a national policy
- Regulate product labeling to ensure labels on antimicrobials appropriately reflect best practices to reduce AMR

Recommended International Instrument: Recommendation and/or Regulation
To strengthen education on the effective use of antimicrobials, the most appropriate solution is a WHO Recommendation under Article 23 of WHO’s Constitution. The solutions to address the lack of education can be pursued through an overarching Recommendation that will not legally bind all Member States. The nature of the problem requires only that WHO provide a framework promoting education on AMR which States may or may not choose to integrate domestically. Coordination among States is not required. A Recommendation under Article 23 is a strong starting point for countries that do not currently have any measures in place to address AMR because there are a number of cost-effective and simple ways in which it can be implemented.

A Recommendation reinforces a global norm and not does not immediately alter the legal status quo. It would allow for States to address problems using individualized State-centric measures within their existing infrastructure. A more stringent instrument may not adequately reflect each State’s healthcare delivery system, needs of healthcare providers and citizen awareness.

This problem may also be addressed using a WHO Regulation under Article 21(a). When health care providers are educated on ways to prevent AMR, they will make better informed treatment decisions and promote awareness among their patients. This will contribute to the prevention of the international spread of disease. States that do not expressly opt out of the Regulation will be bound by it. However, the lack of imposable sanctions renders this instrument a less favourable option than a Recommendation. A Regulation could establish minimum education standards for citizens and health care providers. Therefore, it is unlikely that States will require a strong-handed approach to ensure compliance to the standards introduced in the Regulation.

Problem 8: Weak infection control practices
Weak infection control practices are another strain on conservation measures. The state of infection control practices comprises: guidelines and protocol on sanitation, reactionary and varied international practices, inadequate sanitary practices and insufficiently researched patterns of microbial spread. The last issue is of particular importance to determine the nature of prevention efforts and where they should be targeted. Additionally, there is currently a lack of appropriate data collection. This negatively impacts the accuracy of the conclusions drawn from the data resulting in less informed clinical and policy decision-making.

Recommended International Instrument: Treaty
The desired state of infection control includes: vigilant enforcement of guidelines on sanitation, a comprehensive understanding of microbial spread patterns, preventative infection control practices, and a wide-scale reduction of
Problem 9: Weak and uncoordinated surveillance

Global surveillance of AMR is not adequately coordinated or harmonized.\(^1\) While some developed countries have strong national surveillance systems, laboratory capacity and modern diagnostic techniques, many LMICs have fragmented surveillance systems, if any. A lack of funding for surveillance in LMICs negatively impacts their capacity to collect quality information.\(^{30}\) This impedes global surveillance efforts. The lack of collaborative surveillance for AMR compromises the international community’s ability to identify, monitor, systematically compare and evaluate AMR globally.

While there are existing domestic and regional surveillance systems such as CAESAR, ReLAVRA and EARS-Net, there is currently no global consensus on how AMR data should be collected. Without a standardized method, real-time trends are inconsistent and States cannot adequately compare AMR data with their global counterparts.

A Global Antimicrobial Surveillance System (GLASS) is being developed by WHO to support its Global Action Plan on Antimicrobial Resistance.\(^{31}\) GLASS gathers clinical, laboratory and epidemiological surveillance data on antimicrobials that pose a global health threat and enables a comparison of AMR rates between States. GLASS aims to provide evidence that can promote informed decisions to drive local, national and global health strategies.
regional action on AMR. However, domestic-level participation in GLASS has been limited because involvement is subject to the fulfillment of certain criteria, and is dependent upon agreement of the national government.

**Recommended International Instrument: Treaty**

Weak and uncoordinated surveillance of AMR is a problem that is most appropriately addressed by a WHO Treaty pursuant to Article 19. The coordination required to establish a functional surveillance system among States is best served by an instrument that values uniform compliance by incentivizing State approval. The most effective way of ensuring accountability within this coordinated surveillance effort is through the creation of a centralized body to ensure that States have a national surveillance mechanism and the necessary laboratory capacity to support the tracking of patterns of resistant microbes, as well as identify trends and outbreaks. The success of any surveillance effort is also reliant upon the proper collection of relevant data, which would be monitored by a centralized body. Although self-reported data is better than no data at all, it is crucial that a centralized body receive the most current data to ensure appropriate action. The quality of data collected is a challenge that has been faced prominently by the International Health Regulations. It has been stated that “[a] large degree of freedom is given to each individual government and therefore different levels of reporting are common, with substantial emphasis on passive reporting.” Arguably, enforcement mechanisms would solve this issue.

A Treaty could integrate GLASS and build upon it, as the centralized body. GLASS is in its early implementation phase and is being evaluated in 2019; therefore, by the time a Treaty is established, more will be known regarding the effectiveness of GLASS. The results of this evaluation can inform whether GLASS should serve as the centralized body best suited to govern all aspects of AMR, beyond the scope of surveillance. Some of the criteria to join GLASS can be financially onerous on States; they include the requirement of laboratory capacity, epidemiological capacity, and a national diagnostic stewardship program. As such, the involvement of all States is not guaranteed. A Treaty would allow for financial commitments to be made in order for less developed countries to meet the criteria for enrolment.

**Problem 10: Over-promotion and marketing of antimicrobials**

Currently, there is no global system in place to monitor the marketing or promotion of antimicrobials for human use by industry or retailers. Marketing the use of certain antimicrobials over others and incentivizing health professionals to over-promote the utility of certain drugs,
induces a general belief that the promoted drugs are essential. As a result, marketing and over-promotion increase the demand for certain prescriptions.

**Recommended International Instrument: Regulation**
The over-promotion and marketing of antimicrobials are best addressed by a Regulation, under Article 21(d) of WHO's Constitution, which allow for "standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce". If addressed using a Regulation, the over-promotion and marketing of antimicrobials can be resolved within the context of the international marketplace, wherein a ban can be instituted. Banning the promotion and marketing of antimicrobials based on price or packaging from industry or retailers would re-establish accurate prescription practices. A WHO Regulation is binding once in force and is applicable to all Member States, unless they explicitly opt out. This may induce wider buy-in and ensure more comprehensive global results for pharmaceutical companies. As a result, there is little investment in R&D for antimicrobials.

**Recommended International Instrument: Treaty**
A global lack of funding and incentives for antimicrobial innovation is a problem that is best addressed by a WHO Treaty. Central to increased funding of R&D is delinking innovation from profit, which can be achieved through a formal, binding and enforceable Treaty. In order to achieve global coordination of practices pertaining to AMR through a global R&D framework, intergovernmental management and incentive-driving programs to award innovation are required. These could include patent pools and prizes, as well as the transfer of intellectual property rights through bilateral and multilateral treaties. States must be encouraged to adopt practices through a binding international mechanism. The content of the treaty may include the creation of a global AMR research fund in order to pool resources to encourage R&D. This could be included using an additional Protocol.

**Innovation**

**Problem 11: Lack of incentives for developing new antimicrobials**
Many of the antimicrobials used today were produced between the 1940s and the end of the 1970s. Since then, there has been a significant decline in the development of new antimicrobials due to a decrease in the number of big pharmaceutical companies involved in R&D in this area. The loss of commercial interest by big pharma in antibiotic discovery can be attributed to low returns on R&D investments. When pharmaceutical companies invest large sums of money in drug development, their shareholders expect high returns on their investment. The costly nature of production, paired with high shareholder expectations, narrows the range of R&D projects based on the evaluation of financial return.

Unlike medicines developed for chronic illnesses, antimicrobials are prescribed for a short period of time. New antimicrobials might also be subject to a government conservation regime which prevents physicians and veterinarians from easily and widely prescribing them. This typically results in lower profits for pharmaceutical companies. As a result, there is little investment in R&D for antimicrobials.

**Summary of Gap Analysis and Instrument Recommendation**
Adopting a Regulation under Article 21 of the WHO Constitution is a legally viable option. Based on the above-noted problems, the Regulation could fall under subsections (a) or (d). One of the main reasons that the rate of AMR is increasing is because disease is not being treated adequately and therefore continues to spread across borders. Article 21(a) is reserved for procedures preventing the spread of disease; therefore, any measure that promotes the treatment of disease using the proper drug, decreases both the rate of AMR and the spread of disease globally. The applicability of Article 21(d) is also justified for any measure establishing standards in regards to the “safety, purity and potency” of antimicrobials. Pursuant to Article 22 of the WHO Constitution, a Regulation would come into force after due notice has been given of its adoption by the World Health Assembly, unless a Member State notifies the Director-General of rejection or reservations within the period stated in the notice. Since adoption does not require a formal “opting-in” mechanism, it could be argued that the...
**Potential solution to Problem 11**

**Financial approaches**
- Delink innovation from profit
- Fund public sector research and clinical trials
- Provide grants to small- and medium-sized innovative companies and universities to develop new products
- Set milestones and prizes to reward antimicrobial innovation
- Implement indirect taxes on antimicrobials to fund AMR research
- Create purchase and procurement agreements for antimicrobials that encourage innovation

**Participatory approaches**
- Establish patent pools
- Promote equitable licensing
- Establish production and marketing agreements for a needs-based number of treatments per year
- Create intergovernmental consortium to manage distribution and preservation of antibiotics

**Other approaches**
- Create a global framework on R&D for AMR
- Remove data exclusivity
- Enable transferable intellectual property rights through bilateral or multilateral agreements

Regulation may be adhered to more widely as it requires States to “contract out”.38

A Recommendation adopted under Article 23 of the WHO Constitution also allows for a broad range of discretion with regards to subject matter. The language used in this type of instrument is generally more permissive and the instrument itself is non-binding, unless optional contractual agreements form part of the Recommendation.

Lastly, adopting a Treaty under Article 19 of the WHO Constitution could be useful in addressing the problems outlined above. Unlike a Regulation under Article 21, provisions adopted under a Treaty are not limited to enumerated grounds. Additionally, unlike a Recommendation under Article 23 or a United Nations (UN) General Assembly Resolution, the provisions would be binding on the Member States. A Treaty, if articulated within the text, could have the additional advantage of imposing enforcement mechanisms through the formal arbitration of the International Court of Justice. Notwithstanding these advantages, a challenge that may be faced in establishing such a Treaty is the requirement of express consent from each participating State.

In practice, if only one instrument was to be selected, a Treaty has the ability to address a multi-faceted global health issue such as AMR. It could integrate all necessary content.

The use of international instruments such as a UNGA Resolution, UN Treaty or Customary International Law would not be the most effective means to address AMR globally.

Countries that already have legislation or other measures in place to address AMR are encouraged to strengthen these according to the terms of the selected international agreement.39 For example, States who have enrolled in GLASS should build on their existing capacity and assist in the strengthening of other countries’ capacity-building.
<table>
<thead>
<tr>
<th>PROBLEM AREA</th>
<th>INTERNATIONAL INSTRUMENT</th>
<th>NUMBER OF SOLUTIONS ADDRESSED</th>
<th>PERCENT OF TOTAL</th>
<th>CUMULATIVE PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of incentives for new antimicrobials</td>
<td>Treaty</td>
<td>13</td>
<td>23.21%</td>
<td>23.21%</td>
</tr>
<tr>
<td>Suboptimal regulation of antimicrobial prescription and availability for humans</td>
<td>Treaty</td>
<td>6</td>
<td>10.71%</td>
<td>33.93%</td>
</tr>
<tr>
<td>Weak infection control practices</td>
<td>Treaty</td>
<td>6</td>
<td>10.71%</td>
<td>44.64%</td>
</tr>
<tr>
<td>Lack of education on effective use of antimicrobials</td>
<td>Recommendation and/or Regulation (Article 21(a))</td>
<td>6</td>
<td>10.71%</td>
<td>55.36%</td>
</tr>
<tr>
<td>Insufficient knowledge sharing</td>
<td>Regulation (Article 21(a))</td>
<td>6</td>
<td>10.71%</td>
<td>66.07%</td>
</tr>
<tr>
<td>Use of antimicrobials for growth promotion or routine prevention in animals</td>
<td>Regulation (Article 21(d))</td>
<td>6</td>
<td>10.71%</td>
<td>76.79%</td>
</tr>
<tr>
<td>Over-promotion and marketing of antibiotics</td>
<td>Regulation (Article 21(d))</td>
<td>3</td>
<td>5.36%</td>
<td>82.14%</td>
</tr>
<tr>
<td>Insufficient financial resources for health systems infrastructure in LMICs</td>
<td>Treaty</td>
<td>3</td>
<td>5.36%</td>
<td>87.50%</td>
</tr>
<tr>
<td>Weak and uncoordinated surveillance</td>
<td>Treaty</td>
<td>3</td>
<td>5.36%</td>
<td>92.86%</td>
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<tr>
<td>Insufficient funding for access to antimicrobials</td>
<td>N/A</td>
<td>2</td>
<td>3.57%</td>
<td>96.43%</td>
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<tr>
<td>Use of same antimicrobials in agriculture, aquaculture and humans</td>
<td>Regulation (Article 21(a) or 21(d))</td>
<td>2</td>
<td>3.57%</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

Table 2: Problem Area and International Instrument Pairing (Weighted) in Descending Order
A summary of the gap analysis can be found in the Web Appendix.

Table 2 shows a breakdown of the problem areas, the number of solutions needed to be implement for each problem in order to reach the desired state, the percentage those solutions present in relation to all of the problems, and the international instrument assigned to address each problem drawn from the preceding discussion.

**INSTRUMENT PRIORITIZATION**

Crafting international agreements can consume millions of dollars, which are used to pay for the cost of salaries, negotiations and logistics, as well as millions more in maintenance costs for new governance structures, conferences and annual reporting. As a result, the implementation of all of the instruments discussed above may be impractical and too demanding on human and capital resources.

In order to increase the ease of implementation of a suite of international instruments to combat AMR, the most high-impact instruments must be prioritized to deliver maximal return for resources spent. Based on a modified Pareto analysis, a Treaty under Article 19 and a Regulation under Article 21 of the WHO Constitution should be prioritized when choosing the instrument to combat AMR on an international scale. This conclusion was derived by calculating the sum of the proportion of solutions that could be addressed by each instrument. A full explanation of the methodology of this analysis is found in the Appendix.

Table 3 shows a summary of the relative impacts of each international instrument as an indication of the reach it would have in addressing AMR on an international level. Based on this table, implementation of a Treaty and a Regulation would encompass over 80% of the present solutions that stand between the current state of AMR and the desired state. A single Regulation could include solutions under both subsections 21(a) and 21(d). Therefore, a suite consisting of a Treaty and a Regulation could cover almost 100% of the proposed solutions. The relative impact and cumulative distribution of AMR problem areas can be found in Figure 1.

**ROLE OF THE WORLD HEALTH ORGANIZATION**

AMR is a global health issue that impacts multiple industries. It could be addressed by various bodies within different sectors and through diverse approaches. Notwithstanding these options, there are a number of key reasons why WHO remains the most important forum through which to address this issue, and through which to adopt an international instrument. This determination is established by considering the WHO Constitution, WHO’s reputation as a leader in global health, the

<table>
<thead>
<tr>
<th>Treaty under Article 19</th>
<th>Regulation under Article 21(a)</th>
<th>Regulation under Article 21(d)</th>
<th>Recommendation under Article 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>55.36%</td>
<td>25.00%</td>
<td>19.64%</td>
<td>10.71%</td>
</tr>
</tbody>
</table>

Table 3: Relative Impact of International Instruments
international character of AMR as a global health problem, and WHO’s previous success in the implementation of international instruments.

The WHO Constitution

WHO’s Constitution came into force in April 1948. It is a foundational legal structure that allows for the creation of binding and non-binding international instruments. It provides options for instruments by which international law can be created: binding Treaties under Article 19; binding Regulations under Article 21; and non-binding recommendations under Article 23. The character of the Constitution provides legitimacy and these international instruments can help address AMR.

WHO as a Leader in Global Health

WHO’s objective is to ensure “attainment by all peoples of the highest possible level of health”\(^2\)\(^2\). To attain this goal, the organization frequently leads successful global health initiatives. Frameworks such as the FCTC and the IHR have demonstrated that WHO has the necessary influence, capacity, and authority to build a coalition of Member States’ towards taking action on matters of global health.

AMR is a Global Health Concern

AMR is a multi-faceted issue affecting the trade, agriculture, and pharmaceutical sectors, among others. However, at its core, AMR is a health issue. The most threatening aspect of this problem is its effect on people’s health. Although other sectors may be affected by AMR’s reach, it requires health-oriented solutions in order to be adequately addressed.

Previous Success in the Implementation of International Instruments

Since 1948, WHO has rarely used its power to enact international legally-binding instruments. However, WHO
has experienced success with the creation of both a Treaty (FCTC) and a Regulation (IHR) under Articles 19 and 21 of its Constitution. The FCTC, which entered into force in February 2005, is binding on 180 Member States and remains the only global health treaty negotiated under the power of Article 19. Similarly, the revised IHR, most recently entered into force in June 2007, remains the only binding regulation adopted under the power of Article 21.

WHO has also continuously influenced States and their policies using Recommendations, under Article 23 of its Constitution. “[Dissemination] of guides, information, or the findings of expert bodies” are also examples of ways in which WHO has endeavoured to guide States in dealing with international health matters without imposing obligations on those States. The success of these instruments has been attributed to the fact that WHO, an authoritative international health organization, acted as an impartial and independent body in leading the international community in addressing public health concerns.

Other Considerations

If WHO is to advance the adoption of an international instrument to address AMR, it is prudent to consider the response that other regulated sectors may have to this endeavour. Specifically, the agricultural sector may not wish to be governed by the health sector and, in turn, demonstrate resistance.

This report has not focused on the political feasibility of the WHO adopting an international instrument to address AMR. That topic is covered in a separate report.41

**CONCLUSION**

Global coordinated action is needed to address the cross-border health threat of AMR. Without an international concerted effort, AMR will worsen and actions of individual countries to mitigate it will become ineffective.

The modified Pareto analysis presented in this report identified six problems for which the gap between the current and desired state was widest. These problems are: lack of incentives for new antimicrobials; suboptimal regulation of antimicrobial prescription and availability for humans; weak infection control practices; lack of education on effective use of antimicrobials; insufficient knowledge sharing; and use of antimicrobials for growth promotion or routine prevention in animals. The content of the selected international instrument(s) should include a focus on these problems.

The preferred suite of international instruments is a Treaty under Article 19 and a Regulation under Article 21 of the WHO Constitution. The use of these two instruments together can effectively bridge the gap between the current and desired states. While this suite of instruments is recommended, in
practice, the scope of a Treaty provides for the inclusion of all recommended solutions, including those that would be addressed by a Regulation alone.

WHO would be the most effective organization through which an international response on AMR could be coordinated. This is attributed to WHO’s leadership in global health, the breadth of its mandate and available tools, and the nature of AMR as a global health threat.

### Key Messages

1. Antimicrobial resistance is a global health threat that must be addressed through concerted global action.

2. An international instrument is a mechanism by which this effort can be coordinated.

3. WHO is the most appropriate body to facilitate development, negotiation and implementation of an international instrument addressing antimicrobial resistance.

4. The best-suited international instruments are a Treaty under Article 19 and a Regulation under Article 21 of WHO’s Constitution.

5. The content of the selected instrument(s) should address six key problems, including the lack of incentives for new antimicrobials, suboptimal regulation of antimicrobial prescription and availability for humans, weak infection control practices, lack of education on effective use of antimicrobials, insufficient knowledge sharing, and use of antimicrobials for growth promotion or routine prevention in animals.
REFERENCES


Follow the link below to view an additional web appendix ›
www.globalstrategylab.org/clinic/reports/content-of-amr-agreement-2016_web-appendix.pdf

### Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial Resistance</td>
</tr>
<tr>
<td>CAESAR</td>
<td>Central Asian and Eastern European Surveillance of Antimicrobial Resistance</td>
</tr>
<tr>
<td>DAH</td>
<td>Development Assistance for Health</td>
</tr>
<tr>
<td>EARS-Net</td>
<td>European Antimicrobial Resistance Surveillance System</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FAO</td>
<td>The Food and Agriculture Organization of the United Nations</td>
</tr>
<tr>
<td>FCTC</td>
<td>WHO Framework Convention on Tobacco Control</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GLASS</td>
<td>Global Antimicrobial Resistance Surveillance System</td>
</tr>
<tr>
<td>GSL</td>
<td>Global Strategy Lab</td>
</tr>
<tr>
<td>ICJ</td>
<td>International Court of Justice</td>
</tr>
<tr>
<td>IDA</td>
<td>International Development Association</td>
</tr>
<tr>
<td>IHR</td>
<td>International Health Regulations</td>
</tr>
<tr>
<td>IMF</td>
<td>International Monetary Fund</td>
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<tr>
<td>IP</td>
<td>Intellectual property</td>
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<tr>
<td>LMICs</td>
<td>Low-and-Middle Income Countries</td>
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<tr>
<td>NGO</td>
<td>Non-governmental organization</td>
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<tr>
<td>OIE</td>
<td>World Organization for Animal Health (Office International des Epizooties)</td>
</tr>
<tr>
<td>PIP Framework</td>
<td>Pandemic Influenza Preparedness Framework</td>
</tr>
<tr>
<td>PEITTP</td>
<td>Protocol to Eliminate Illicit Trade in Tobacco Products</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>ReLAVRA</td>
<td>Latin American Surveillance Network of Antimicrobial Resistance (Red Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos)</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UNGA</td>
<td>United Nations General Assembly</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
**Glossary of Terms**

**Antibiotic stewardship** describes the reduction of inappropriate and unnecessary uses of antibiotics globally. It encompasses uses in both animal and human as well as uses in local communities and in hospitals (State of the World’s Antibiotics, p. 62).

**Gap** refers to the difference between the current state and the desired state in the global response to combat AMR.

**Health care providers** include health care professionals such as physicians, nurse-practitioners, nurses, etc. as well as community workers.

**International instruments** refers to any of the following: a Treaty adopted under section 19 of the WHO Constitution, a Regulation adopted under section 21 of the WHO Constitution, a Recommendation adopted under section 23 of the WHO Constitution, Customary International Law, a UN General Assembly Resolution or a UN Treaty.

**Modified Pareto Analysis** is a method tailored in this report for prioritizing the international instruments based on the number of solutions each can contain. In this report, this tool has been used to determine which instrument would capture 80% of the solutions.

**Protocol** is a supplement to a “parent” treaty (or “umbrella” treaty) to address a specific issue addressed in the “parent” treaty. It is in itself also recognized as a treaty.

**Solutions** address the gap between the current state and desired state for each problem. These solutions are suggested as content for the international instrument.

**Methodology**

An extensive literature review was conducted to determine the current and desired state of AMR globally. Issues uncovered in the current and desired state were categorized into eleven central problems. The eleven problems were further sorted into the broad headings of Access, Conservation and Innovation to reflect the organization of the existing literature. A gap analysis was conducted to identify the discrepancy between the current and desired state for each problem.

Additional literature-based research was carried to identify different types of international instruments with consideration of their jurisdictional reach, salient features, benefits, drawbacks, and lessons learned from past implementation schemes. Following this analysis, the eleven problems were matched to an international legal instrument most suited to embody content that would overcome the gaps between the current and desired state.

Selection criteria for the legal instruments included, but was not limited to: enforceability, resource demands, jurisdiction, and whether the instrument was binding or non-binding on Member States. The decision further relied on case studies of existing international agreements such as the Framework Convention on Tobacco Control Protocol, the PIP Framework, and the IHR. The applicability of each instrument to a given problem was evaluated and compared against other possible instruments and then, the most appropriate instrument or instruments was identified.

In order to prioritize the problems and select the best instrument or suite of instruments that could be implemented to combat AMR, a modified Pareto analysis was conducted. In this modified analysis, an instrument, or suite of instruments, able to overcome at least 80% of the gaps between the current state and desired state of AMR was sought in accordance with the Pareto Principle. (The Pareto Principle states that there is an unequal relation between inputs and outputs such that some inputs have a disproportionate impact on outcomes. In this case, the selection of only a single instrument or small suite of instruments may address the vast majority of gaps identified in the gap analysis.) To conduct the modified Pareto analysis, the number of gaps identified from the literature review was tallied for each given problem and presented as a percentage of the total number of gaps for all eleven problems. This was
calculated by summing the number of gaps identified under each problem area and dividing it by the total number of gaps for all problem areas. This gave the relative impact of each problem as they relate to each other. The most appropriate international instrument or instruments was then assigned to each problem.

The relative impact of each international instrument was calculated by summing the impacts of the problems it addressed. When more than one instrument could viably address one problem, they were both counted separately towards the Pareto analysis in order to analyze the potential impact of each individual instrument. Those instruments able to address the largest proportion of gaps were selected as the recommended suite of instruments once the sum of the gap proportion for those instruments reached 80% or greater. These instruments were therefore identified as priority. No instrument in the recommend suite had overlapping capacity to address a given problem and therefore, there was no double counting.