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and Kevin Outterson

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## LETTER FROM THE EDITORS

When a journal has been continuously publishing for more than forty years, the opportunities to try something truly new are rare indeed. But with this very special issue of the *Journal of Law, Medicine & Ethics*, we are indeed doing something we have never attempted before. This issue — one of two supplements that accompany our regular issue — is the first ever edition of *JLME* to be *online only*. It is still an issue of *JLME* in every sense of the word: it has covers, a table of contents, and a group of outstanding articles. It is available to all of our members at [aslme.org](http://aslme.org) and to our journal's readers at the website of our publishing partner, Wiley. If you wish, you may print it out and hold it in your hands. But make no mistake, this "virtual" issue of *JLME* is a first for our publication. We hope you like it.

The supplement, "Antibiotic Resistance," is co-guest edited by *JLME's* editor-in-chief Kevin Outterson and Steven Hoffman. This supplement focuses on the need to establish an international agreement for antibiotic policy. The authors argue that such an agreement should address access, surveillance, prevention, infection control, the needs of the under-served, accountability, and which forums, such as WHO, can help facilitate this policy. That this issue is online only reflects (at least partly) just how "hot off the presses" it actually is. The editorial office of *JLME* agreed to publish the symposium in late spring, and papers were still being revised in meetings in Sweden in June of 2015. It is only because of the dedicated work of guest editors Kevin and Steven that this issue made it to press in so timely a fashion. We are proud that this issue serves as our inaugural exploration of online publishing, and we hope you enjoy reading it as much as we enjoyed bringing it to fruition.

Ted Hutchinson  
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## Symposium Articles

### SYMPOSIUM

## Antibiotic Resistance

Guest Edited  
by Steven J.  
Hoffman and  
Kevin Outterson

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*Letter from  
the Editors*

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### INTRODUCTION

#### **What Will It Take to Address the Global Threat of Antibiotic Resistance?**

*Steven J. Hoffman and Kevin Outterson*

### DESCRIBING THE PROBLEM

#### 1. A CROSS-BORDER PROBLEM

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#### **Antibiotic Resistance Spreads Internationally Across Borders**

*Tamar F. Barlam and Kalpana Gupta*

Antibiotic-resistant (ABR) bacteria develop when bacteria are exposed to antibiotics either during treatments in humans or animals or through environmental sources contaminated with antibiotic residues. Resistant bacteria selected by medical, agricultural, and industrial use spread globally through international travel, the export of animals and retail products, and the environment. It is essential that nations work together to identify how to reduce emergence and amplification of resistant bacteria through sensible antibiotic treatment guidelines and restrictions, concerted efforts for surveillance, and infection control.

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#### **Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance**

*Nils Daulaire, Abhay Bang,  
Göran Tomson, Joan N. Kalyango,  
and Otto Cars*

Universal access to effective antimicrobials is essential to the realization of the right to health. At present, 5.7 million people die from treatable infections each year because they lack this access. Yet, community-based diagnosis and appropriate treatment for many of the leading causes of

avoidable infectious deaths has been shown to be feasible and effective, demonstrating that strategies to reach the under-served need to receive high priority. This is a necessary part of a broad strategy to assure the long-term benefits of antimicrobials and to combat antimicrobial resistance, both because the lack of systematic and rigorous efforts to assure effective coverage increases the likelihood of antimicrobial resistance, and because global efforts aimed at antimicrobial stewardship and innovation cannot succeed without explicitly addressing the needs of the under-served. Elements of this strategy will include clear evidence-based treatment protocols, a robust international framework and locally tailored regulations, active engagement with communities and local health providers, strong attention to program management and cost considerations, a focus on the end user, and robust surveillance and response to emerging resistance patterns. Only by balancing the needs of universal access with stewardship and innovation, and assuring that they are mutually reinforcing can a global strategy hope to effectively address antimicrobial resistance.

#### 3. INNOVATION FOR ANTIBIOTICS

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#### **The Global Innovation Model for Antibiotics Needs Reinvention**

*Manica Balasegaram, Charles Clift, and  
John-Arne Røttingen*

The dangers presented by antibiotic resistance (ABR) have now established themselves as a global health security issue. From an international policy perspective, three key pillars have been established — responsible access, conservation, and innovation. These pillars are intrinsically linked, meaning that any attempt to address one, must take into account the implications for the other two. This article attempts to address all three of these pillars.



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**History Teaches Us That Confronting  
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*Scott H. Podolsky, Robert Bud,  
Christoph Gradmann, Bård Hobaek,  
Claas Kirchhelle, Tore Mitvedt,  
María Jesús Santasmases, Ulrike Thoms,  
Dag Berild, and Anne Kveim Lie*

Antibiotic development and usage, and antibiotic resistance in particular, are today considered global concerns, simultaneously mandating local and global perspectives and actions. Yet such global considerations have not always been part of antibiotic policy formation, and those who attempt to formulate a globally coordinated response to antibiotic resistance will need to confront a history of heterogeneous, often uncoordinated, and at times conflicting reform efforts, whose legacies remain apparent today. Historical analysis permits us to highlight such entrenched trends and processes, helping to frame contemporary efforts to improve access, conservation and innovation.

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**Antibiotic Resistance Is a Tragedy of  
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*Aidan Hollis and Peter Maybarduk*

Antibiotics may be thought of as a common pool resource that can be depleted over time; the economics of this problem are relatively well known. The importance of antibiotics to human health means that limiting access through privatization is undesirable. Therefore, other solutions to prevent overuse are essential — stewardship programs, and for non-human use, taxation, all within the context of an international agreement. To solve problems of access while offering adequate rewards for innovation, a key tool is delinking prices from payment to innovators.

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**An Integrated Systems Approach is  
Needed to Ensure the Sustainability  
of Antibiotic Effectiveness for Both  
Humans and Animals**

*Anthony D. So, Tejen A. Shah, Steven Roach,  
Yoke Ling Chee, and Kieve E. Nachman*

The growing demand for animal products and the widespread use of antibiotics in bringing food animals to market have heightened concerns over cross-species transmission of drug resistance. Both the biology and emerging epidemiology strongly support the need for global coordination in stemming the generation and propagation of resistance, and the patchwork of global and country-level regulations still leaves significant gaps. More importantly, discussing such a framework opens the door to taking modular steps towards solving these challenges — for example, beginning among targeted parties rather than all countries, tying accountability to financial and technical support, or taxing antibiotic use in animals to deter low-value usage of these drugs. An international agreement would allow integrating surveillance data collection, monitoring and enforcement, research into antibiotic alternatives and more sustainable approaches to agriculture, technical assistance and capacity building, and financing under the umbrella of a One Health approach.

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**Much Can Be Learned about Addressing  
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*Steinar Andresen and Steven J. Hoffman*

Antibiotic resistance (ABR) is a common-pool resource challenge. This means that efforts to address ABR can learn from similar collective action problems faced within the environmental sector. Multilateral environmental agreements are the backbone of global environmental governance. Their ability to effectively solve environmental problems depends on the problem structure and the regime's problem-solving capacity. The success or failure of environmental agreements is mainly determined by the problem structure, including the degree of political consensus and scientific certainty. But agreements' institutional design also matter because they can change the problem structure and problem-solving capacity. Based on experiences with environmental agreements, an international ABR agreement should contain robust reporting/verification procedures, sanctions for non-compliance, assistance for implementation, majority vote decision-making rules, a strong secretariat, an independent scientific panel, and specific commitments. More research on global strategies for achieving collective action is needed to help inform future institutional designs that are both effective and politically feasible.

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8. ACCOUNTABILITY

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**Addressing Antibiotic Resistance  
Requires Robust International  
Accountability Mechanisms**

*Steven J. Hoffman and Trygve Ottersen*

A proposed international agreement on antibiotic resistance will depend on robust accountability mechanisms for real-world impact. This article examines the central aspects of accountability relationships in international agreements and lays out ways to strengthen them. We provide a menu of accountability mechanisms that facilitate transparency, oversight, complaint, and enforcement, describe how these mechanisms can promote compliance, and identify key considerations for a proposed international agreement on antibiotic resistance. These insights can be useful for bringing about the revolutionary changes that new international agreements aspire to achieve.

9. INTERNATIONAL LAW

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**International Law Has a Role to Play in  
Addressing Antibiotic Resistance**

*Steven J. Hoffman, John-Arne Røttingen,  
and Julio Frenk*

If an international legal agreement is needed for any of today's global health challenges, it would be antibiotic resistance (ABR). This challenge is transnational, its solution justifies coercion, tangible benefits are likely to be achieved, and other commitment mechanisms have thus far not been successful. Since addressing ABR depends on near-universal and interdependent collective action across sectors, states should utilize an international legal agreement — which formally represents the strongest commitment mechanism available to them.

10. LEGALIZING COMMITMENTS

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**Some Global Policies for Antibiotic  
Resistance Depend on Legally Binding  
and Enforceable Commitments**

*Asha Behdinan, Steven J. Hoffman,  
and Mark Pearcey*

To address the challenge of antibiotic resistance (ABR), the international community must ensure access, conservation and innovation of antibiotics. These goals can be significantly advanced through ten global policies that have been recommended to form part of an international legal agreement. Policies that could be central to this agreement include the establishment of standards, responsible antibiotic use regulations, and strengthening global surveillance systems. Funding for access, mobilizing resources for infrastructure, strengthening infection control practices, and regulating antibiotic marketing could also be helpful if included in a legal agreement. Incentives for innovation could also be included to mobilize support for its implementation. The inclusion of these policies in an international legal agreement could effectively support global collective action towards several ABR policy goals, some of which may depend on it for their achievement.

11. CONVENING FORUM

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**Effective Global Action on Antibiotic  
Resistance Requires Careful  
Consideration of Convening Forums**

*Zain Rizvi and Steven J. Hoffman*

Global collective action is needed to address the growing transnational threat of antibiotic resistance (ABR). Some commentators have recommended an international legal agreement as the most promising mechanism for coordinating such action. While much has been said about what must be done to address ABR, far less work has analyzed how or where such collective action should be facilitated — even though the success of any international agreement depends greatly on where it is negotiated and implemented. This article evaluates four different forums that states may use to develop an international legal agreement for antibiotic resistance: (1) a self-organized venue; (2) the World Health Organization; (3) the World Trade Organization; and (4) the United Nations General Assembly. The need for a multisectoral approach and the diverse institutional landscape suggest that an effective response may best be coordinated through linked action pursued through multiple forums.

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## INTRODUCTION

# What Will It Take to Address the Global Threat of Antibiotic Resistance?

*Steven J. Hoffman and Kevin Outterson*

**O**f the many global health challenges facing the world today, only a small number require global collective action. Most health challenges can be fully addressed through action at local, regional or national levels.

What kind of actions must be taken to address the global threat of antibiotic resistance (ABR)? What legal, political and economic tools might be needed to achieve this level of action?

In March 2015 the Dag Hammarskjöld Foundation<sup>1</sup> convened a workshop in Uppsala, Sweden to address these questions in partnership with the Global Strategy Lab,<sup>2</sup> the *Journal of Law, Medicine & Ethics* (*JLME*),<sup>3</sup> the Norwegian Institute of Public Health,<sup>4</sup> and ReAct – Action on Antibiotic Resistance.<sup>5</sup> Eleven concise articles were commissioned to explore whether ABR depended on global collective action, and if so, what tools could help states and non-state actors to achieve it. This work built upon previous efforts of the Dag Hammarskjöld Foundation and its partners to address ABR, as well as instigate further research that is needed to inform relevant global policies, initiatives, and actions going forward.

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**Steven J. Hoffman, B.H.Sc., M.A., J.D.,** is an Associate Professor of Law and Director of the Global Strategy Lab at the University of Ottawa with courtesy appointments as an Assistant Professor of Clinical Epidemiology & Biostatistics (Part-Time) at McMaster University and Adjunct Associate Professor of Global Health & Population at Harvard University. He previously worked for the Ontario Ministry of Health & Long-Term Care, World Health Organization, and the Executive Office of the United Nations Secretary-General. **Kevin Outterson, J.D., LL.M.,** is a Professor of Law and the N. Neal Pike Scholar in Health and Disability Law at Boston University School of Law, an Associate Fellow at Chatham House, and the Editor-in-Chief of the *Journal of Law, Medicine & Ethics*.

### The Problem of Antibiotic Resistance

This peer-reviewed *JLME* series begins with a detailed description of ABR. The medical evidence is clear that antibiotic resistance spreads across borders through many vectors. Tamar Barlam and Kalpana Gupta highlight the medical evidence that underpins the conclusion that resistance is a transnational health risk and thus a truly global problem.<sup>6</sup> Even countries with extraordinary programs in antibiotic stewardship can face multi-drug resistant diseases when a traveler returns home from abroad.

While medical evidence is central to this effort, narrow disciplinary perspectives can hinder a full view of the field. To a physician, ABR is salient when a patient in the intensive care ward develops an untreatable and deadly bacterial infection. The problem is a lack of new drugs and the solution is to develop new treatments. To an infection control specialist, the problem is the nosocomial transmission of multi-drug resistant pathogens in hospitals. Solutions include better hospital infection control, including active surveillance. Public health officials might look even further back, at the chain of events that allowed multi-drug resistant bacteria to evolve due to improper antibiotic stewardship, including perhaps indiscriminate use of antibiotics among both humans and animals.

None of these disciplinary perspectives are wrong, but they give a limited view of a complex systems problem. For this reason, we sought from the beginning to include people from diverse academic and professional disciplines in this project, including physicians, public health practitioners, epidemiologists, economists, historians, lawyers, political scientists, and social activists — all of whom were committed to advancing global health, especially among the poorest populations on the planet. ABR is a complex problem,



Figure 1

**Policy Tripod for Addressing Antibiotic Resistance**

one best addressed through interdisciplinary work including academics, clinicians and policymakers across varied contexts.

Our interdisciplinary approach yielded a three-pronged approach to tackling ABR: (1) Access, (2) Conservation, and (3) Innovation (see Figure 1).<sup>7</sup>

Access, or lack thereof, is the cause of more people dying today from susceptible bacteria than from resistant bacterial pathogens,<sup>8</sup> despite warnings of a looming antibiotic apocalypse.<sup>9</sup> Inadequate access to existing antibiotics is a global health crisis of the first order that currently receives insufficient attention. But antibiotic access cannot stand alone as a solution. Promoting global access to antibiotics will speed resistance unless it is coupled with strong conservation programs to ensure appropriate use. Access and conservation themselves may actually work at cross-purposes unless integrated into a single program. In addition, achieving universal access for low- and middle-income populations could undermine commercial incentives to invest in the research and development (R&D) necessary to bring innovative new antibiotics to market. The article by Nils Daulaire and colleagues takes a bold stance on the crisis of antibiotic access, but they also recognize the imperative to integrate the solution with both conservation and innovation. While access could possibly be addressed on a country-by-country basis, an integrated solution requires coordinated action across borders.

Conservation cannot stop resistance, but it can certainly slow the rate of the emergence and spread of multi-drug resistant organisms. Conservation slows the rate of bacterial evolution, buying us time to develop alternatives. Conservation also includes activities that are welcome even in the absence of resistance because preventing an infection is always better than treating one. Public health measures like vaccines, clean food, safe drinking water, and infection control all support conservation by reducing the demand for antibiotics in the first instance.<sup>10</sup> But conservation, despite many positive attributes, also faces obstacles. Conservation attempts to limit the inappropriate use of antibiotics, but the difficulty lies in defining “inappropriate,” including use in resource-poor settings where access is the most pressing problem. Furthermore, conservation programs reduce the demand for antibiotics, which may encourage pharmaceutical and biotechnology companies to flee the field. Few companies want to step up R&D investments in a declining market. Most importantly, conservation is a global collective action problem: while most conservation efforts will be implemented nationally, they work best when every country participates. For some countries, financial support will be necessary, as recently articulated in the World Health Organization’s Global Action Plan on Antimicrobial Resistance.<sup>11</sup>

Innovation is the third leg of the tripod. We clearly need new antibiotic drugs to tackle emerging multi-drug resistant diseases and the market is not responding adequately to the challenge.<sup>12</sup> Traditional drug

innovation models would promote either higher prices or larger volumes in order to drive innovation, but for antibiotics, the first would constrain access and the latter might undermine conservation. Crafting an effective new innovation model for antibiotics is necessarily a global endeavor, as described in this series by Manica Balasegaram, Charles Clift, and John-Arne Røttingen.<sup>13</sup> They propose new global institutional arrangements to fund R&D and reward innovation for antibiotics, harmonized with the goals of access and conservation.

### Learning from Different Perspectives

To broaden our understanding of the problem, this series also explores four additional disciplinary perspectives on ABR, rooted in history, economics, “One Health,” and the environment. The recent work on the history of antibiotics is vibrant, woven together in the article by Scott Podolsky and colleagues.<sup>14</sup> The antibiotic era is only seven decades old, but our collective memories need refreshing. Most salient to the present efforts are issues of who controls the use of antibiotics. Conservation and stewardship programs today are marching into prescriber autonomy battles that have been underway for decades in many settings. They also remind us that the current regulatory regime for prescription drugs was largely a response to problems with safety and efficacy of antibiotics. This is a timely reminder since the U.S. Food & Drug Administration and European Medicines Agency have greatly relaxed those standards in recent years, specifically to boost antibiotic innovation.

Three key points arise from the economic analysis by Aidan Hollis and Peter Maybarduk.<sup>15</sup> First, antibiotics are a global public good and the solution must address the “commons” problem. If we treated antibiotics as uniquely valuable and exhaustible, we would stop using them in low-value ways like animal growth promotion and human viral infections. Second, from an economics perspective, addressing the triad of access, conservation and innovation requires global coordination, as national-level solutions would be vulnerable to free riding, perverse financial incentives, and inadequate commitment mechanisms. Finally, they apply the work of Elinor Ostrom on the design and governance of coalitions to manage commons to emerging global governance options for antibiotics.

The One Health movement seeks to understand the many linkages between human and animal health, integrating approaches to improve planetary health. The task given to Anthony So and colleagues was expansive, and could easily have been the subject of its own series. But the primary message shines clearly through the mounds of data: human health and ani-

mal health are deeply intertwined and therefore any solution to ABR must include, as a core component, animal health.<sup>16</sup> It might be tempting to “simplify” the solution by cabining animal issues in a separate response, but that would be a profound mistake.

The final perspective article by Steinar Andresen and Steven J. Hoffman reminds us that ABR is not the only global collective action problem and that we have much to learn from how other sectors address “commons” problems like it.<sup>17</sup> Their article benefits from the decades that Andresen has spent studying multilateral environmental agreements, first relating to oceans and more recently to climate change. They argue that while the international system is inherently weak, states can craft agreements to achieve global collective action if they are designed appropriately. In other words, institutional design matters. Learning from the environment, effective agreements include good procedures for reporting, enhancing compliance, and supporting implementation. Non-state actors must be engaged and mixed legal/political approaches should be considered.

### Moving Towards Global Collective Action

The series ends with four articles that explore the mechanisms, instruments and forums available to states for achieving global collective action on ABR. Steven J. Hoffman and Trygve Ottersen highlight the need to put accountability at the core of any international agreement for it to achieve real-world impact.<sup>18</sup> They start by defining “accountability” — a term used too often in so many different ways — as a relationship involving answerability and enforceability. Building on this definition, they sketch out a taxonomy of accountability mechanisms covering transparency, oversight, complaint and enforcement. This taxonomy then serves as a menu of options for global decision-makers to embed accountability into the core of any kind of international agreement, either for ABR or other issues. Like guests at a restaurant, they do not recommend ordering every item from the menu. That might be unhealthy. But in the absence of empirical studies evaluating each mechanism’s effectiveness, they advise global decision-makers to incorporate at least one mechanism from each category and rigorously evaluate their impact.

Questions around the exact kind of international instrument needed to address ABR are taken up in the next article by Steven J. Hoffman, John-Arne Røttingen and Julio Frenk, who make a strong argument in favor of pursuing an international *legal* approach.<sup>19</sup> Whereas all three co-authors have previously taken stands against the adoption of new global health laws,<sup>20</sup> they see something different in ABR. Specifi-

cally, they think it is the only health challenge for which an international legal approach has thus far been proposed whereby (1) the problem has a significant transnational dimension, (2) the solution justifies the use of an instrument with coercive features, (3) the outcome of utilizing international law is likely beneficial, *and* (4) the implementation of needed actions have not been achieved through other instruments. These four features, which the trio put forward elsewhere as a cri-

priate convening forum for pursuing it will need to be made. Zain Rizvi and Steven J. Hoffman argue that just as much attention should be given to how and where global collective action on ABR is facilitated as the specific actions that are needed.<sup>23</sup> This is because the success of any international agreement depends greatly on where it is negotiated and implemented. In their article, the two co-authors evaluate four different forums through which states could develop an interna-

**Our goal for this series was to start providing evidence-informed guidance for how states and non-state actors could muster a comprehensive response to the global threat of ABR — addressing the access, conservation and innovation imperatives — while inspiring new lines of inquiry. We acknowledge this work is only a start because we know that much additional research and analysis is needed. Our real innovation here is having taken a scientific approach to global strategy whereby we drew upon a range of disciplines to systematically assess how instruments, institutions and initiatives could be designed to foster collective action on ABR and maximize impact. Our hope is that many more researchers, policymakers, activists, and social commentators will join the fray and continue this important work.**

teria for considering new global health laws,<sup>21</sup> make ABR uniquely well-suited for international legal intervention among the range of issues that vie for global decision-makers' attention.

Should the decision be made to pursue negotiation of an ABR international legal agreement, then the exact content of such an agreement will need to be crafted. Asha Behdinan and colleagues take up this challenge by assessing ten possible global ABR policies covering access, conservation and innovation and dividing them into three categories: those policies that depend on legalization to be effective (mostly conservation); those policies that would be strengthened if legalized (mostly access); and those that could be pursued separately but which might help mobilize support for implementation of the other ABR policies if included as part of a grand bargain (mostly innovation).<sup>22</sup> The vitally important argument is that some conservation policies that are desperately needed to address ABR might be impossible to implement without the strength of an international legal agreement behind them. The collective action problems undermining action in some areas are just too great.

Following selection of the most appropriate international instrument, a decision about the most appro-

prate legal agreement: self-organized venue; World Health Organization (WHO); World Trade Organization; and United Nations General Assembly (UNGA). While WHO and UNGA seem particularly promising, ultimately it is clear that an effective response is probably best coordinated through linked action pursued through several forums.

### Concluding Thoughts

So, what kind of actions must be taken to address the global threat of ABR? Every article in this series points towards a common goal: the highest level of global collective action possible across countries, spanning sectors, and among all relevant stakeholders. What legal, political and economic tools might be needed to achieve this level of action? Each article reveals different lessons to be learned. While an international legal framework addressing ABR is recommended, such a framework is still only an implementation vehicle for other tools — whether those are global standards, funding agreements, industry engagement, monitored benchmarks, market incentives, or accountability mechanisms.

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to the global threat of ABR — addressing the access, conservation and innovation imperatives — while inspiring new lines of inquiry. We acknowledge this work is only a start because we know that much additional research and analysis is needed. Our real innovation here is having taken a scientific approach to global strategy whereby we drew upon a range of disciplines to systematically assess how instruments, institutions and initiatives could be designed to foster collective action on ABR and maximize impact.<sup>24</sup> Our hope is that many more researchers, policymakers, activists, and social commentators will join the fray and continue this important work. If we wait too long, we might end up missing today's policy window that has been created by the Global Health Security Agenda launch in February 2014, the adoption of WHO's Global Action Plan on Antimicrobial Resistance in May 2015, the White House Forum on Antibiotic Stewardship and the G7's communiqué in June 2015, and the ongoing O'Neill Review on Antimicrobial Resistance in the United Kingdom, among many other contributing efforts and events.

We have many reasons to be hopeful. In the same month as this series is published, Professor Otto Cars, a grandfather of the ABR research field (and co-author of the second article in this series), was awarded Sweden's H.M. The King's Medal for his contributions to medical science. It demonstrates, in Professor Cars's own words, that ABR research "in the twilight zone in-between science and politics is officially being recognized."<sup>25</sup> We have also started to hear from the world's wealthiest countries that they are prepared to use public money to support antibiotics innovation. A major injection of sustainable financing for R&D of antibiotics could transform the ABR challenge and provide the necessary political leverage to achieve progress on the access and conservation imperatives as well.

We conclude by thanking everyone who made this series possible, including all of our authors, peer-reviewers, coordinators, and publishers. We are especially pleased with the timely process at *JLME* and our partners' commitment to open-access publication.

We hope you enjoy reading the series as much as we enjoyed editing it.

## References

1. D. Hammar skjöld Foundation, "Who We Are," available at <<http://www.daghammarskjold.se/who-we-are>> (last visited June 10, 2015).
2. Global Strategy Lab, "Mission," available at <<http://www.globalstrategy.ninja/about>> (last visited June 10, 2015).
3. American Society of Law, Medicine & Ethics, *Journal of Law, Medicine & Ethics*, "Back Issues and Articles," available at <[http://www.aslme.org/Back\\_Issues\\_And\\_Articles?journal=JLME](http://www.aslme.org/Back_Issues_And_Articles?journal=JLME)> (last visited June 10, 2015).
4. Norwegian Institute of Public Health, "Better Health for All," available at <<http://www.fhi.no/eway/?pid=240>> (last visited June 10, 2015).
5. ReAct – Action on Antibiotic Resistance, "Who We Are," available at <<http://www.reactgroup.org/who-we-are.html>> (last visited June 10, 2015).
6. T. F. Barlam and K. Gupta, "Antibiotic Resistance Spreads Internationally Across Borders," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
7. S. J. Hoffman, K. Outtersen, J.-A. Røttingen, O. Cars, C. Clift, and Z. Rizvi et al., "An International Legal Framework to Address Antimicrobial Resistance," *Bulletin of the World Health Organization* 93, no. 2 (2015): 66.
8. N. Daulaire, A. Bang, G. Tomson, J. N. Kalyango, and O. Cars, "Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
9. Review on Antimicrobial Resistance, "Tackling Drug-Resistant Infections Globally," available at <<http://amr-review.org/home>> (last visited June 11, 2015).
10. C. Clift, U. Gopinathan, C. Morel, K. Outtersen, J.-A. Røttingen, and A. D. So, *Towards a New Global Business Model for Antibiotics: Report from the Chatham House Working Group on New Antibiotic Business Models* (Chatham House, 2015).
11. World Health Organization: Draft Global Action Plan on Antimicrobial Resistance, World Health Organization, available at <[http://www.who.int/drugresistance/AMR\\_DRAFT\\_GAP\\_1\\_Oct\\_2014\\_for\\_MS\\_consultation.pdf](http://www.who.int/drugresistance/AMR_DRAFT_GAP_1_Oct_2014_for_MS_consultation.pdf)> (last visited June 11, 2015).
12. K. Outtersen, J. H. Powers, G. W. Daniels, and M. B. McClellan, "Repairing the Broken Market for Antibiotic Innovation," *Health Affairs* 34, no. 2 (2015): 277-285.
13. M. Balasegaram, C. Clift, and J.-A. Røttingen, "The Global Innovation Model for Antibiotics Needs Reinvention," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
14. S. H. Podolsky, R. Bud, C. Gradmann, B. Hobaek, C. Kirchhelle, T. Mitvedt, M. J. Santesmases, U. Thoms, D. Berild, and A. Kveim Lie, "History Teaches Us That Confronting Antibiotic Resistance Requires Stronger Global Collective Action," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
15. A. Hollis and P. Maybarduk, "Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
16. A. D. So, T. A. Shah, S. Roach, Y. L. Chee, and K. E. Nachman, "An Integrated Systems Approach is Needed to Ensure the Sustainability of Antibiotic Effectiveness for Both Humans and Animals," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
17. S. Andresen and S. J. Hoffman, "Much Can Be Learned about Addressing Antibiotic Resistance from Multilateral Environmental Agreements," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
18. S. J. Hoffman and T. Ottersen, "Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
19. S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "International Law Has a Role to Play in Addressing Antibiotic Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
20. S. J. Hoffman and J.-A. Røttingen, "A Framework Convention on Obesity Control?" *The Lancet* 378, no. 9809 (2011): 2068; S. J. Hoffman and J.-A. Røttingen, "Be Sparing With International Laws," *Nature* 483, no. 7389 (2012): 275; S. J. Hoffman and J.-A. Røttingen, "Dark Sides of the Proposed Framework Convention on Global Health's Many Virtues: A Systematic Review and Critical Analysis," *Health and Human Rights* 15, no. 1 (2013): E117-E134; S. J. Hoffman and J.-A. Røttingen, "Assessing the Expected Impact of Global Health Treaties: Evi-

- 
- dence from 90 Quantitative Evaluations," *American Journal of Public Health* 105, no. 1 (2015): 26-40; S. J. Hoffman, J.-A. Rottingen, and J. Frenk, "Assessing Proposals for New Global Health Treaties: An Analytic Framework," *American Journal of Public Health* (2015): e1-e8.
21. See Hoffman, Rottingen, and Frenk, *supra* note 20.
  22. A. Behdinan, S. J. Hoffman, and M. Pearcey, "Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
  23. Z. Rizvi and S. J. Hoffman, "Effective Global Action on Antibiotic Resistance Requires Careful Consideration of Convening Forums," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
  24. S. J. Hoffman, "A Science of Global Strategy," in J. Frenk and S. J. Hoffman, eds., *"To Save Humanity": What Matters Most for a Healthy Future* (New York: Oxford University Press, 2015): at 173-175.
  25. ReAct – Action on Antibiotic Resistance, "Royal Recognition and New Antibiotics Center Confirmed," available at <<http://www.reactgroup.org/news/496/18.html>> (last visited June 10, 2015).
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# Antibiotic Resistance Spreads Internationally Across Borders

*Tamar F. Barlam and Kalpana Gupta*

## Introduction

Antibiotic resistance (ABR) poses an urgent public health risk. High rates of ABR have been noted in all regions of the globe by the World Health Organization.<sup>1</sup> ABR develops when bacteria are exposed to antibiotics either during treatments in humans or animals or through environmental sources contaminated with antibiotic residues (Figure, Panel A). Spread beyond those administered antibiotics occurs through direct contact with the infected or colonized person or animal, through contact or ingestion of retail meat or agricultural products contaminated with ABR organisms, or through the environment. ABR bacteria spread from individuals to populations and across countries (Figure, Panel B).

## Antibiotic Use in Human Medicine

It is well described that use of antibiotics in human medicine results in ABR organisms that can disseminate internationally. In a 2013 report, the Centers for Disease Control and Prevention (CDC) labeled *Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae*, and drug-resistant *Neisseria gonorrhoeae* as the most urgent ABR threats in the U.S.<sup>2</sup> Those three compelling examples, however, support the need for worldwide mitigating actions.

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A recent report of *C. difficile* genetic epidemiology describes a perfect storm between antibiotic resistance, antibiotic use, and global spread.<sup>3</sup> The study used whole genome sequencing to evaluate the worldwide spread of fluoroquinolone-resistant *C. difficile* 027/NAP1/BI in health care facilities. This specific hypervirulent *C. difficile* strain is associated with significant morbidity and mortality. The investigators found that there were two genetically distinct lineages, both with mutations conferring high-level fluoroquinolone resistance. One lineage, FQR1, originally emerged in the northeastern U.S. and was subsequently transmitted to the Republic of Korea and Switzerland. The second lineage, FQR2, was found to have rapidly disseminated across continents, starting in North America and traveling to continental Europe, the UK and Australia. Acquisition of fluoroquinolone resistance is considered to be the key element driving the global spread of these lineages, fueled by liberal use of fluoroquinolones and international travel.<sup>4</sup>

Carbapenem-resistant *Enterobacteriaceae* (CRE) mediated by New Delhi metallo-beta-lactamase-1 (NDM-1) was first reported in 2008<sup>5</sup> and is another example of clinically important ABR driven by antibiotic use and disseminated by international travel across continents. *Enterobacteriaceae* are bacteria well known for their propensity to develop resistance and to cause serious, including fatal, disease. Infections caused by *Enterobacteriaceae* containing extended-spectrum beta-lactamases (ESBL), e.g., CTX-M, were described prior to NDM-1. ESBL limit the utility of many antibiotics; carbapenems are often the drugs of last resort. The emergence of CRE mediated by NDM-1 has further limited therapeutic options to a critical level.<sup>6</sup>



Figure

**Development and Spread of Antibiotic Resistance**

**Figure** The development of antibiotic-resistant organisms (A) through human and non-human use of antibiotics is followed by spread (B) from local to global environments.

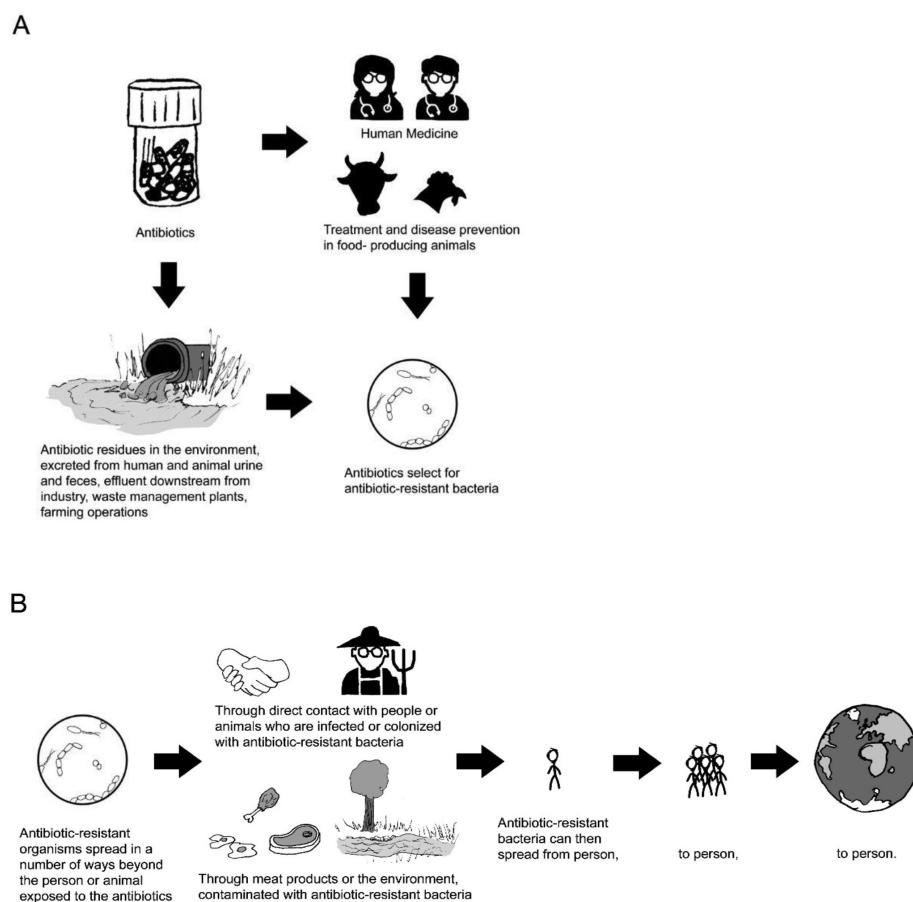


Illustration by Nathaniel Barlam

NDM-1 was initially identified from a man who traveled from his residence in Sweden to New Delhi, India and was hospitalized for treatment of an infection. On his first day back in Sweden, a highly resistant *Klebsiella pneumoniae* isolate was grown from his urine. Subsequently an *Escherichia coli* isolate was grown from stool; both species were found to carry NDM-1. Molecular studies confirmed that the NDM-1 gene was located on transferable plasmids (extra-chromosomal genetic material) in the *K. pneumoniae* and *E. coli* isolates, supporting the concept that resistance spread between the species. Further studies

have identified NDM-1-positive *Enterobacteriaceae* in almost every continent.<sup>7</sup> Travel, including medical tourism, is a key feature of the international spread of these highly resistant bacteria within health care facilities.<sup>8</sup> Importantly, hospitals are not the only reservoir for NDM-1 bacteria; studies have demonstrated that samples of pooled water from streets as well as from drinking water can also be positive for the bacteria.

*N. gonorrhoeae* causes gonorrhea, a common and clinically important sexually transmitted disease. Until now, the bacteria have been extremely susceptible to fluoroquinolones, and these infections were relatively

easy to treat. However, fluoroquinolone resistance in *N. gonorrhoeae* is spreading worldwide and impacting choices for therapy. Soaring rates of antibiotic resistance have been reported in every continent, with evidence of high-level fluoroquinolone resistance (MICs of ciprofloxacin >1.0 mg/L).<sup>9</sup> The story progresses even further with emergence of multi-drug resistant *N. gonorrhoeae*, further restricting treatment options. Treatment failure due to antibiotic resistance has led to a change in CDC guidelines that now recommend an injectable agent, ceftriaxone, in combination with either azithromycin or doxycycline.

### Antibiotic Use in Food-Producing Animals

Development and spread of ABR bacteria is also promoted by use in food-producing animals (FPA). In food-animal production, antibiotics are not only administered to treat sick animals, but also given routinely to prevent illness (prophylaxis) or promote growth. That nontherapeutic antibiotic use is given for much of the animal's life, often at sub-inhibitory doses which particularly select for ABR (see below). ABR bacteria that develop in FPAs reach human hosts through several pathways. ABR *Salmonella*, *Campylobacter*, enterococci, and *E. coli* commonly contaminate retail meats<sup>10</sup> and are linked to human infections. Those meats are distributed both locally and globally. For example, a Swiss study identified and characterized 24 ESBL-producing *Enterobacteriaceae* from both domestic and imported poultry meat.<sup>11</sup> A study from the UK cultured chicken breasts for *E. coli* and identified isolates producing the CTX-M ESBL enzyme. One of 62 UK samples contained this enzyme compared with 10 of 27 imported samples. The South American poultry meat contained CTX-M-2, the dominant genotype in human infections in South America but a rare cause to date of those infections in the UK.<sup>12</sup>

There is strong evidence that contaminated meats contribute to ABR *Salmonella* and *Campylobacter* gastroenteritis, but whether they cause extra-intestinal infections, such as urinary tract infections (UTIs) caused by *E. coli*, is more controversial. A recent systematic review examined the evidence that extra-intestinal human infections with ESBL *E. coli* originated from FPAs. The authors reviewed evidence for both transmission of the ABR bacterial organisms (whole bacterium transmission or WBT) and transfer of ABR

genetic material between bacteria (mobile genetic elements or MGE). Six studies supported WBT between poultry meat and humans. Transfer of MGE between bacteria from different species of animals (poultry, pigs, and cattle) and human *E. coli* was found in 13 geographically diverse studies. Seventeen studies did not support WBT, although 8 of those studies did find MGE-mediated transmission. Three of 4 observational epidemiological studies found ABR transmission between FPA and human *E. coli*. Overall, the literature supports a connection, but further study is needed to quantify the frequency and magnitude of the issue.<sup>13</sup>

ABR bacteria in FPAs can also spread directly to farmers and then to the community. A study in the 1980s examined the spread of nourseothricin, an agent used to medicate pigs that has no equivalent in human medicine. The farmers had nourseothricin-resistant *E. coli* in their gut, as did the members of that community. In addition, nourseothricin-resistant *E. coli* UTIs

**New research emphasizes how sub-inhibitory levels of antibiotics are an important contributor to ABR by selecting for pre-existing resistant strains, by generating genetic and phenotypic variability, and by acting as signaling molecules to influence bacterial activities such as biofilm formation and gene expression. These resistant strains grow as well as organisms that are fully susceptible to antibiotics; thus, resistance imparts no fitness cost.**

were identified.<sup>14</sup> In a more recent example, a Danish study compared farms with and without high 3rd and 4th generation cephalosporin use for the presence of ESBL-producing isolates in humans and pigs. Nineteen of 195 human participants were colonized, and 18 of those 19 had direct animal contact. In 10 farms, the same resistance gene was detected in both pig and human feces; in four farms, the isolates were proven identical in pigs and humans by many scientific methods, i.e., enzyme analysis, phylotype, PFGE type and multilocus sequence typing.<sup>15</sup>

### Antibiotic-Resistant Bacteria and the Environment

Resistant bacteria contaminate the environment due to industrial sources and large farming operations. For example, researchers sampled river sediment

upstream and downstream from a treatment plant that processed human, animal, and industrial waste. The samples downstream from the plant contained a marked increase in genes encoding the plasmid-mediated ESBL enzyme, CTX-M, in multiple species including *E. coli* and *Aeromonas*. They also demonstrated that the gene could be transferred easily between different bacterial species abundant in waste effluent.<sup>16</sup> In addition to ABR bacteria, actual antibiotic drug residues are commonplace as 20-80% of antibiotics are excreted in active forms into the environment from urine and feces.<sup>17</sup> Drug residues are found in waste water and sludge from farming operations but also in rivers, lakes, and drinking water. ABR bacteria and antibiotic drug residues have also been found in flies<sup>18</sup> and dust<sup>19</sup> originating from industrial farms.

New research emphasizes how sub-inhibitory levels of antibiotics are an important contributor to ABR by selecting for pre-existing resistant strains, by generating genetic and phenotypic variability, and by acting as signaling molecules to influence bacterial activities such as biofilm formation and gene expression. These resistant strains grow as well as organisms that are fully susceptible to antibiotics; thus, resistance imparts no fitness cost. The minimal concentration of antibiotic that selects for specific resistance mutations in different bacterial species can be 10- to 100-fold lower than the minimal concentration of the drug needed to treat the infection. Thus, antibiotic levels in the nanogram per milliliter range, a level comparable to the residues found in the environment, can promote resistance.<sup>20</sup>

### Infection and Asymptomatic Colonization in Returning Travelers

When spread of ABR bacteria results in overt infection, there are opportunities for containment through proper treatment, infection control, and surveillance. However, ABR infections can persist and spread due to asymptomatic colonization. An outbreak of carbapenem-resistant *K. pneumoniae* at the U.S. National Institutes of Health Clinical Center resulted in 18 infections and 11 deaths, more than three weeks after the index patient was discharged. The authors determined the ability of the organism to silently colonize patients in the hospital contributed to the ongoing outbreak.<sup>21</sup>

Strong evidence shows that people can become asymptomatically colonized with resistant pathogens after international travel. In a recent study, German travelers were studied for fecal colonization with ABR *Enterobacteriaceae* before and after travel to one of 53 different countries. ESBL-producing *E. coli* and *K.*

*pneumoniae* were present in 6.8% of study volunteers pre-travel but post-travel, 30.4% were colonized with ESBL *E. coli* and 8.6% were colonized with ESBL *K. pneumoniae*. Travel to India and SE Asia had the highest acquisition rates for those ABR bacteria. Although half the individuals had a clinical bout of gastroenteritis associated with the travel, the rest were totally asymptomatic. Colonization persisted for six months in 8.6%.<sup>22</sup> In another study conducted in the Netherlands with a similar pre- and post-travel design, metagenomics DNA was extracted from fecal samples of volunteers. ESBL *Enterobacteriaceae* increased from 9% pre-travel to 33.6% post-travel, while quinolone-resistance genes *qnrB* and *qnrS* increased from 6.6% and 8.2% pre-travel to 36.9% and 55.7% post-travel, respectively.<sup>23</sup> Fecal colonization is of special interest because of the potential for MGE transfer of ABR among the diverse bacterial species within the gut microbiome. Colonization with other ABR bacteria, such as methicillin-resistant *Staphylococcus aureus*, in travelers has also been reported.<sup>24</sup>

### Summary

Resistant bacteria selected by medical, agricultural, and industrial use spread globally through travelers, the export of animals and retail products, and the environment. Resistant bacterial strains may not persist if there is no selective pressure from local antibiotic use. However, this is not true for most ABR bacteria, where low fitness cost of the resistance and co-selection of other markers linked on MGE sustain those bacteria.<sup>25</sup> Thus, it is essential that nations work together to identify how to reduce emergence and amplification of resistant bacteria through sensible antibiotic treatment guidelines and restrictions. Concerted efforts for surveillance — to understand when new threats are brought across borders — and infection control — to minimize the spread and risk for outbreaks of ABR organisms — require global cooperation and solutions.

### References

1. World Health Organization, *Antibiotic Resistance: Global Report on Surveillance* (2014), available at <[http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf)> (last visited May 8, 2015).
2. Centers for Disease Control and Prevention (CDC), "Antibiotic Resistance Threats in the United States. 2013," available at <<http://www.cdc.gov/drugresistance/threat-report-2013/>> (last visited May 8, 2015).
3. D. N. Gerding and F. C. Lessa, "The Epidemiology of *Clostridium difficile* Infection Inside and Outside Health Care Institutions," *Infectious Disease Clinics of North America* 29, no. 1 (2015): 37-50.
4. M. He et al., "Emergence and Global Spread of Epidemic Healthcare-Associated *Clostridium Difficile*," *Nature Genetics* 45, no. 1 (2013): 109-113.
5. D. Yong et al., "Characterization of a New Metallo-β-Lactamase Gene, *bla*NDM-1, and a Novel Erythromycin Esterase Gene



- Carried on a Unique Genetic Structure in *Klebsiella Pneumoniae* Sequence Type 14 from India," *Antibiotic Agents and Chemotherapy* 53, no. 12 (2009): 5046-5054.
6. A. P. Johnson and N. Woodford, "Global Spread of Antibiotic Resistance: The Example of New Delhi Metallo- $\beta$ -Lactamase (NDM)-Mediated Carbapenem Resistance," *Journal of Medical Microbiology* 62, part 4 (2013): 499-513.
  7. J. S. Molton et al., "The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective from Asia," *Clinical Infectious Diseases* 56, no. 9 (2013): 1310-1318.
  8. B. A. Rogers et al., "Country-to-Country Transfer of Patients and the Risk of Multi-Resistant Bacterial Infection," *Clinical Infectious Diseases* 53, no. 1 (2011): 49-56.
  9. D. Yong et al., "Epidemiological Characteristics and Molecular Basis of Fluoroquinolone-Resistant *Neisseria Gonorrhoeae* Strains Isolated in Korea and Nearby Countries," *Journal of Antibiotic Chemotherapy* 54, no. 2 (2004): 451-455; M. Pérez-Losada et al., "Distinguishing Importation from Diversification of Quinolone-Resistant *Neisseria Gonorrhoeae* by Molecular Evolutionary Analysis," *BMC Evolutionary Biology* 7, article 84 (2007).
  10. F. M. Aarestrup et al., "Resistance in Bacteria of the Food Chain: Epidemiology and Control Strategies," *Expert Review of Anti-Infective Therapy* 6, no. 5 (2008): 733-750.
  11. H. Abgottspon et al., "Characteristics of Extended-Spectrum Cephalosporin-Resistant *Escherichia coli* Isolated from Swiss and Imported Poultry Meat," *Journal of Food Protection* 77, no. 1 (2014): 112-115.
  12. R. E. Warren et al., "Imported Chicken Meat as a Potential Source of Quinolone-Resistant *Escherichia coli* Producing Extended-Spectrum Beta-Lactamases in the UK," *Journal of Antibiotic Chemotherapy* 61, no. 3 (2008): 504-508.
  13. B. Lazarus et al., "Do Human Extra Intestinal *Escherichia coli* Infections Resistant to Expanded-Spectrum Cephalosporins Originate from Food-Producing Animals? A Systematic Review," *Clinical Infectious Diseases* 60, no. 3 (2015): 439-452.
  14. R. Hummel et al., "Spread of Plasmid-Mediated Nourseothricin Resistance Due to Antibiotic Use in Animal Husbandry," *Journal of Basic Microbiology* 26, no. 8 (1986): 461-466.
  15. A. M. Hammerum et al., "Characterization of Extended-Spectrum Beta-Lactamase (ESBL)-Producing *Escherichia coli* Obtained from Danish Pigs, Pig Farmers and Their Families from Farms with High or No Consumption of Third- or Fourth-Generation Cephalosporins," *Journal of Antibiotic Chemotherapy* 69, no. 10 (2014): 2650-2657.
  16. G. C. A. Amos et al., "Waste Water Effluent Contributes to the Dissemination of CTX-M-15 in the Natural Environment," *Journal of Antibiotic Chemotherapy* 69, no. 7 (2014): 1785-1791.
  17. D. I. Andersson and D. Hughes, "Microbiological Effects of Sublethal Levels of Antibiotics," *Nature Reviews Microbiology* 12, no. 7 (2014): 465-478.
  18. J. P. Graham et al., "Antibiotic Resistant Enterococci and Staphylococci Isolated from Flies Collected Near Confined Poultry Feeding Operations," *Science of the Total Environment* 407, no. 8 (2009): 2701-2710.
  19. G. Hamscher et al., "Antibiotics in Dust Originating from a Pig-Fattening Farm: A New Source of Health Hazard for Farmers?" *Environmental Health Perspectives* 111, no. 13 (2003): 1590-1594.
  20. See Andersson and Hughes, *supra* note 17.
  21. E. S. Snitkin et al., "Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing," *Science Translational Medicine* 4, no. 148 (2012): 148ra116.
  22. C. Lübbert et al., "Colonization with Extended-Spectrum Beta-Lactamase-Producing and Carbapenemase-Producing *Enterobacteriaceae* in International Travelers Returning to Germany," *International Journal of Medical Microbiology* 305, no. 1 (2015): 148-156.
  23. C. J. Von Wintersdorff et al., "High Rates of Antibiotic Drug Resistance Gene Acquisition after International Travel, The Netherlands," *Emerging Infectious Diseases* 20, no. 4 (2014): 649-657.
  24. Y. P. Zhou et al., "The Role of International Travel in the Spread of Methicillin-Resistant *Staphylococcus aureus*," *Journal of Travel Medicine* 21, no. 4 (2014): 272-281.
  25. D. I. Andersson and D. Hughes, "Antibiotic Resistance and Its Cost: Is It Possible to Reverse Resistance?" *Nature Reviews Microbiology* 8, no. 4 (2010): 260-271.

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# Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance

*Nils Daulaire, Abhay Bang, Göran Tomson, Joan N. Kalyango, and Otto Cars*

## Introduction

The right to health is enshrined in the constitution of the World Health Organization<sup>1</sup> and numerous other international agreements. Yet today, an estimated 5.7 million people die each year (Table 1) from treatable infectious diseases, most of which are susceptible to existing antimicrobials if they were accessible. These deaths occur predominantly among populations living in poverty in low- and middle-income countries, and they greatly exceed the estimated 700,000 annual deaths worldwide currently attributed to antimicrobial resistance (AMR).<sup>2</sup> Ensuring universal appropriate access to antimicrobials is not only a critical part of realizing the right to health, it is necessary for mobilizing effective collective action against the development and spread of AMR.

## A Strategy for Universal Access

The 1980s saw a dramatic global expansion of child health efforts, but they did not initially address pneumonia, which kills nearly a million children under five annually<sup>3</sup> and is the leading global cause of child deaths. Since bacterial pneumonia requires timely

case management and treatment with antibiotics, this seemed like too much to ask of rudimentary primary health care systems and relatively unskilled health workers. However, a series of community-based intervention trials in the 1980s demonstrated that community health workers could reliably carry out presumptive diagnosis of pneumonia and treat cases with oral antibiotics, resulting in substantial mortality reduction among the population of children served.<sup>4</sup> Oral co-trimoxazole (trimethoprim/sulfamethoxazole) was used as the first line treatment of choice. More recent studies have utilized oral amoxicillin.<sup>5</sup>

These studies proved that it was feasible to provide wide-scale antibiotic access for effective treatment of childhood pneumonia, and their findings were adopted by WHO and UNICEF and incorporated into health facility-based Integrated Management of Childhood Illnesses and integrated Community Case Management programs.<sup>6</sup> However, proof of effectiveness and even policy adoption does not necessarily translate into general application. Although every region has shown progress in appropriate care-seeking for suspected childhood pneumonia, still only 30% of children with suspected pneumonia in sub-Saharan Africa receive antibiotics.<sup>7</sup> Much work remains to be done.<sup>8</sup>

Similarly, neonatal sepsis kills more than a third of a million newborn babies each year,<sup>3</sup> predominantly in low-income communities. Case fatality in the pre-antibiotic era was reported to be 90 percent.<sup>9</sup> Work carried out in India demonstrated that early community-level antibiotic treatment of newborns with presumed neonatal sepsis significantly reduced neonatal mortality.<sup>10</sup> Injectable gentamicin and oral co-trimoxazole were administered in the household by female

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Table 1

### Global Deaths (Thousands) Due to Selected Infections Amenable to Antimicrobial Treatment (2013)<sup>3</sup>

Lower respiratory infections/pneumonia*	2,466
Tuberculosis	1,290
Malaria	855
Neonatal sepsis and infections	366
Meningitis	304
Intestinal infections*	221
Sexually transmitted infections*	142
Maternal sepsis and infections	24
TOTAL	5,668

\*All ages, excludes viral aetiologies

health workers. This field trial again provided clear evidence that assuring effective access to appropriate, low-cost antibiotics was feasible and could have a major impact on infant deaths in the world's poorest societies.

Similar findings have come from community-based programs aimed at malaria and tuberculosis.<sup>11</sup> Assessments carried out in a variety of settings have found that appropriately trained and supervised community workers are more likely to follow diagnosis and treatment protocols than either doctors or pharmacists,<sup>12</sup> minimizing the likelihood of development of resistance.

While it is clear that a large proportion of deaths caused by infections could be averted by full access to timely and appropriate antimicrobial treatment, this needs to be done under well-managed conditions, since inappropriate antimicrobial treatment is at best ineffective and at worst a contributor to the accelerated spread of resistance. A clear warning comes from the evidence of rapidly emerging artemisinin-resistant malaria in areas of Southeast Asia in which inappropriate and inadequate dosing, often driven by widespread and poorly managed commercial distribution of monotherapy, dubious quality drugs and weak application of global norms, appears to be the leading culprit.<sup>13</sup> This has obvious implications for the application of novel therapeutics discussed in other papers of this series.<sup>14</sup>

Even when well-managed, however, AMR will inevitably increase over time due to selective pressure. Warnings came early that the most common bacterial cause of childhood pneumonia, *Streptococcus pneumoniae*, was becoming increasingly resistant to co-

trimoxazole.<sup>15</sup> However, the process towards a policy change was lengthy, and it was not until 2005 that the WHO changed its treatment recommendations and included amoxicillin as an alternative to co-trimoxazole<sup>16</sup> (the latest recommendations only include amoxicillin).<sup>17</sup> Similarly, in the treatment of neonatal sepsis, antibiotic resistance to the first line treatments (gentamicin and procaine benzylpenicillin) has long been evident in hospital settings among leading bacterial causes, such as *Staphylococcus aureus*, *Klebsiella* and *Escherichia coli*.<sup>18</sup> Although use of these antibiotics may still be retained in many settings, the changing resistance patterns need to be taken into consideration.

The prospect of diminishing effectiveness of first-line antimicrobials has serious implications for the affordability and accessibility of appropriate treatment. The potential need to shift to drugs that are costlier and more difficult to administer will have the greatest adverse impact on those living in low-income and underserved communities, reinforcing the need for mutual reinforcement of efforts aimed at improved access and those aimed at stewardship. Meaningful access is dependent on good stewardship and vice versa.<sup>19</sup>

### Policy Implications

Implications for global efforts to reduce health inequity and assure the highest attainable standard of care for *all* the world's people are clear. New drug regimens and tailored programmatic approaches are on the table as we look to assure *appropriate* access to *effective* antimicrobials for all who need them to address the major infectious killers. However, the implications for the dissemination, use, and stewardship of innovative *new* antimicrobials consistent with a commitment to universal access make it clear that the world cannot afford to squander the next generation of therapeutics — or else, in a generation or less, we could once again be left with nothing.

### Treatment Protocols

In order to assure that antimicrobials — both those currently in existence with clear therapeutic value, and novel future drugs — are accessible for all and effective for the longest possible time, the introduction of new treatment regimens should be carried out in light of what has been learned in programs focused on widespread and appropriate access, and that these efforts be directly tied to the development and introduction of new therapeutics. As a first step in this process, the global scientific community will need to strengthen its assessment of appropriate treatment

and usage, defining parameters for deciding which antimicrobials are effective in which areas of the world and useful at various levels of health care systems. This is an evidence-based normative process, and is reflected in the development of previous effective antimicrobial programs. Furthermore, this is not a static effort, but needs to be continuously reviewed and updated based on dynamics of use and evidence of emerging resistance.

#### *International Framework and Regulations*

Based on this assessment at the global level, national authorities, supported as necessary with external technical assistance and resources that could be guided and supported by an overarching international framework, must take responsibility for defining appropriate and evidence-based treatment regimens suited to both the local microbial ecology and delivery systems within their countries. We also must recognize the pluralistic nature of health systems, especially in low- and middle-income countries where the majority of drugs are often provided by a little-regulated private sector. This must, therefore, be a comprehensive health-systems approach<sup>20</sup> that assures universal access, and defines the key conditions and levels of care at which each important antimicrobial will be used. Crucially, this must be reinforced by international support for universalization of access, as well as agreements and strengthened regulatory regimes that reduce the likelihood of system-wide misuse, particularly of newly introduced drugs.

#### *Community*

For the right to health to be an important consideration of this process, and for universal access to be a central principle, the large majority of serious but common infections will need to be addressed within the communities in which they occur. As was demonstrated with the studies cited, large-scale impact can only be achieved with programs that are focused on and driven by community needs and realities.

The result of this process will be a rigorous clarification of who (what type of health provider) can use which antimicrobials (first, second, third line, novel), where (community, first level facility, hospital, tertiary hospital), and for what conditions (common but serious infections, rarer and more difficult to treat). This calls for a basic system of referral and care, and would be enormously undermined by a situation in which antimicrobials were permitted to simply flood the market with limited regulatory oversight. After all, access to antibiotic treatment is highly sought after by the rich and poor globally, and where governments have been unable to provide this access, markets have

emerged to meet this demand. In the absence of supportive institutional arrangements, undesirable practices inevitably predominate.

#### *Providers*

The first line of such a system must be the presence of and effective access to knowledgeable and ubiquitous providers. The level of educational background of such providers will be highly context-specific to the countries involved, but in many of the poorest and most under-served areas, they will likely be community members with limited primary or secondary education who have been put through a highly selective and targeted training program that teaches them to do a few things extremely well. Health workers must also be continually prompted to carry out effective and routine follow-up of their patients under treatment, both as a basic standard of care, and to assure assiduous adherence to treatment regimens as a key tool of stewardship.

#### *Program Management*

Training and deployment of community-level workers are not in themselves sufficient to assure effective, good quality care. The ongoing effectiveness of such efforts is highly dependent on a reliable system of management, supply, financing, and support of these health care providers. While such programs do not need to be national in scope, national authorities must see to it that there is full coverage of their most at-risk communities and that obstacles to the effective management of their programs are dealt with as a top policy priority.

#### *Cost*

A key element in getting access to care to the community will be the affordability of the antimicrobials, and principles of both stewardship and global solidarity suggest that pricing and financing of novel antimicrobials at the national and subnational level must be undertaken with an eye towards innovative mechanisms, as described elsewhere in this series.<sup>14</sup> We cannot allow high cost to drive the poor out of the market. However, we must also assure that neither low cost nor excessive cost push novel antimicrobials into an unmanaged marketplace with high risk of counterfeiting and uncontrolled drug quality.

#### *End Users*

Low price is not in itself sufficient to assure low-income people the benefits of antimicrobial treatment. The implementation of a sustained effort to achieve system-wide changes in the use both of existing, still-effective antibiotics and future, new antibiotics requires informed and committed collaboration



at national and global levels. It will here be especially important to ensure the perspective of the end user, particularly the most under-served, within a system of controlled distribution and use of a new antibiotic.

appropriate and managed use, and the emergence of resistance would be significantly slowed.

Universal access to and rational use of antibiotics in public health programs has been proven feasible.

**The world has a collective responsibility to preserve antibiotic effectiveness and access for all, and to see to it that the *right to health* is translated into meaningful action. Ensuring universal and appropriate access to essential medicines is a necessary precondition to any policy on restricting the use of antimicrobials in low-income settings; absent this, any restriction is likely to be ethically and politically challenged, or simply ignored.**

### Data

Surveillance data are essential for providing information on trends and magnitude of resistance, but there is as yet no global system to address this need. Absence of essential epidemiological data leads to delayed or suboptimal revisions of treatment guidelines, and strengthens the vicious circle of injudicious use of antibiotics by prescribers. This missing link has become critical, and if not addressed could well lead to recommendations to increase access to treatments that turn out to be ineffective. Additionally, good monitoring and data systems will allow early recognition of patterns of treatment failure that would allow far more rapid recognition of and response to emergence of resistance, allowing programs to make necessary adjustments before such resistance has had a chance to become widespread.

### Conclusion

The world has a collective responsibility to preserve antibiotic effectiveness and access for all, and to see to it that the *right to health* is translated into meaningful action. Ensuring universal and appropriate access to essential medicines is a necessary precondition to any policy on restricting the use of antimicrobials in low-income settings; absent this, any restriction is likely to be ethically and politically challenged, or simply ignored.

The ideas put forward in this paper are not a promise of an end to the development of AMR, nor will they by themselves assure that all the world's people have effective access to antimicrobials at all times when they are critically needed. But by working towards universal access to appropriate treatment, coupled with meaningful efforts at regulation and stewardship, the balance of the world's depletable resource of antimicrobials would shift significantly towards

Unless the world's poorest populations, and the low- and middle-income countries in which they live, can be assured of universal access to effective antimicrobials, the current dynamic of misuse and accelerating resistance will not be reversed. This a clear example of a *global governance for health* issue,<sup>21</sup> where rich countries should set aside earmarked funds to assist in assuring universal effective access for the poor as part of a global grand bargain that in turn helps to protect the continued effectiveness of these drugs for all. Every country on earth stands to benefit from this effort.

### References

1. World Health Organization, *Constitution of the World Health Organization* (July 22, 1946).
2. J. O'Neill, *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations* (2014); Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2013* (2013); European Center for Disease Control and European Medicines Agency, *The Bacterial Challenge: Time to React* (2009).
3. GBD 2013 Mortality and Causes of Death Collaborators, "Global, Regional, and National Age-Sex Specific All-Cause and Cause-Specific Mortality for 240 Causes of Death, 1990-2013: A Systematic Analysis for the Global Burden of Disease Study 2013," *The Lancet* 385, no. 9963 (2015): 117-171.
4. M. R. Pandey, N. Daulaire, E. S. Starbuck, R. M. Houston, and K. McPherson, "Reduction in Total Under-Five Mortality in Western Nepal through Community-Based Antimicrobial Treatment of Pneumonia," *The Lancet* 338, no. 8773 (1991): 993-997; A. T. Bang, R. A. Bang, O. Tale, P. Sontakke, J. Solanki, R. Wargantiwar, and P. Kelzarkar, "Reduction in Pneumonia Mortality and Total Childhood Mortality by Means of Community-Based Intervention Trial in Gadchiroli, India," *The Lancet* 336, no. 8709 (1990): 201-206, at 8709; S. Sazawal and R. E. Black, Pneumonia Case Management Trials Group, "Effect of Pneumonia Case Management on Mortality in Neonates, Infants, and Preschool Children: A Meta-analysis of Community-Based Trials," *The Lancet Infectious Diseases* 3, no. 9 (2003): 547-555, at 9.
5. A. Tshefu et al., "Oral Amoxicillin Compared with Injectable Procaine Benzylpenicillin Plus Gentamicin for Treatment of Neonates and Young Infants with Fast Breathing When Referral Is Not Possible: A Randomized, Open-Label, Equivalence Trial," *The Lancet* 385, no. 9979 (2015): 1758-1766.

6. World Health Organization, *Handbook: IMCI (Integrated Management of Childhood Illness)* (2005).
7. United Nations Children's Fund, *Pneumonia and Diarrhea: Tackling the Deadliest Diseases for the World's Poorest Children* (2012).
8. K. Kallander, M. Young, and S. Qazi, "Universal Access to Pneumonia Prevention and Care: A Call for Action," *The Lancet Respiratory Medicine* 2, no. 12 (2014): 950-952, at 12.
9. R. M. Freedman, D. L. Ingram, I. Gross, R. A. Ehrenkranz, J. B. Warshaw, and R. S. Baltimore, "A Half Century of Neonatal Sepsis at Yale: 1928 to 1978," *American Journal of Diseases of Children* 135, no. 142 (1981): 140-144, at 142.
10. A. T. Bang, R. Bang, S. B. Baitule, M. H. Reddy, and M. D. Deshmukh, "Effect of Home-Based Neonatal Care and Management of Sepsis on Neonatal Mortality: Field Trial in Rural India," *The Lancet* 354, no. 9194 (1999): 1955-1961.
11. J. Nsungwa-Sabiti, S. Peterson, G. Pariyo, J. Ogwal-Okeng, M. Petzold, and G. Tomson, "Home Based Management of Fever Improves Malaria Treatment Practices in Uganda," *Transaction of Royal Society of Tropical Medicine and Hygiene* 101, no. 12 (2007): 1199-1207; A. Arshad, R. A. Salam, Z. S. Lassi, J. K. Das, I. Naqvi, and Z. A. Bhutta, "Community Based interventions for the Prevention and Control of Tuberculosis," *Infectious Diseases of Poverty* 3 (2014): 27-37.
12. K. D. Rao, T. Sundararaman, A. Bhatnagar, G. Gupta, P. Kokho, and K. Jain, "Which Doctor for Primary Health Care? Quality of Care and Non-physician Clinicians in India," *Social Science & Medicine* 84 (2013): 30-34.
13. K. M. Tun, M. Imwong, K. M. Lwin, A. A. Win, T. M. Hlaing, T. Hlaing, and K. Lin et al., "Spread of Artemisinin-Resistant *Plasmodium Falciparum* in Myanmar: A Cross-Sectional Survey of the K13 Molecular Marker," *The Lancet Infectious Diseases* (forthcoming 2015).
14. M. Balasegaram, C. Clift, and J. A. Røttingen, "A Pathway towards an Alternative Business Model for Antibiotic Innovation: A framework, Fund and Institutional Mechanism," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
15. I. N. Okeke, R. Laxminarayan, Z. A. Bhutta, A. G. Duse, P. Jenkins, T. F. O'Brien, A. Pablos-Mendez, and K. P. Klugman, "Antimicrobial Resistance in Developing Countries. Part I: Recent Trends and Current Status," *The Lancet Infectious Diseases* 5, no. 8 (2005): 481-493; D. R. Feikin, S. F. Dowell, O. C. Nwan-yawu, K. P. Klugman, P. N. Kazembe, L. M. Barat, and C. Graf et al., "Increased Carriage of Trimethoprim/Sulfamethoxazole-Resistant *Streptococcus Pneumoniae* in Malawian Children after Treatment for Malaria with Sulfadoxine/Pyrimethamine," *Journal of Infectious Diseases* 181, no. 4 (2000): 1501-1545.
16. G. B. Grant, H. Campbell, S. F. Dowell, S. M. Graham, K. P. Klugman, E. K. Mulholland, M. Steinhoff, M. W. Weber, and S. Qazi, World Health Organization Department of Child and Adolescent Health and Development, "Recommendations for Treatment of Childhood Non-severe Pneumonia," *The Lancet* 9, no. 3 (2009): 185-196.
17. World Health Organization, *Revised WHO Classification and Treatment of Childhood Pneumonia at Health Facilities: Implications for Policy and Implementation*, WHO Department of Maternal, Child, Newborn and Adolescent Health, Geneva (2014).
18. A. K. Zaidi, W. C. Huskins, D. Thaver, Z. A. Bhutta, Z. Abbas, and D. A. Goldmann, "Hospital-Acquired Neonatal Infections in Developing Countries," *The Lancet* 365, no. 9465 (2005): 1175-1188.
19. C. Nathan and O. Cars, "Antibiotic Resistance – Problems, Progress, and Prospects," *New England Journal of Medicine* 371, no. 19 (2014): 1761-1763.
20. G. Tomson and I. Vlad, "The Need to Look at Antibiotic Resistance from a Health Systems Perspective," *Upsala Journal of Medical Sciences* 119, no. 2 (2014): 117-124.
21. O. P. Ottersen, J. Frenk, and R. Horton, "The Lancet-University of Oslo Commission on Global Governance for Health, in collaboration with the Harvard Global Institute," *The Lancet* 378, no. 9803 (2011): 1612-1613.

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# The Global Innovation Model for Antibiotics Needs Reinvention

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## Introduction

The dangers presented by antibiotic resistance (ABR) have now established themselves as a global health security issue. From an international policy perspective, three key pillars have been established: responsible access, conservation, and innovation. These pillars are intrinsically linked, meaning that any attempt to address one must take into account the implications for the other two.

An urgent need exists to address the innovation failure in ABR. In the field of anti-bacterials, the pipeline remains anemic in terms of therapeutics with novel mechanisms of action, new drug classes and strategies involving radically different, innovative approaches.<sup>1</sup> The key reasons for this failure have already been well established.<sup>2</sup> The slow development of new antibiotics is the result of a poor and uncertain commercial market and scientific challenges in research and development (R&D). If strong responsible use and conservation strategies are put into place, this further undermines the R&D incentive that derives from market value. The response from policymakers, states, and regions has been to introduce various economic and incentive strategies, such as the Innovative Medicines Initiative's (IMI) New Drugs for Bad Bugs program in the E.U. and the U.S. Generating Antibiotic Incentives Now Act (GAIN)<sup>3</sup> and regulatory simplification to facilitate

new drug development.<sup>4</sup> However, it is unclear if new regulatory pathways or extended periods of exclusivity will help overcome upstream scientific challenges, ensure the development of antibiotics serving global public health needs, and promote access together with conservation.

A multiplicity of publications, commissions, and reports has investigated this issue highlighting major problem areas and possible solutions. The concept of delinkage has been proposed to develop new business models to promote innovation into new antibiotics.<sup>2</sup> Delinkage would mean breaking the link between reward for R&D and innovation on the one hand and revenues (price and volume) of sales of an innovative product on the other. The concept is relevant in that it removes perverse incentives on the innovator (and others in the value chain) to increase utilization of a new antibiotic above levels defined by public health needs.

It is worth noting that the World Health Organization (WHO) Consultative Expert Working Group on Research and Development (CEWG)<sup>5</sup> saw the concept of delinkage as a guiding principle for alternative and credible business models for biomedical innovation, and the concept has been supported in the WHO as well as by several business stakeholders. Furthermore, the CEWG also saw multiple combined strategies such as an open approach to R&D (including pre-competitive R&D platforms, open source and open access schemes), prizes (e.g., milestone prizes), equitable licensing, and patent pools as practical means to promote innovation through delinkage.

There is now a need to move beyond concepts, recognizing that current initiatives are as yet insufficient to address needs. This paper proposes to look at three key and interrelated steps that may help in moving

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There is now a need to move beyond concepts, recognizing that current initiatives are as yet insufficient to address needs. This paper proposes to look at three key and interrelated steps that may help in moving towards an alternative business model for antibiotic innovation that will promote needs-driven R&D while securing responsible access. The justification for a legal framework will be explored as a key enabler. Additionally, the need to go beyond a legal framework in order to implement an alternative business model will also be discussed.

towards an alternative business model for antibiotic innovation that will promote needs-driven R&D while securing responsible access. The justification for a legal framework will be explored as a key enabler. Additionally, the need to go beyond a legal framework in order to implement an alternative business model will also be discussed.

### Key Principles towards a Successful Business Model for ABR

Drawing from the extensive work undertaken over the last several years, key principles can be derived that would underpin an improved and creative business model for ABR:

- First and foremost, there needs to be a clear reflection of an increased societal willingness to invest in the development of new antibiotics.
- Any alternative business model should be based on incentives that promote responsible use, as well as access and conservation. This also requires new, suitable, financial push-and-pull mechanisms to reward innovators. Delinkage using a variety of combined strategies may provide a platform for such an alternative model.
- Based on the needs, gaps and public health importance of the issue, adequate, sustainable and long-term financing must be mobilized.
- Such financing will largely need to come from the public sector and the antibiotics developed will need to be seen as global public goods.<sup>6</sup>
- As ABR is a truly global problem, innovation must transcend just local and regional perspectives; this begins with defining public health needs (e.g., through global threat assessments and then the creation of target product profiles or TPPs), but also continues into financial and regulatory incentives and mechanisms.
- Control and conservation mechanisms in the “antibiotic market” need to be defined at a global level, but adapted and adhered to nationally by governments, manufacturers, and distributors.

Linking incentives and rewards to conservation mechanisms may be useful.

- Monitoring, coordinating, and prioritizing R&D funding and activities will be important to ensure limited public resources can achieve maximal impact.
- While maintaining the need to harness the strength of the private sector, cooperation, knowledge sharing, and regulated use will be essential throughout the product development and marketing life cycle.

### Looking at Alternative Models

A recent Big Innovation Centre/Chatham House publication and an upcoming Working Group report on business models for antibiotic innovation have already elucidated potential business models, including using examples specifically applied in other industries.<sup>7</sup> These include insurance schemes, long-term service provision contracts, a corporate bond model, a value-based sales model, and a delinked payment regime to fund R&D allowing the final product to be made available at marginal cost.<sup>8</sup>

Recommendations have also been made for incentives that could be useful in the field of antibiotic innovation. In practice, some of these incentives proposed have already been piloted. These include traditional large-scale grants, milestone payments (notably by BARDA in the US), prizes (e.g., the recently introduced Longitude Prize) and advance marketing commitments (as used for the pneumococcal vaccine).<sup>9</sup>

The challenge in all of these policy proposals and models to date is how to move beyond a piecemeal series of national and international actions to a truly coordinated global response. Such a response should also seek to ensure that it would not compromise the conservation of, and responsible access to, future antibiotics, nor undermine access and innovation in other key public health areas – for instance by creating incentives (such as extended exclusivity) that actually require increased sales of antibiotics in order to generate revenue. Efforts should be focused on pro-



posals that come closest to delinkage of both R&D as well as the production/supply of antibiotics. For example, according to the Big Innovation Centre/Chatham House report, a viable business model could be a hybrid between a service provision contract – similar to what is currently being used in several industries – and an upfront revenue system as used, for instance, in academic publishing. In reality this may translate into contractual grants and milestone payments with clear clauses on timelines, transfer or sharing of IP rights, product supply, and marketing.

Another key issue to consider is who would be the paying customer. Rather than being a broad network of individuals within a health insurance system or a state, it would ideally be all countries or health systems that would potentially use the products developed. So, for example, a network of countries and funders could therefore come together to develop service-based contracts, prize payments and fixed, advance market commitments for a series of antibiotic R&D needs, possibly specified through TPPs developed.

### Operationalizing a New Business Model

It should be feasible to consider an adapted business model using a combination of the proposals and incentives above in an international framework, capable of implementation through existing entities. There are three key elements in moving towards a new business model: (1) a global, potentially legal, framework; (2) an antibiotic R&D innovation fund; and (3) a global institutional mechanism for ABR.

#### *A Global Framework*

Both a global framework for R&D and an international framework have already been proposed. The CEWG report recommended a global framework for R&D, taking particular account of the health needs of developing countries. To date, a Global R&D Observatory with monitoring and coordination functions, as well as a voluntary pooled R&D fund for demonstration projects on neglected tropical diseases are being created.<sup>10</sup> The WHO Executive Board also endorsed looking into longer-term needs.

In relation to resistance, there is also a proposal for a binding international legal framework via a WHO regulation or a UN general assembly treaty to encompass access, conservation and innovation.<sup>11</sup> Both legal mechanisms are viable and not mutually exclusive options. Considering the wider innovation needs,

it would nonetheless be useful to develop an R&D framework concerning key public health areas, notably infectious diseases, where market failure exists. Ideally, a framework would need to cover a few important aspects, including guaranteeing access through licensing or other means, securing conservation through stronger internationally agreed regulatory and trade instruments, and pooling and coordinating incentives for innovation that are conditional on the two first criteria. The ability to develop such a framework depends on how discussions between Member States advance at WHO during 2015. Following the events around the Ebola outbreak in 2014 and international recognition for the need to deal proactively with public health issues affecting health security, a clear opportunity exists to advance the agenda around antibiotic innovation and ABR in general.

It is important to see the legal framework as the glue that enables the subsequent measures to work. This cannot be underestimated because there are multiple objectives (access, conservation, innovation) that must be simultaneously addressed, and the efforts required need international collaboration with a long-term perspective. Short-term individual donor depen-

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dent initiatives will lack staying power and broader legitimacy.

An international regulatory platform where production, trade, sales, and utilization of antibiotics can be more tightly governed may be best achieved by utilizing international law, which can serve as a blueprint for national legislation and policies. However, more restrictive regulations can only work equitably if they are combined with mechanisms that both foster both access and ensure innovation.

Developing a legal framework combining these three objectives may result in a negotiation process

where benefits and disadvantages across the three areas may be properly balanced so that all constituencies may perceive sufficient net long-term advantages out of a bargaining process which would necessarily involve short-term losses for some participants. It will also be necessary to consider sufficient enforcement processes, which in the end may also need to be linked and balanced against economic interests as in trade agreements.

#### *An Antibiotic R&D Innovation Fund*

As part of a new global framework, it would be useful to consider a new R&D innovation fund to support the development of new antibiotics. The fund should be linked to a normative framework as discussed above. The concept of a fund needs to take into account several issues. Should it be dedicated towards antibiotic innovation or work more broadly on all elements of resistance? How should a fund coordinate with, include, or incorporate existing funders?

The fund should be a vehicle for monitoring research flows, setting priorities, coordinating with other funding actors, and setting strategy. The global observatory being established in WHO could be further developed for such a purpose.<sup>12</sup>

Funding must largely come from the public purse with the aim of delivering global public goods in the context of a long-term global investment perspective for health security and public health. The size of such a pooled fund would need to be sufficient to ensure sufficient strength and ability to coordinate with different funding streams. A recent call by Jim O'Neill, Chair of the U.K. government's review on antimicrobial resistance, mentioned the need to create a US\$2 billion innovation fund.<sup>13</sup> Such a figure would be consistent with both the CEWG report and Lancet Commission for Investing in Health.<sup>14</sup> The U.S. government has called for an additional US\$800 million in BARDA funding to support clinical development of antibiotics.<sup>15</sup>

As noted above, the fund should support models in which the cost and reward for R&D is delinked from sales and supply by creating a separate competitive innovation market using the range of incentives already discussed. It would need to be decided which existing institution could best host such a fund, or whether a new, dedicated institution is required. Currently, a fund has been established in WHO's Special Programme for Research and Training in Tropical Diseases (TDR) to support demonstration R&D projects for diseases that particularly impact developing countries.

#### *A Global Institutional Mechanism for ABR*

A third key element of a global response would be a global institutional mechanism for ABR, to promote and accelerate the evolution of the antibiotic business model as well as to promote improved surveillance, infection control and responsible use. The entity will be directly related to and supported by the R&D fund, which in turn would be empowered by a framework. In other words, a treaty will facilitate or create a fund, which will then financially support a new, more operational entity.

Part of developing forward-looking responsible access and conservation strategies for new antibiotics will be to consider models to set up an "antibiotic drug facility" that could already focus on existing priority antibiotics. Close collaboration with global experts, WHO and relevant global health actors, such as the Global Fund to Fight AIDs, Tuberculosis and Malaria, will be key, including in areas such as quality standardization and assurance, procurement, pharmacovigilance, and implementing/monitoring rationale use schemes. In addition, responsible licensing standards between originator and generic companies could be applied to also promote responsible access. It has been suggested that the Medicines Patent Pool could play a role in this area.

The entity would play key roles including promoting R&D into antibiotics, developing and assisting states and regions in implementing conservation strategies for new antibiotics, and implement the disbursements of "delinked funds" for R&D employing an alternative business model armed with a range of different incentive mechanisms. For instance, this could include substantive grants, milestone and end stage prizes with clear access and conservation clauses, patent pooling and buyouts. While the initiative would not aim to be the sole source of antibiotic funding, it would be differentiated from other funders and especially other global health entities because it would fill key roles across access, conservation and R&D for innovation.

Key tasks for the entity might include:

- Financing R&D for products that are reserved for human use; possibly also financing alternative product lines that can then be reserved for veterinary/animal husbandry use.
- Developing global public health-orientated TPPs and a portfolio of projects (e.g., of products in development) by using a variety of new innovative financing instruments, including loans, grants, prizes, and collaborative research models to de-link the costs of R&D from the price of the product.

- Creating an international network of public and private entities from countries (e.g., companies, academic research institutes, not for profit product development partnerships) from all income levels engaged in research for new antibiotic agents.
- Taking measures to ensure any new products developed are used responsibly on a global level while also focusing on access programs for those most in need.
- Promotion of surveillance and laboratory capacities.

## Conclusion

The reformation of the innovation business model is necessary in order to develop the next generation of antibiotics. The necessary reforms are feasible. However antibiotics need to be considered as global public goods and funding and conservation strategies largely need to come from public interventions. Reform of the innovation model can be enabled through three steps requiring national and international intervention: a legal framework (such as a WHO regulation), creation of an international, long-term pooled antibiotic innovation R&D fund, and establishment of an institution to carry this work forward. Such an idea has been proposed and endorsed by other reports.<sup>16</sup> Each can be done concurrently; practically a well-set up initiative may even assist in the solid foundation of the other two aspects. Indeed, WHO and other entities have practically discussed these issues in recent months.<sup>17</sup> It is essential now that countries seriously consider collectively supporting and funding such proposals in order to deal with the growing threat of ABR.

## References

1. M. S. Butler, M. A. Blaskovich, and M. A. Cooper, "Antibiotics in the Clinical Pipeline in 2013," *Journal of Antibiotics* 66 (2013): 571-599.
2. K. Outterson, *New Business Models for Sustainable Antibiotics* (Chatham House, London: Royal Institute of International Affairs, 2014).
3. K. Outterson, J. H. Powers, G. W. Daniel, and M. B. McClellan, "Repairing the Broken Market for Antibiotic Innovation," *Health Affairs* 34, no. 2 (2015): 277-285.
4. Report on the event, "Best Use of Medicines Legislation to Bring New Antibiotics to Patients and Combat the Resistance Problem," European Medicines Agency, London, November 2013, available at <[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2013/12/WC500158230.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/12/WC500158230.pdf)> (last visited May 14, 2015).
5. World Health Organization, *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination*, Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (2012), available at <[http://www.who.int/phi/CEWG\\_Report\\_5\\_April\\_2012.pdf?ua=1](http://www.who.int/phi/CEWG_Report_5_April_2012.pdf?ua=1)> (last visited May 14, 2015).
6. A. Hollis and P. Maybarduk, "Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation," *Journal of Law, Medicine & Ethics* 43, no. 2 (2015): available via aslme.org.
7. E. Jaczynska, K. Outterson, and J. Mestre-Farrandiz, *Business Model Options for Antibiotics: Learning from Other Industries* (Big Innovation Centre/Chatham House, London: Royal Institute of International Affairs, 2015); Chatham House Working Group, *New Antibiotic Business Model* (Chatham House, London: Royal Institute of International Affairs, 2015).
8. See Hollis, *supra* note 6.
9. Longitude Prize, available at <<https://longitudeprize.org/>> (last visited May 14, 2015); Gavi, "Pneumococcal AMC," available at <<http://www.gavi.org/funding/pneumococcal-amc/>> (last visited May 14, 2015).
10. Follow-up of the report on the Consultative Expert Working Group on Research and Development: Financing and Coordination, available at <[http://apps.who.int/gb/ebwha/pdf\\_files/WHA67/A67\\_28Add1-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_28Add1-en.pdf)> (last visited May 14, 2015).
11. S. J. Hoffmann, K. Outterson, J. A. Rottingen, O. Cars, C. Clift, Z. Rizvi, F. Rotberg, G. Tomson, and A. Zorset, "An International Legal Framework to Address Antimicrobial Resistance," *Bulletin of the World Health Organization* (2015): 93/2/15-152710.
12. J. A. Rottingen, S. Regmi, M. Eide, A. J. Young, R. F. Viergever, C. Årdal, J. Guzman, D. Edwards, S. A. Matlin, and R. F. Terry, "Mapping Available Health R&D Data: What's There, What's Missing and What Role for a Global Observatory," *The Lancet* 382, no. 9900 (2013): 1286-1307.
13. K. Grogan, "AMR Review Head O'Neill Calls for \$2 Billion Innovation Fund," *Pharma Times*, available at <[http://www.pharmatimes.com/Article/15-02-27/AMR\\_review\\_head\\_O'Neill\\_calls\\_for\\_2\\_billion\\_innovation\\_fund.aspx](http://www.pharmatimes.com/Article/15-02-27/AMR_review_head_O'Neill_calls_for_2_billion_innovation_fund.aspx)> (last visited May 14, 2015).
14. D. T. Jamison, L. H. Summers, and G. Alleyne et al., "Global Health 2035: A World Converging within a Generation," *The Lancet* 382, no. 9908 (2013): 1898-1955.
15. President's Council of Advisors on Science & Technology, Report to the President on Combating Antibiotic-Resistant Bacteria (September 2014) at 3, available at <[https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast\\_carb\\_report\\_sept2014.pdf](https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf)> (last visited May 14, 2015).
16. See WHO, *supra* note 5; Holli, *supra* note 6; Jaczynska et al., *supra* note 7.
17. World Health Organization, "Innovation for Antibiotics Development and Preservation," available at <[http://www.who.int/phi/implementation/consultation\\_innnap/en/](http://www.who.int/phi/implementation/consultation_innnap/en/)> (last visited May 14, 2015).

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# History Teaches Us That Confronting Antibiotic Resistance Requires Stronger Global Collective Action

*Scott H. Podolsky, Robert Bud, Christoph Gradmann, Bård Hobaek, Claas Kirchhelle, Tore Mitvedt, María Jesús Santesmases, Ulrike Thoms, Dag Berild, and Anne Kveim Lie*

**A**ntibiotic development and usage, and antibiotic resistance in particular, are today considered global concerns, simultaneously mandating local and global perspectives and actions. Yet such global considerations have not always been part of antibiotic policy formation, and those who attempt to formulate a globally coordinated response to antibiotic resistance will need to confront a history of heterogeneous, often uncoordinated, and at times conflicting reform efforts, whose legacies remain apparent today. Historical analysis permits us to highlight such entrenched trends and processes, helping to frame contemporary efforts to improve access, conservation and innovation.

## Heterogeneity of National Responses

Antibiotics were the best known and most widely prescribed of the post-WWII “wonder drugs,” allowing medicine to powerfully rebrand itself in such industrialized states as the United Kingdom (U.K.) and the United States (U.S.).<sup>1</sup> From the beginning, however, clinicians and infectious disease experts expressed concerns regarding the unique ecological features of antibiotics and the hazards of overuse. As early as

1954, Britain’s Lindsey Batten, in the context of widely documented staphylococcal resistance, could wonder aloud at the Royal Society of Medicine: “Those deadly staphylococci...are not pirates or privateers accidentally encountered, they are detachments of an army. They are also portents....We should study the balance of Nature in field and hedgerow and throat and gut before we seriously disturb it. Again, we may come to the end of antibiotics. We may run clean out of effective ammunition and then how the bacteria and moulds will lord it.”<sup>2</sup> Yet attempts to reform the antibiotic market and to ensure the rational use of antibiotics took very different forms in different states, both with respect to therapeutic prescribing, and with respect to the agricultural use of antibiotics.

In the U.S., the largest producer of antibiotics throughout the antibiotic era, would-be reformers have long expressed concerns about the dangers of indiscriminate usage. During the early 1950s, in particular, Ernest Jawetz drew repeated attention to the role of the laboratory — and hoped-for improvements in diagnostics — in offsetting “shotgun” therapy, guiding “rational” therapy in its place, and reducing the incidence of missed diagnoses, adverse effects, super-

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infections, and antibiotic resistance.<sup>3</sup> He lamented to his fellow infectious disease experts towards the end of the decade: “Is it asking for too much that in a few areas man behave as a rational being?”<sup>4</sup>

Yet throughout ensuing decades, the most iconic antibiotic reforms in the U.S. focused on the market entry of individual new drugs, rather than on the overall supply of antibiotics or on prescribing itself. As of the 1950s, the Food and Drug Administration (FDA) only formally adjudicated drug safety, rather than efficacy. And in the setting of widespread staphylococcal resistance, not only to penicillin but to such “broad-spectrum” drugs (introduced in the late 1940s and early 1950s) as chloramphenicol and tetracycline, companies began introducing and widely marketing “fixed-dose combinations” of two or more antibiotics. Therapeutic reformers like Maxwell Finland and

stantial, very substantial studies” — including *in vitro*, animal, and uncontrolled human studies — to justify Panalba’s utility, but that the FDA’s actions impinged on the prescribing prerogative of the clinician.<sup>6</sup> Yet the judiciary found in favor of the FDA, representing both the conceptual apotheosis of the controlled clinical trial in therapeutic evaluation in the U.S., as well as a key moment of FDA empowerment with respect to antibiotics. But no agency was authorized to govern antibiotic use more generally, and by the 1970s, when “irrational” antibiotic prescribing was becoming increasingly documented and stewardship programs were first being implemented and studied in the U.S., it appeared that the withdrawal of the fixed-dose combination antibiotics had only engendered resentment and agitation over the prospect of the further centralized restriction of therapeutic autonomy.<sup>7</sup>

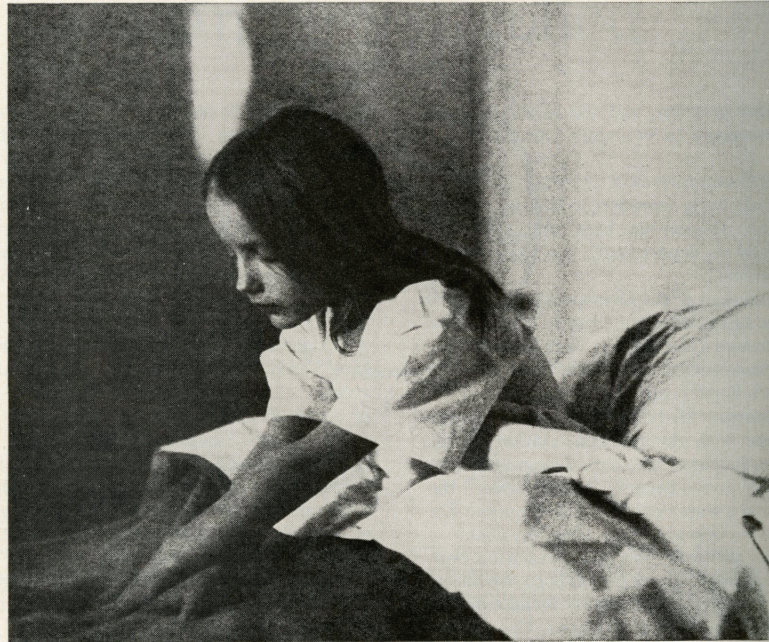
In the U.S., the largest producer of antibiotics throughout the antibiotic era, would-be reformers have long expressed concerns about the dangers of indiscriminate usage. During the early 1950s, in particular, Ernest Jawetz drew repeated attention to the role of the laboratory — and hoped-for improvements in diagnostics — in offsetting “shotgun” therapy, guiding “rational” therapy in its place, and reducing the incidence of missed diagnoses, adverse effects, superinfections, and antibiotic resistance. He lamented to his fellow infectious disease experts towards the end of the decade: “Is it asking for too much that in a few areas man behave as a rational being?”

Harry Dowling tested such remedies and found them no more efficacious than their component parts. They used these results to rally around the need to test new drugs via rigorously controlled studies, rather than through “testimonials” masquerading as serious science. These efforts contributed to the passage of the 1962 Kefauver-Harris amendments that mandated that new drugs be proved efficacious via “well-controlled investigations.”<sup>5</sup>

By 1966, the FDA, through the National Academy of Sciences-National Research Council, instituted the Drug Efficacy Study and Implementation (DESI) process, whereby pre-1962 drugs could be retrospectively reviewed; and by 1969, all of the fixed-dose combination antibiotics would be withdrawn from the market. One of the most financially successful withdrawn drugs was Panalba (a mixture of tetracycline and novobiocin), produced by the Upjohn Company. The company took the FDA to court. They stated not only that Upjohn had conducted a number of “sub-

Scandinavia represents an instructive alternative approach, grounded in an ongoing concern with the overall ecology of the market. Norway, in 1928, was among the first countries to mandate centralized approval prior to entry of drugs onto the marketplace. Its regulations were from the beginning oriented against a “flood” of dubious drugs, requiring new drugs to be “medically justified,” and from 1938, “needed.”<sup>8</sup> Scandinavian health authorities argued that drugs — and especially antibiotics — could not solely be treated as market commodities.<sup>9</sup> This regulatory framework was able to accommodate early concerns over antimicrobial resistance; and as early as 1947, the *possibility* of antibiotic resistance led to the rejection of penicillin products thought to invite indiscriminate use.<sup>10</sup> The so-called “clause of need” — facilitated by the presence of a relatively small pharmaceutical industry, but also politically motivated and largely supported by the medical community — was actively used to maintain a low number of drugs

in potentially-serious  
pediatric infections,



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on the market. From the 1960s, antibiotics were singled out for a particularly strict registration practice, with new drugs rejected when these met no specific clinical need not already covered by well-known or cheaper drugs. For example, the cephalosporins for a long time remained in marginal use in large part due to this practice. The regulations do not by themselves explain low levels of antibiotic use in Scandinavia, but provided one powerful tool among many in the hands of concerned experts, and took part in shaping prescribing patterns and patient expectations that appear to persist to this time.

The point of such examples is that not only are a variety of national responses possible, but that such a variety of national responses has in fact been taken, permitting us to consider the contexts in which they were taken and the legacies they retain today. The same heterogeneity has applied to the use of antibiotics in agriculture, especially with respect to growth promotion. In Great Britain, by the 1960s, concerns (especially as voiced by Andy Andersen) over the spread of antibiotic resistance from animals to humans led to the 1969 Swann report, banning therapeutically relevant antibiotics such as penicil-



lin and tetracyclines for growth promotion.<sup>11</sup> Yet the impact of the Swann report was limited. In Britain and other European states who adopted the Swann recommendations, while non-therapeutic antibiotic usage could be banned, veterinarians could simply switch to therapeutic overprescribing.<sup>12</sup> And in the U.S., the FDA was preoccupied with the regulation of carcinogens in food and heavily influenced by a 1966 *ad hoc* committee report on agricultural antibiotics that reflected scientific uncertainty over the relationship between such antibiotics and the development of resistance in humans. As a result, the FDA failed to assert itself against industry opposition and did not convince Congress to enact Swann-inspired bans in 1972 and 1977.<sup>13</sup>

As described elsewhere in the series,<sup>14</sup> beginning in the 1980s several European states began to enact more aggressive measures. Nevertheless, such approaches still retain a regional, if not national, character. The U.S. only began addressing antibiotic usage in agriculture with voluntary, but permanent label restrictions on medically important antibiotic growth promoters in December of 2013, pointing to the enduring heterogeneity of responses to this seemingly global concern.

### The Limits to Global Responses

Indeed, such global concerns would seem to call for a *global* response, but attempts at such a coordinated response to antibiotic usage and resistance have been slow in coming. The initial “global” efforts in the 1940s of organizations like the United Nations Relief and Rehabilitation Administration – focused on the transfer of antibiotic-producing capabilities to war-torn states – did not concern antibiotic overuse, but rather the potential *lack* of antibiotic availability in such countries.<sup>15</sup> By the late 1950s, though, the World Health Organization became concerned with antibiotic misuse and resistance, convening a meeting in Geneva in May of 1959. “Counter-propaganda” regarding antibiotic “misuse consequent on unscrupulous advertising” was considered, along with proposed efforts to reduce “self-medication” in “countries in which antibiotics are freely available by the public,” and members considered the need to standardize and coordinate antibiotic resistance testing as a prelude to guiding antibiotic usage at both local and global levels.<sup>16</sup> However, the debate over laboratory standardization would dominate WHO antibiotic involvement over the ensuing decade;<sup>17</sup> and while the organization would make scattered efforts to address antibiotic resistance, its efforts remained inconsistent for many years. At the same time, faith in the capacity of the pharmaceutical industry to keep up with evolving bacteria helped to mute potential concerns.

By the late 1960s and 1970s, though, concerns over the horizontal transmission of antibiotic resistance via plasmids that knew neither species nor state boundaries, and parallel concerns regarding the emergence of so-called “superbugs,” served to reinvigorate efforts to confront antibiotic resistance as a potentially globally connected phenomenon.<sup>18</sup> In January of 1981, Stuart Levy convened a meeting in Santo Domingo on the “Molecular Biology, Pathogenicity, and Ecology of Bacterial Plasmids,” at which 147 scientists from around the world signed a joint “Statement Regarding Worldwide Antibiotic Misuse.”<sup>19</sup> Among other things, the gathered scientists called for focusing attention on the over-promotion of antibiotics, the worldwide usage of antibiotics without prescription, and their use in animal feeds; and Levy used the Statement as a springboard to the formation of the Alliance for the Prudent Use of Antibiotics, intending for the organization to serve as an explicitly *international* (the 31 members of its initial scientific advisory board came from 25 different countries) catalyst for efforts to confront antibiotic misuse and overuse. Levy’s efforts, while critical to the rise of an explicitly global focus on antibiotic usage and resistance (and helping to further stimulate the re-engagement of the WHO with antibiotic resistance and surveillance), were nevertheless limited by the lack of U.S. federal engagement with public health concerns throughout the 1980s.<sup>20</sup>

By the late 1980s and early 1990s, however, Levy would find a key ally in Joshua Lederberg, who had won the Nobel Prize in 1958 for his discovery of bacterial genetic exchange, and who had coined the very term *plasmid* in 1952.<sup>21</sup> Lederberg served as the head of the Rockefeller University in New York City at the height of the AIDS epidemic, becoming concerned that AIDS would not be the last of such coming plagues. He called on his country’s Institute of Medicine to convene a committee on emerging infections; and the ensuing 1992 report, which linked antibiotic resistance concerns to the larger emerging infections discourse, served as a truly catalytic factor in the ensuing global response to antibiotic resistance.<sup>22</sup> At the same time, industry’s appreciation of antibiotics had changed. In the 1950s and 1960s, resistance had created markets and effectively fostered the development of antibiotics like the Beecham Group’s methicillin.<sup>23</sup> By the 1980s, however, disenchantment with the commercial potential of such medicines had developed within the companies, further creating spaces for antibiotic reformers.

In this context, the WHO convened a series of working groups and meetings on antibiotic resistance throughout the 1990s, while European countries — amid the formation of the European Union — began

to take more aggressive measures with respect to antibiotic resistance, initially epitomized by the establishment of the European Antimicrobial Resistance Surveillance System (EARSS, now EARS-Net). Countries outside Europe could by 2001 draw on the WHO's "Global Strategy for Containment of Antimicrobial Resistance" in designing their own efforts, at the same time that global efforts concerning HIV, tuberculosis, and malaria were scaling up.<sup>24</sup>

Such momentum has persisted to this point, with multiple national efforts initiated to confront antibiotic resistance, and scattered bilateral or multilateral attempts rendered to harmonize efforts. The WHO, in 2014, provided its own first global report on antibiotic resistance surveillance<sup>25</sup> and a Global Action Plan is being adopted in 2015. And yet, despite the WHO's

would do well to examine the biosocial approaches taken in addressing HIV, tuberculosis, and malaria.

With respect to conservation — and its grounding in surveillance and stewardship — the aspiration to a worldwide surveillance infrastructure guiding rational therapy is longstanding, dating back at least to the interest of the WHO in the 1950s. At the very least, history reminds us in this respect — as with calls for improved diagnostics — that merely surfacing the need for an intervention does not ensure the material investment in making that intervention a reality. Stewardship efforts, moreover, have had to confront differing notions of therapeutic autonomy in differing states and cultures, grounded in complex relationships between doctors and their patients, through which physicians in certain countries have long gained

**This is, in many ways, a propitious time to consider a global framework addressing antibiotic resistance. Antibiotic resistance has been surfaced and politicized as a global concern mandating global coordination. Yet contemporary efforts will need to confront both the structural factors that impede the rational delivery of antibiotics worldwide, as well as legacies of heterogeneity, in order to confront this critical public health concern.**

reports, neither adequate funding nor the related implementation of suggested measures has followed. And despite successful political mobilization against antibiotic resistance, no formal global mechanism for harmonizing individual national efforts exists to this time. The globalization of antibiotic resistance discourse and efforts, slow to develop, still bears the imprints of its state-centered origins.

### **Historical Context to an Integrated Approach**

What does historical reflection tell us about contemporary approaches to unite access, conservation, and innovation within a single global regulatory framework? Overuse and underuse represent two sides of the same coin, pointing to the structural and economic factors that impede the rational delivery of health care more broadly. The efforts of those working to rationally treat HIV, tuberculosis, and malaria — and their engagement with issues of access — have historically been separated from those working to confront antibiotic resistance more generally. Yet recent attention to antibiotic resistance in India has served to further focus attention on such structural factors; and those considering broader issues of antibiotic resistance, in both the developing world and the developed world,

the trust of their patients through prescribing antibiotics, while resenting interference into this complex relationship from external regulators, managers, and insurance companies. Regarding antibiotics in agriculture, would-be reformers continue to confront powerful interests and lobbies, further pointing to the challenges facing those who would reform these policies.

Finally, with respect to innovation, there is a clear need for ongoing investment in new vaccines, diagnostics, and therapeutics. Yet we should be mindful of prior faith in technological fixes to antibiotic resistance, epitomized by early enthusiasm over methicillin in the 1960s. And there are historical ironies in contemporary discussions about lowering regulatory standards in order to speed new antibiotics to market. The present FDA clinical trial standards for pharmaceuticals, as described earlier, was constructed in the 1960s out of concern for poorly designed antibiotic studies; we should be wary of the downstream effects of weakening that regulatory machinery.

This is, in many ways, a propitious time to consider a global framework addressing antibiotic resistance. Antibiotic resistance has been surfaced and politicized as a global concern mandating global coordination. Yet contemporary efforts will need to confront both



the structural factors that impede the rational delivery of antibiotics worldwide, as well as legacies of heterogeneity, in order to confront this critical public health concern.

## References

1. R. Bud, *Penicillin: Triumph and Tragedy* (New York: Oxford University Press, 2007).
2. L. W. Batten, "Discussion on the Use and Abuse of Antibiotics," *Proceedings of the Royal Society of Medicine* 48 (1955): 355-364.
3. See, e.g., E. Jawetz and M. S. Marshall, "The Role of the Laboratory in Antibiotic Therapy," *Journal of Pediatrics* 37, no. 4 (1950): 545-554.
4. E. Jawetz, "Patient, Doctor, Drug, and Bug," *Antibiotics Annual* (1957-1958): 287-295.
5. S. H. Podolsky, *The Antibiotic Era: Reform, Resistance, and the Pursuit of a Rational Therapeutics* (Baltimore: Johns Hopkins University Press, 2015): at 43-87.
6. S. Temko, oral arguments "In the Matter of Novobiocin-Tetracycline Drugs; Calcium Novobiocin-Sulfamethizole Tablets (Upjohn Co.), Arlington, VA, August 13, 1969," Box 88-78-36, FDA Division of Dockets Management, Rockville, Maryland.
7. See Podolsky, *supra* note 5, at 112-139.
8. Negotiations of the Storting (Norwegian Parliament): Ot.prp.51 1928; Ot.prp.50 1938. See also M. Andrew, B. Jøldal, and G. Tomson, "Norway's National Drug Policy. Its Evolution and Lessons for the Future," *Development Dialogue* 1 (1995): 25-53.
9. A. Kveim Lie, "Producing Standards, Producing the Nordic Region: Antibiotic Susceptibility Testing, from 1950-1970," *Science in Context* 27, no. 2 (2014): 215-248.
10. "Meetings of the Director of Health and His Expert Council," 4/22/47, 6/27/47, Archives of the Norwegian Medicines Agency.
11. See Bud, *supra* note 1, at 163-191.
12. U. Thoms, "Between Promise and Threat: Antibiotics in Food in Germany 1950-1980," *NTM. Zeitschrift für Geschichte der Wissenschaften, Technik und Medizin* 20, no. 3 (2012): 181-214.
13. C. Kirchhelle, *Pyrrhic Progress. Antibiotics in Western Food Production (1949-2013)*, Ph.D. Thesis, Oxford University (forthcoming).
14. A. So et al., "One Health Perspective: An Integrated Systems Approach Is Needed to Ensure the Sustainability of Antibiotic Effectiveness for Both Humans and Animals," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
15. See Bud, *supra* note 1, at 75-96; M. J. Santesmases, "Distributing Penicillin: The Clinic, the Hero and Industrial Production in Spain, 1943-1952," in V. Quirke and J. Slinn, eds., *Perspectives on Twentieth-Century Pharmaceuticals* (Oxford: Peter Lang, 2010).
16. "Report to the Director-General, Scientific Group on Antibiotics Research, Geneva, 26-30 May 1959," Box 10, ff 6, Selman Waksman papers, Rutgers University.
17. C. Gradmann, "Sensitive Matters: The World Health Organization and Antibiotic Resistance Testing, 1945-1975," *Social History of Medicine* 26, no. 3 (2013): 555-574.
18. T. Watanabe, "Infective Heredity of Multiple Drug Resistance in Bacteria," *Bacteriological Reviews* 27 (1963): 87-115; J. A. Osmundsen, "Are Germs Winning the War against People?" *Look* (October 18, 1966): 140-141.
19. S. B. Levy, R. C. Clowes, and E. L. Koenig, eds., *Molecular Biology, Pathogenicity, and Ecology of Bacterial Plasmids* (New York: Plenum, 1981).
20. See Podolsky, *supra* note 5, at 158-167.
21. See Bud, *supra* note 1, at 196-198.
22. J. Lederberg and R. E. Shope, eds., *Emerging Infections: Microbial Threats to Health in the United States* (Washington, D.C.: National Academy Press, 1992).
23. C. Gradmann, "Re-Inventing Infectious Disease: Antibiotic Resistance and Drug Development at the Bayer Company 1945-1980," *Medical History* 60, no. 2 (forthcoming 2016).
24. World Health Organization, *WHO Global Strategy for Containment of Antibiotic Resistance* (Geneva: World Health Organization, 2001).
25. World Health Organization, *Antimicrobial Resistance: Global Report on Surveillance* (Geneva: World Health Organization, 2014).

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# Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation

*Aidan Hollis and Peter Maybarduk*

## Introduction

Antibiotic resistance presents a classic example of the “tragedy of the commons.” In this eponymous tragedy, the commons — shared, public access lands — are overgrazed because farmers can send their livestock onto the land at a zero price. The “tragedy” occurs because overgrazing destroys the land and reduces its ability to provide fodder. The application to antibiotics is obvious: the use of antibiotics creates selection pressure leading to increased proportions of resistant bacteria in the patient and the environment. The increase in frequency of resistant organisms diminishes the effectiveness of antibiotics in treating future infections; thus, the long-term value of the antimicrobial resource is reduced. This problem is aggravated when individuals or companies misuse antibiotics — for example, by not using them to treat a bacterial infection, or by taking only a partial course, or by feeding them at low doses to livestock — resulting in increased resistance with little or no compensating benefit.<sup>1</sup> In the language of economics, there is a “negative externality” from antimicrobial use. At a national level, governments pay attention mostly to domestic issues, without considering the externalities imposed on other countries. Thus, most countries have policies that are too lax, since the benefits from antimicrobial consumption are local, but the costs of resistance are local and global. The overall goals of effective policy must address problems of access to antibiotics, as well as effective conservation and innovation.

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Despite increased levels of resistance, investment in antibiotic innovation has been inadequate.<sup>2</sup> New antibiotics are typically reserved for resistant bacteria, which may lead to slow uptake for some innovative products. As a result, the volume of sales during the period of exclusivity (the first 10 to 15 years) may be expected to be relatively small.<sup>3</sup> A further related problem is that resistance is often shared across drugs within the same class, so that increased volume of sales of one molecule may undermine the effectiveness of a different, but related, molecule.

The combination of these “commons” problems suggests that some kind of global coordinated response is desirable, through an international agreement that combines tools to reduce inappropriate use and to increase investment into developing new antibiotics. At the same time, there is a pressing need to increase access to antibiotics in some settings, since lack of access to effective antibiotics is deeply problematic for human health and may accelerate the development of resistance.<sup>4</sup> In this short article, we discuss the insights of economics into possible solutions.

## Conservation Mechanisms

Economists have extensively studied issues relating to the tragedy of the commons. One solution is privatizing the commons. This is essentially an application of the “Coase Theorem,” according to which negotiations over an asset will lead to an efficient outcome, provided the rights to the asset are well defined.<sup>5</sup> This approach has also been proposed for antibiotics: extending the period of exclusivity, possibly indefinitely, would give the patentee the ability to charge high prices and thus indirectly restrain overuse by some users.<sup>6</sup> In effect,

the patentee would have an incentive to maximize the present discounted value of its invention's profitability. Extending the period of exclusivity would also, of course, modestly increase incentives to invest in new antibiotics. Extending exclusivity, however, is only effective if it deters use by consumers who are willing or able to pay little. A solution in which poor people are prevented from accessing drugs that could save their lives is not a desirable solution, nor is it likely

designed to reduce low-value uses of antibiotics, while also supporting innovation and enabling appropriate access where needed.<sup>8</sup>

An important observation is that such policies would differ across countries according to the particular administrative capabilities, culture, clinical practice, and bacterial flora of each country. For example, in many countries the number of health workers is relatively low, there is inadequate diagnostic capacity,

**Along with conservation, incentives to develop new antibiotics and access to those products represent additional key issues that an international agreement should address. Conservation policies do not enhance development incentives: they simply delay the time at which new antibiotics must be developed. Thus, the proposed agreement should include mechanisms to support the development of new antibiotics, a goal that faces significant obstacles.**

one to which low-income countries would agree. This Coasean solution would also not address the problem of cross-drug resistance, and it would not address the more general problem of misuse of existing unpatented antibiotics.

A Pigouvian tax on antibiotics is another possible solution. Such a tax could increase the price for use by all consumers, but again would harm access by the poor without doing much to deter inappropriate use by insured or affluent patients. This suggests that it would be much more appropriately applied for industrial and agricultural uses where there is a more equal sensitivity to costs.<sup>7</sup> A particular advantage of this approach is that distinguishing between growth promotion and other subtherapeutic uses (e.g., metaphylaxis, prophylaxis) is difficult and may be non-verifiable. A user fee of this sort would also generate revenues that could support conservation or innovation activities. An international agreement to charge Pigouvian taxes on antibiotics for non-human use could create a centralized, pooled fund, or could fund local activities in each country. If a tax were applied to human-use antibiotics, we suggest that would only be appropriate in high-income countries.

A third possible solution is to impose regulations on usage or new policies to support conservation activities. Such an approach gives everyone the same limited access and may therefore be perceived as fair. An international antibiotic agreement could require countries to establish regulations and policies

and it is almost impossible for people in rural areas to obtain antibiotics prescribed by a physician based on a laboratory-diagnosed infection.<sup>9</sup> Thus, a standard that might be appropriate for high-income countries would effectively bar many people from accessing antibiotics at all.

Similarly, in other countries, despite a larger number of health care workers, antibiotics are used extensively without prescription, based on self-diagnosis. Preventing this culturally customary behavior would be difficult, and would involve real costs of regulating the sale of pharmaceuticals, particularly antibiotics. For many drug retailers, antibiotics sold without a prescription are an important source of revenue. For example, a recent study showed that in northern Vietnam, antibiotics sold without a prescription made up 21% (16%) of revenues in urban (rural) pharmacies.<sup>10</sup> Eliminating such sales is challenging given the financial consequences to pharmacy owners, and likely would take many years.

### **Innovation and Delinkage**

Along with conservation, incentives to develop new antibiotics and access to those products represent additional key issues that an international agreement should address. Conservation policies do not enhance development incentives: they simply delay the time at which new antibiotics must be developed. Thus, the proposed agreement should include mechanisms to

support the development of new antibiotics, a goal that faces significant obstacles.<sup>11</sup>

Increased profitability of antibiotics, however, generally seems to imply that consumers or governments are going to be paying more. The only way to obtain higher revenues from consumers is through extending exclusivity or adding taxes on antibiotics, which, as we described above, is not an attractive or sufficient option for therapies for people and is likely infeasible in the context of an international agreement. Governments would have to contribute more, perhaps through increased subsidies to the development process. Thus, one aspect of the agreement would be focused on increasing and coordinating public funding to support innovation in antibiotics. This would naturally be matched by a public interest in ensuring increased access to antibiotics when needed. The challenge is to maintain private sector interest in investing in antimicrobial research, along with prices that enable widespread access when needed.

To achieve these seemingly conflicting goals, a model with “delinkage” could be used. Delinkage, in which the profit stream of the innovator is delinked from prices and volumes, offers more flexibility in how innovation is rewarded; for example, the innovator could obtain prizes or other payments connected to the extent to which important pathogens continue to be susceptible to the drug after 5 or 10 years. Such payments would be funded directly by governments. Delinkage, which has come to be a central part of international discourse on pharmaceutical pricing, was recommended by the 2012 report of the WHO Consultative Expert Working Group on Research and Development, and is of particular relevance for antibiotics.<sup>12</sup>

### Economics of Coalitions

There are two important strands of literature on solving “commons” problems through an agreement: the theory of cooperative games, which focuses on the conditions for establishing a stable coalition; and Elinor Ostrom’s work on how local communities have organized themselves to extract the most from commonly held resources.

A key insight from games theory is that a coalition requires that each of the players individually, and any group of the players collectively, should not be able to do better by leaving the coalition. In the context of an international agreement on antibiotics, demonstrating that at least a large number of countries are better off in the coalition is challenging because benefits and costs of participation differ substantially across countries with varying incomes, capacities, and objectives.

Many low-income countries have limited administrative capacity to establish and enforce conservation policies and at the same time are dealing with many other pressing priorities. (Low-income countries are also likely to be the ones the most seriously affected by resistant organisms, since they have the least resources to control infections in other ways.) For such countries, it is essential to include a mechanism to support investments in surveillance, conservation, and innovation. The *Montreal Protocol on Substances that Deplete the Ozone Layer* provides a positive example of such a support mechanism. During the last 25 years, its Multilateral Fund, financed by high-income countries, has committed over \$3 billion for implementation of projects including industrial conversion, technical assistance, training and capacity building in qualifying countries.<sup>13</sup>

Delinkage, if implemented appropriately, could also provide an incentive for lower-income countries to commit to an antibiotics agreement, since it would mean that price would not be a barrier to use of new antibiotics where needed. However, to make delinkage effective in sustaining commitment, it would be necessary that low prices be available only if the country was in compliance with the agreement. This would be practically and ethically challenging. From a practical perspective, there would have to be a process to decide whether countries were non-compliant, and then a mechanism established to prevent such countries from purchasing patented antibiotics at the low prices available elsewhere. From an ethical perspective, this would require “punishing” sick people because of policy failure on the part of their government. Using a tool such as the Multilateral Fund designed explicitly to support compliance would be more productive. First, in countries with severe resource constraints, such a fund could provide direct financial support for desired conservation activities. Second, a fund would enable a more nuanced approach to non-compliance. For example, countries that failed to direct resources appropriately to effective conservation policies might receive less funding or none at all.

Delinkage could be of particular importance for middle-income countries, which typically have better public health care facilities than low-income countries, but face limited financial capacity to purchase expensive new antibiotics. While delinkage would improve access and also increase the overall attractiveness of an international agreement on antibiotics, it is difficult to see how it could be easily tied to compliance with obligations under the agreement. One possible tool to discourage non-compliance would be reduced funding to support surveillance and conservation; of course, this could be self-defeating.



High-income countries could find the economics of an antibiotics agreement compelling, even with substantial financial support for conservation activities in low-income countries. If resistant organisms develop and spread in other countries, they will also pose a significant health threat in rich countries, regardless of local conservation policies and practices.

**Failure to invest in conservation represents a political failure perhaps caused by the trade-off between the certain costs of conservation incurred today and the uncertain benefits of reduced resistance in the future. An international antibiotics agreement could help to resolve this problem by addressing both the externality as well as providing a commitment device for governments.**

High-income countries have even more (but still limited) resources and capability to support conservation policies appropriate to their situation. In principle, a country that does not participate in, or comply with the agreement may have lower costs from conservation, while benefiting from less resistance caused by use of antibiotics in other countries. However, in practice, resistance against specific antibiotics has a strong local component, and countries, such as Sweden, that have aggressively pursued antimicrobial stewardship programs have seen meaningful changes in resistance levels nationally. Thus, there are good local reasons for investing in conservation activities, which are buttressed by the important externalities in other countries.

Failure to invest in conservation represents a political failure perhaps caused by the trade-off between the certain costs of conservation incurred today and the uncertain benefits of reduced resistance in the future. An international antibiotics agreement could help to resolve this problem by addressing both the externality as well as providing a commitment device for governments.

What mechanisms could be used to discipline high-income countries that fail to live up to their commitments under the agreement? Depending on the type of non-compliance, some combination of moral suasion and trade restrictions may be possible. For example, trade restrictions might be possible on agricultural products, if the non-compliance related to agricultural use of antibiotics.

The second strand of literature on solving “commons” problems relates to the research of Ostrom on “design principles” of stable local common pool resource management.<sup>14</sup> While her research focused on *local* cooperation, several of Ostrom’s insights are relevant for agreements between governments as well. First, she noted that rules regarding the appropriation and provision of common resources should be adapted to local conditions. The implication in the context of antimicrobial innovation and conservation is that an agreement must respect the significant differences in needs and capacities of different governments while also providing a common foundation for achieving its goals. Second, she noted that there must be effective monitoring with accountability of the monitors. This is particularly difficult for antibiotic conservation since the key metrics relate not only to the volume of use but also how products are used.

Along with monitoring, Ostrom’s principles include graduated sanctions for rule violations. In international treaties such as Kyoto, the difficulty of applying sanctions has always been a serious obstacle. The Montreal Protocol, which uses positive financial support to induce participation, rather than punitive sanctions, provides a positive model of implementing graduated sanctions. There are a variety of collaborative research activities that could be limited for different degrees of non-compliance. (Delinkage, while it offers other important benefits, does not easily offer a mechanism to enable graduated sanctions for non-compliance.)

One of the key principles Ostrom outlines is the importance of having “resource appropriators” (i.e., countries that use antibiotics) participate in the decision-making process.<sup>15</sup> Inclusiveness in setting up the terms of an international agreement creates the legitimacy that is essential for sustainability. This is particularly important in the case of an antibiotic agreement because of the differences in conservation goals and targets across countries. Assuming that an agreement evolved over time with conditions and its goals, it would be essential to have the widest ongoing participation in the governance of the agreement.

## Summary

Antibiotics are of enormous importance to global health, yet face multiple challenges: owing to overuse and misuse, their value is being undermined by resistance, even while millions of people lack effective access to these life-saving products. Individual countries lack the motivation, the commitment, and the

resources to address important issues of conservation and innovation. If designed appropriately, an international agreement could substantially mitigate these problems, and provide an important improvement in global health in the decades to come.

## References

1. T. F. Barlam and K. Gupta, "Antibiotic Resistance Spreads Across Borders," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015).
2. M. Balasegaram, C. Clift, and J.-A. Röttingen, "A Pathway towards an Alternative Business Model for Antibiotic Innovation: A Framework, Fund and Institutional Mechanism," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
3. H. Grabowski, and G. L. R. Mortimer, "Recent Trends in Brand-Name and Generic Drug Competition," *Journal of Medical Economics* 17, no. 3 (2013): 207-214.
4. N. Daulaire, A. Bang, G. Tomson, J. N. Kalyango, and O. Cars, "Universal Access to Effective Antimicrobials: An Essential Feature of Global Collective Action against Antimicrobial Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
5. R. H. Coase, "The Problem of Social Cost," *Journal of Law and Economics* 3, no. 1 (1960): 1-44.
6. A five-year extension has already been implemented in the U.S. under Title VIII of the 2012 Food and Drug Administration Safety and Innovation Act. For a proposed indefinite exclusivity extension, see E. Kades, "Preserving a Precious Resource: Rationalizing the Use of Antibiotics," *Northwestern University Law Review* 99, no. 2 (2005): 611-674. Kades' proposal is effectively rebutted in M. K. Outtersen, "The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Global Public Health," *University of Pittsburgh Law Review* 67, no. 1 (2005): 67-123.
7. See A. Hollis and Z. Ahmed, "Preserving Antibiotics, Rationally," *New England Journal of Medicine* 369, no. 26 (2013): 2474-2476, and A. D. So, T. A. Shah, S. Roach, Y. L. Chee, and K. E. Nachman, "International Agreement to Address the Contribution of Animal Agriculture to Antibiotic Resistance: A One Health Approach," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
8. Foreexamples of potential policies, see: A. Behdinan, S. J. Hoffman, and M. Pearcey, "Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
9. The low number of health workers in some African countries is particularly troubling. See, for example, the WHO African Health Workforce Observatory, available at <<http://www.hrh-observatory.afro.who.int/en/hrh-country-profiles/profile-by-country.html>> (last visited May 7, 2015).
10. D. Nga et al., "Antibiotic Sales in Rural and Urban Pharmacies in Northern Vietnam: An Observational Study," *BMC Pharmacology and Toxicology* 15, no. 6 (2014), available at <<http://www.biomedcentral.com/2050-6511/15/6>> (last visited May 15, 2015).
11. See Balasaegaram, *supra* note 3; K. Outtersen, J. H. Powers, G. W. Daniel, and M. B. McClellan, "Repairing the Broken Market for Antibiotic Innovation," *Health Affairs*, 34, no. 2 (2015): 277-285; and points 30 and 31 of the Antibiotic Resistance Coalition – Civil Society Declaration on Antibiotic Resistance, available at <<http://www.reactgroup.org/uploads/ARC-declaration/ARC-declaration-May-22-2014.pdf>> (last visited May 7, 2015).
12. See K. Outtersen, "New Business Models for Sustainable Antibiotics," Centre on Global Health Security Working Group Papers, Chatham House (The Royal Institute of International Affairs), Working Groups on Antimicrobial Resistance, Paper 1 (2014): 14-10; K. Outtersen, T. Pogge, and A. Hollis "Combating Antibiotic Resistance through the Health Impact Fund," in I. G. Cohen, ed., *The Globalization of Health Care* (New York/Oxford: Oxford University Press, 2013); and WHO, *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination*, Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination (2012), available at <[http://www.who.int/phi/cewg\\_report/en/](http://www.who.int/phi/cewg_report/en/)> (last visited May 13, 2015).
13. See Multilateral Fund for the Implementation of the Montreal Protocol, available at <<http://www.multilateralfund.org/default.aspx>> (last visited May 7, 2015) and PAPER 7.
14. E. Ostrom, *Governing the Commons: The Evolution of Institutions for Collective Action* (Cambridge: Cambridge University Press, 1990).
15. *Id.*

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# An Integrated Systems Approach is Needed to Ensure the Sustainability of Antibiotic Effectiveness for Both Humans and Animals

*Anthony D. So, Tejen A. Shah, Steven Roach, Yoke Ling Chee, and Keeve E. Nachman*

## Background

Antimicrobial resistance is a critical public health challenge, and the contribution of the widespread use of antimicrobials in food animals to bacterial drug resistance and human infection demands greater policymaker attention.<sup>1</sup> Global consumption of antimicrobials in food animal production by 2030 is projected to rise by two-thirds due to increases in both food animal production and demand for animal products.<sup>2</sup> In the United States (U.S.), the volume of antibiotics sold for use in food-producing animals is at least three times greater than that sold for human use.<sup>3</sup> A One Health approach that emphasizes the connections among the health of humans, animals, and the environment is needed to address antibiotic resistance in an integrated manner. This approach holds the promise of collaboration across multiple disciplines, including doctors, veterinarians, food safety professionals, and environmental health experts.<sup>4</sup>

Bacteria become resistant to an antibiotic through either genetic mutation or horizontal transfer of genes. While antibiotics are used for treating infections in food animal production, globally they are often administered in feed and water for other purposes.<sup>5</sup> In this paper, non-therapeutic antibiotic administration, as distinguished from treatment, is defined as uses that occur in the absence of a veterinarian's diagnosis of disease in a single animal or within a flock

or herd. Therapeutic uses are also characterized by the determination of a specific microbiological agent believed to be responsible for the disease risk, and are confined to a pre-determined duration that typically does not extend across the majority of the lifespan of the animal.

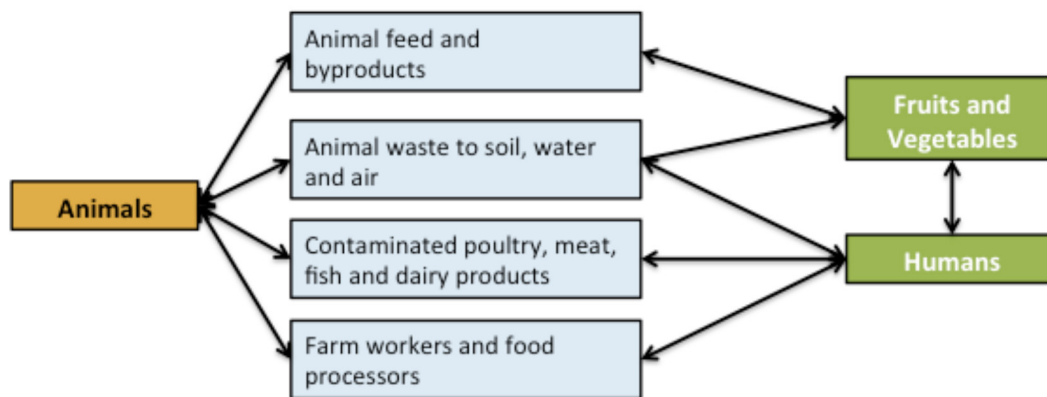
The World Health Organization (WHO), along with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE), has held several consultations and concluded in a scientific assessment report that "there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials."<sup>6</sup> Prolonged courses of low-dose antibiotics, which are typical for non-therapeutic uses of antibiotics in food animals, increase the selective pressure for drug-resistant bacterial strains.<sup>7</sup> Studies have shown that the cross-species transmission of these antibiotic-resistant bacteria occurs through direct contact with animals or indirectly through contaminated food, water, and animal waste from livestock operations, which reenters the food chain through groundwater and fertilizers in farm fields (See Figure 1).<sup>8</sup>

The U.K. government's Swann Committee, the U.S. Food and Drug Administration (FDA) Task Force and the WHO have all found enough evidence of risk of cross-species transmission of resistance to recommend that antibiotics important for treating infec-

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Figure 1

**Selected Pathways for Transmission of Antibiotic Resistance from Animals to Humans**

tions in humans should not be used for non-therapeutic purposes.<sup>9</sup> Despite these recommendations, certain antibiotics classified by WHO in its top tier — “critically important” for human medicine — are used for non-therapeutic purposes in animals in the U.S. The European Medicines Agency has taken steps to better control non-therapeutic use of critically important antibiotics in animals in the European Union.<sup>10</sup>

Non-therapeutic use of antibiotics may result from the belief that the cost of antibiotic treatment to the producer is offset by gains in productivity, either in increased weight in food animal production or reduced costs from avoiding clinical and subclinical disease. However, a study based on Perdue company data found that productivity gains in poultry production due to the use of antibiotic growth promoters (AGPs) failed to offset the cost of antibiotics, and several other studies of commercial broilers have found no link between non-therapeutic use of antibiotics and increased productivity.<sup>11</sup> Antibiotics did not result in higher productivity when fed to pigs during finishing, but significantly improved productivity in nursery pigs.<sup>12</sup> Moreover, the phase-out of AGPs from swine production in Denmark did not impact long-term swine productivity.<sup>13</sup> While economic impact may vary by the antibiotics administered, the type of animal and when in the lifecycle antibiotics are applied, studies show that response to AGPs diminish under better nutrition and hygiene practices.<sup>14</sup>

### **Regional and Country-Level Policies Regulating Non-therapeutic Use of Antibiotics**

In 1986, Sweden became the first country to institute a national ban on use of AGPs in food animal production and prohibited the use of antimicrobi-

als without a veterinary prescription.<sup>15</sup> Denmark, the Netherlands, and Germany were also early adopters of antimicrobial control policies and took the first step by banning avoparcin for growth promotion in 1995-96. The market authorization of avoparcin in the EU was subsequently withdrawn in 1997.<sup>16</sup> Since then the EU has implemented a ban on the use of all AGPs and requires veterinary prescriptions for the use of antimicrobials in food animals.<sup>17</sup>

Several countries outside of Europe such as Japan and Taiwan have instituted various regulations, ranging from requiring veterinary oversight for the use of antimicrobials in food animals to guidance or bans on the use of antibiotics for growth promotion.<sup>18</sup> In 2013, the FDA issued guidelines for drug sponsors that encouraged the voluntary withdrawal of antibiotics for growth promotion.<sup>19</sup> However, this measure falls short because it allows drug sponsors to re-label drugs from “growth promotion” uses to “disease prevention,” without effectively changing the overall use of antibiotics.<sup>20</sup> In the U.S., voluntary FDA guidelines have been complemented by market-based reforms stemming from consumer demand for animal products labeled “antibiotic-free.” For over a decade, some restaurant chains have provided antibiotic-free animal products. Nevertheless, these are still voluntary initiatives that are unmonitored and unverified by the FDA and could be reversed by the companies concerned.

While the country and regional level actions take a step in the right direction, there are variations among countries in implementing regulations. An OIE survey of 178 countries found that nearly half of the countries still allowed the use of AGPs.<sup>21</sup> Effective country-level actions are not sufficient to prevent the spread of resistance. For example, ciprofloxacin-resistant *Salmonella enterica* Serotype Kentucky has emerged in



Danish, French, and English patients, most of whom having travelled internationally two weeks before the onset of illness.<sup>22</sup> Both the biology and emerging epidemiology strongly support the need for global coordination.

### Gaps in Global Coordination

At the global level, various UN and multilateral agencies set norms that shape trade in food products across borders, including microbial and chemical food contaminants. A triad of agency relationships forms the heart of international food safety standards and guidelines that could influence the regulation of antibiotic residues and drug-resistant organisms across borders (see Figure 2).

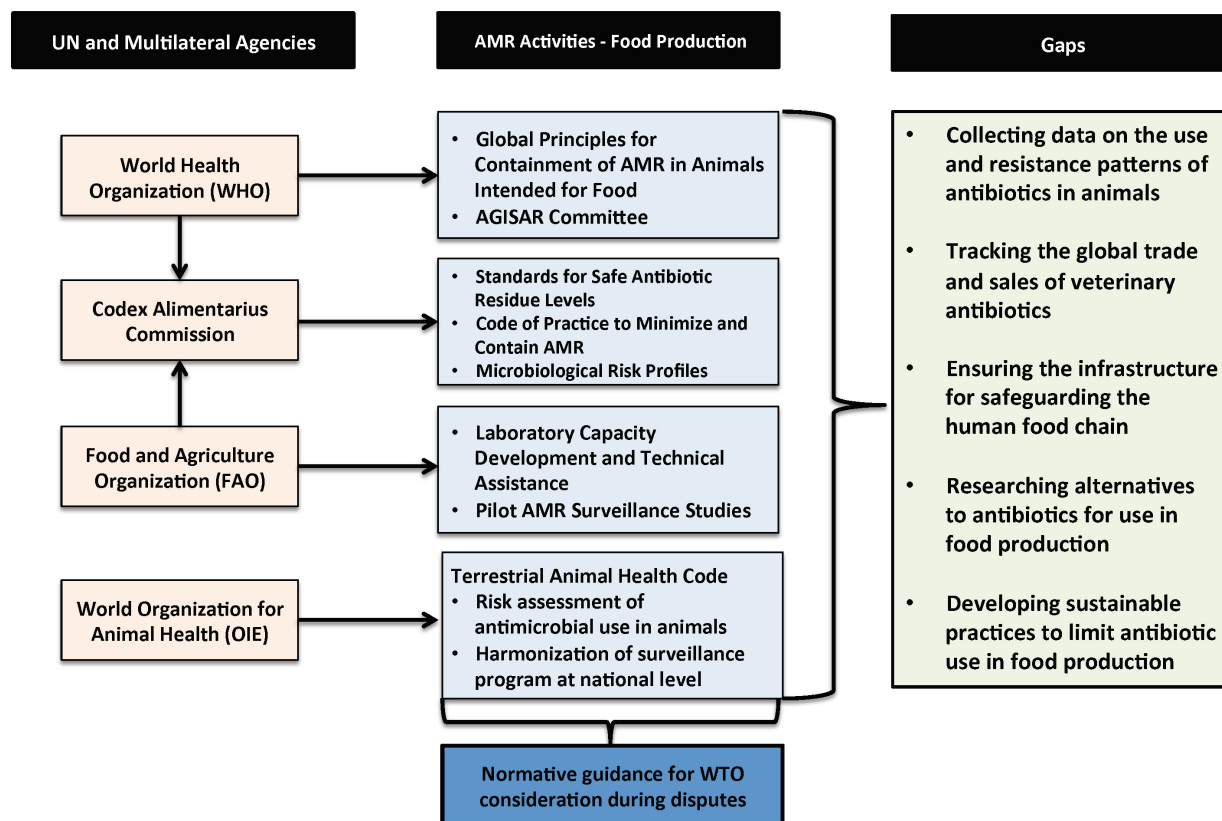
The WHO, along with FAO and OIE, has developed a framework of recommendations for limiting the non-therapeutic use of antimicrobials in food animals and established the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).<sup>23</sup> The AGISAR Committee provides technical support to WHO on containment of antimicrobial resistance

in the food chain, from supporting country-level pilot programs on integrated surveillance to updating the list of critically important antimicrobials for human medicine.<sup>24</sup> The WHO and FAO work collaboratively through the Codex Alimentarius Commission to set international standards for safe antibiotic residue levels and feeding practices as well as develop microbiological risk profiles.<sup>25</sup> Moreover, the OIE's Terrestrial Animal Health Code provides guidance on assessing the risk of antimicrobial use, controlling antimicrobial resistance in food animals, and harmonizing national surveillance and monitoring programs for antibiotic use and resistance in food animals. The OIE also identifies antimicrobials of veterinary importance and sets guidelines for antibiotic susceptibility testing.<sup>26</sup>

These documents provide the normative guidance for consideration by the World Trade Organization (WTO) when a dispute arises. Though the WTO does not develop these international standards, it encourages governments to establish national sanitary and phytosanitary measures consistent with such international standards, guidelines and recommendations.<sup>27</sup>

Figure 2

### Gaps in Global Coordination for Addressing the Use of Antimicrobials in Food-Producing Animals



The WTO Sanitary and Phytosanitary (SPS) Agreement states that “members shall ensure that such measures are not more trade-restrictive than required to achieve an appropriate level of protection, taking into account technical and economic feasibility.”<sup>28</sup> Several cases of trade restrictions have resulted from detection of antibiotic residues in meat, poultry and fish.<sup>29</sup>

This patchwork of global and country-level regulations bearing on the transmission of foodborne AMR still leaves significant gaps, particularly related to collecting data on the use and resistance patterns of antibiotics in animals, tracking the global trade and sales of veterinary antibiotics, ensuring the infrastructure for safeguarding the human food chain, researching alternatives to antibiotics for use in food production, and developing sustainable practices to limit antibiotic use in food animals.

The WHO’s 2014 Global Report on Antimicrobial Resistance Surveillance highlights the lack of harmonized global standards in sampling methodology, diagnostic protocols and reporting procedures across integrated AMR surveillance and monitoring systems in the food chain. It particularly emphasized the need to collect and integrate “data on transmissible [resistance genes] in zoonotic, commensal and pathogenic bacteria from humans, animals and food.”<sup>30</sup> Moreover, there are no international standards setting limits on the presence of resistant bacteria and resistance genes in food, and accordingly, there are currently no international guidelines describing the appropriate response.

Existing regulations fail to adequately monitor veterinary antibiotic use and resistance patterns. In fact, very few OIE member states have official systems to collect antibiotic use data. In response, the OIE has initiated a process to collect quantitative data on antibiotic use and establish a global database.<sup>31</sup> While some European countries track how antibiotics are used in animals, the U.S. does not collect comparable data. Where countries only collect antibiotic sales data primarily from manufacturers, these data need to be supplemented with geographic and species-specific information.

Ongoing global coordination efforts also do not track the movement of antibiotics intended for veterinary use in global trade. The UN Comtrade data track antibiotics (code 2941), but only some classes of antibiotics are separated out in the data, and one cannot distinguish whether antibiotics are destined for human or veterinary use. Along with changing the nature of high-density animal production, collaborative research efforts to find alternatives to the non-therapeutic use of antibiotics are needed. The OIE and the U.S. President’s Council of Advisors on Science and Technology (PCAST) have called for investing in the fundamental research needed to develop alternatives to antibiotics in agriculture.<sup>32</sup>

#### Box 1

##### Denmark’s Experience with Regulating Antibiotic Use in Agriculture

Denmark’s experience in regulating the use of antibiotics in food animals suggests ways to structure effective, country-level surveillance systems. The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP), established in 1995, collects data on the presence of resistance in zoonotic, pathogenic and commensal bacteria from animals, food, and humans. Building on this experience, the Danes later established the VetStat Monitoring Program to track the consumption of antibiotics in livestock. The species-specific sales data collected under VetStat can help investigate the links between antibiotic use in animals and resistance.<sup>33</sup>

Complementing these robust surveillance measures, Denmark initially banned the use of avoparcin, a glycopeptide antibiotic, in 1995 and virginiamycin, a streptogramin antibiotic, in 1998, followed by voluntary restrictions and then eventually a ban on the use of all AGPs along with all EU countries in 2006. The prevalence of vancomycin-resistant enterococci (VRE) in poultry decreased after the ban of avoparcin, from over 80% in 1995 to less than 5% in 1998.<sup>34</sup>

Denmark passed legislation severing ties between the sale of antibiotics and veterinarian income, required veterinary prescriptions for antibiotic use, and prohibited veterinarians from prescribing fluoroquinolones. While the ban on AGPs nearly doubled the annual therapeutic use of antibiotics, there was a net decrease in the use of antibiotics in animals during the same time period.<sup>35</sup> To limit the increasing therapeutic use of antibiotics, the Danish government introduced a new regulation called the “yellow card system” that limits antibiotic use based on the size of the swine farms. Farmers who were outliers consuming the highest level of antibiotics per pig got warning letters, and if they did not work to decrease their farms’ use of antibiotics, financial penalties were applied as well. Since the regulation was implemented, the therapeutic use of antibiotics has decreased by almost 25%.<sup>36</sup>

Despite the comprehensive national policies to limit the use of antibiotics in animals, addressing drug resistance in domestic food animals is still a challenge. For example, prevalence of MRSA in pigs has increased, and the number of new cases of livestock-associated MRSA rose by nearly a third in 2013. Also, Denmark still cannot fully prevent antibiotic-resistant pathogens from entering the food supply through cross-border trade. DANMAP surveillance has shown increased antibiotic resistance in travel-associated infections and imported meat products.<sup>37</sup> These findings point to the need for a framework of global coordination to limit the non-therapeutic use of antibiotics.

### International Agreement

A framework for global coordination is needed to address the risk of cross-border transmission of resistance genes or antibiotic-resistant pathogens, ensure global cooperation such that all countries contribute to collective efforts and reap the benefits, integrate this issue with relevant international trade, environmental and health law, and create public goods such as vaccines and alternatives to antibiotics.

An international agreement might enable the implementation of this global coordination.<sup>38</sup> Whether the agreement is by treaty, convention or regulation, a spectrum of hard (binding) and soft (non-binding) norm instruments might be deployed to ensure monitoring, implementation,

Among the key elements of the framework are:

- An internationally recognized procedure for setting limits on the presence of antibiotic-resistant pathogens or resistance genes in food and for developing recommendations on which antimicrobial medicines should be reserved solely for human use;
- R&D for alternatives to antibiotic use in animal husbandry and aquaculture would be targeted to enable a more effective transition to sustainable approaches to agriculture and a “One Health” strategy to tackling antibiotic resistance;
- A mechanism of accountability provided by the monitoring and surveillance of cross-border

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reporting of progress, and financing of the required activities.<sup>39</sup> Such a framework for global coordination should be guided by the following principles:

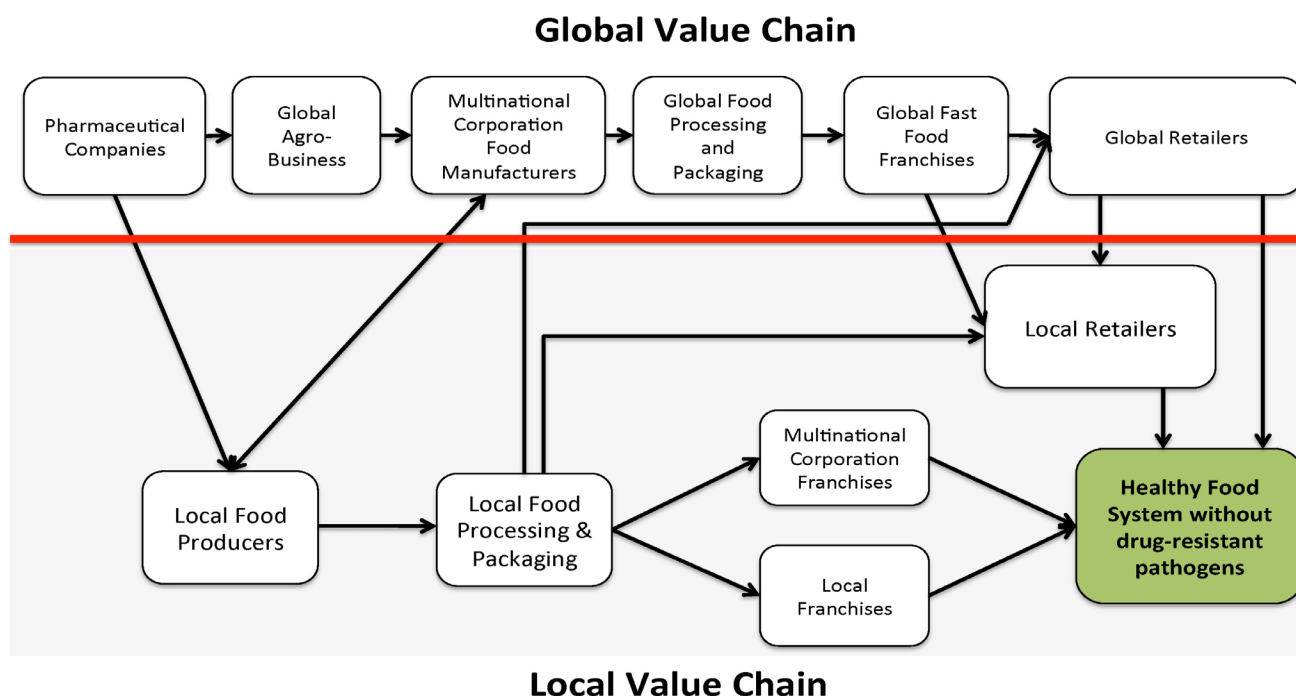
- Acknowledging the different levels of development and local context of countries, flexibility is allowed for implementing the requirements without compromising on the ultimate goals and outcomes;
- Recognizing that the risk of cross-border spread of drug-resistant pathogens is a shared one, the obligation to provide financial and technical support to countries not sufficiently resourced to meet these requirements would also be shared;
- Production of food animals would be conducted in a manner that does not necessitate the routine use of antibiotics and other pharmaceutical crutches;
- Economic incentives that encourage inappropriate antibiotic use should be eliminated, and marketing and promotion of antibiotics for non-therapeutic use should be prohibited; and
- To minimize disruption of food supplies and livelihoods of farmers and farm workers, transition periods would be tied to milestones linked to the availability of such support.

trade of antibiotics and food products;

- Enforcement from the tracking of indicators of potential, cross-border risk of antibiotic resistance through a globally coordinated surveillance system;
- Adequate financing for implementing the framework, including for a global surveillance and enforcement system, and capacity building for countries; and
- Appropriate trade measures that are consistent with the goals of the framework.

Existing recommendations and guidelines on the human and animal use of antibiotics provide a foundation for this work, and previous instruments — from the Framework Convention on Tobacco Control (FCTC) and International Health Regulations to the Pandemic Influenza Preparedness Framework and the Global Code of Practice on International Recruitment of Health Personnel — offer, with appropriate modification, useful precedents. The heavy concentration of the food industry and key import and export markets also suggests that an international agreement might be initially set in motion among targeted parties rather than waiting for a more universally inclusive arrangement.<sup>40</sup> An agreement among Japan, the U.S., the EU,

Figure 3

**Simplified Conceptual Framework of Global and Local Value Chain of Food Animal Production**

**Adapted From:** Gereffi, G., & Christian, M. M. (2010). Trade, transnational corporations and food consumption: A global value chain approach. *Trade, Food, Diet and Health Perspectives and Policy Options*, C. Hawkes, C. Blouin, S. Henson, N. Drager, L. Dubé, eds, 91-110.

and Brazil alone would affect at least a quarter of all global imports and 40% of all global exports of meat, by value.<sup>41</sup> However, any such plurilateral agreement must take into account the needs and impact on other countries, because a coordinated global response is needed.

As depicted by the flows across the red line in the global and local value chain diagram of food animal production (Figure 3), global coordination on the non-therapeutic use of antibiotics might focus on several key points where there is cross-border movement, both of antibiotics and of food products. The tracking of antibiotic use, marketing, promotion, sales and resistance patterns is a key feedback loop in this accountability mechanism. The inspection, monitoring and global data collection of antibiotic-resistant pathogens or genes carried in food products is both sentinel and safeguard against cross-border transmission. National policies tailored to the specific domestic context will be required to ensure compliance and the continued flow of food products across borders.

Countries party to this agreement will differ in their domestic use of antibiotics in food animal production, in their level of food exports, and in their infrastructure for enabling effective monitoring for accountability. An international agreement could offer a flexible set of options to regulate the use of antibiotics in food

animals. A structured risk analysis framework, such as that described in Codex guidelines, can serve as a starting point for assessing what potential hazards from AMR microorganisms or their determinants pose the greatest threat to human health and to the disruption of trade in food products.<sup>42</sup> In addition to national level risk analysis, international standard setting is needed to reduce duplication of efforts, provide guidance to countries without the capacity to carry out such analysis, and lower the risk of trade disputes related to antibiotic resistance threats.

A host of local interventions might abate the inappropriate use of antibiotics in the veterinary sector. These include regulation of veterinary oversight (training, limiting financial incentives for veterinarians to prescribe antimicrobials, prescription requirements, and handling of the distribution as well as the disposal of unused veterinary drugs), of the domestic use and export of antibiotics for use in food animals by industry (marketing authorization, advertising, training and research), and of the roles and responsibilities of others in the supply chain, including wholesale and retail distributors. The development of flexible modules could support countries seeking to implement such measures. As done under FCTC, the Secretariat could also prepare self-assessment checklists



to help parties comply with requirements laid out in the modules.

Technical assistance must accompany the requirements under any international agreement. Some of this support might come in the form of reviews, guidelines, and checklist tools built on a common evidence base and applicable across a range of settings. Other technical assistance would need to be tailored to the country-specific situation. Countries with little infrastructure in place for food safety may require financial resources and expert training to meet these obligations under an international agreement. To keep such information free of financial conflict of interest, public resources will be required to support implementation.

Similarly, an R&D agenda might inform the delivery of this technical assistance, improve point-of-care testing for monitoring the potential spread of AMR determinants, and pave the way to alternatives to antibiotic use in animal husbandry and aquaculture. Such technological alternatives could smooth and lower the costs of transition and compliance. Importantly, both the agenda priority-setting process and the resourcing of this research should be transparent, reflective of the public's interest, and managed in a manner that avoids unnecessary conflict of interest. Public sector financing might piggyback on existing multilateral research programs, like the Consultative Group on International Agricultural Research (CGIAR), be housed at WHO or the Special Programme for Research and Training in Tropical Diseases (TDR), or become part of global initiatives set up to tackle the challenges of antibiotic innovation.

Ensuring predictable financial commitments, a broad donor base, and funding levels that match the scale of activities are challenges facing the implementation of such international agreements. Participating countries could provide appropriations to a Secretariat set up to administer the obligations under such an arrangement, as is the case with International Agency for Research on Cancer or CGIAR. Similar to the support of the Global Influenza Surveillance and Response System, the food industry might contribute to the public good of food safety inspection and monitoring and surveillance as well as research efforts.<sup>43</sup> Alternatively, a tax on antibiotic revenues at the manufacturer or importer level might be levied to offset the costs of the negative externalities caused by the use of their products, as in a Pigouvian tax.<sup>44</sup> However, even without quantifying precisely the negative externality, a user fee applied to the use of antibiotics in animals could be an effective disincentive against low-value usage of these important drugs.

To keep antibiotics effective, the stewardship of these life-saving drugs must involve a One Health

approach. This requires integrating surveillance data collection, monitoring and enforcement, research, technical assistance, and financing under the umbrella of an international agreement. Even in the face of efforts to pass effective domestic measures, countries like Denmark show us that there remain challenges of drug resistance in food animals, and porous borders afford limited protection against trade from countries that do not share these safeguards. An international agreement would help ensure the global coordination needed to accomplish these aims.

## References

1. World Health Organization, *The Evolving Threat of Antimicrobial Resistance: Options for Action* (2012); T. Landers, B. Cohen, T. Wittum, and E. Larson, "A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential," *Public Health Reports* 127, no. 1 (2012): 4-22.
2. T. Van Boeckel, C. Brower, and M. Gilbert et al., "Global Trends in Antimicrobial Use in Food Animals," *Proceedings of the National Academy of Sciences*, 112, no. 18 (2015): 5649-5654.
3. R. Nelson, "FDA Action on Animal Antibiotics Could Still Have Loopholes," *The Lancet Infectious Diseases* 14, no. 5 (2014): 376-377.
4. Executive Office of the President, *National Strategy for Combating Antibiotic-Resistant Bacteria* (2014): 1-33.
5. United States Department of Agriculture, "Feedlot 2011 Part I: Management Practices on U.S. Feedlots with a Capacity of 1,000 or More Head," Animal and Plant Health Inspection Services (2013): 1-143; United States Department of Agriculture, "Swine 2006 Part II: Reference of Swine Health and Health Management Practices in the United States," Animal and Plant Health Inspection Services (2007): 1-78; Y.-G. Zhu, T. Johnson, and J.-Q. Su et al., "Diverse and Abundant Antibiotic Resistance Genes in Chinese Swine Farms," *Proceedings of the National Academy of Sciences* 110, no. 9 (2013): 3435-3440.
6. Food and Agricultural Organization of the United States, World Organization for Animal Health, World Health Organization, "Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment" (2003): 1-35.
7. S. Levy and B. Marshall, "Antibacterial Resistance Worldwide: Causes, Challenges and Responses," *Nature Medicine* 10, no. 12 (2004): S122-S129.
8. B. Marshall and S. Levy, "Food Animals and Antimicrobials: Impacts on Human Health," *Clinical Microbiology Reviews* 24, no. 4 (2011): 718-733; J. Casey, F. Curriero, S. Cosgrove, K. Nachman, and B. Schwartz, "High-Density Livestock Operations, Crop Field Application of Manure, and Risk of Community-Associated MRSA Infection in Pennsylvania," *JAMA Internal Medicine* 173, no. 21 (2013): 1980-1990.
9. U.S. Food and Drug Administration, "Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (2012): 5-14.
10. See United States Department of Agriculture (Swine 2006), *supra* note 5; European Medicines Agency, "Referral Procedure on Veterinary Medicinal Products Containing 3rd and 4th Generation Cephalosporins under Article 35 of Directive 2001/82/EC," Veterinary Medicines and Product Data Management (2012); EMA, "CVMP Guideline on the SPC for Antimicrobial Products (EMA/CVMP/SAGAM/383441/2005)," Veterinary Medicines Division (2014).
11. J. Graham, J. Boland, and E. Silbergeld, "Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis," *Public Health Reports* 122, no. 1 (2007): 79-87; J. Bray, C. Taylor, T. Cherry, and J. Carey, "Performance Comparison

- between the Use and Nonuse of an Enteric Health Medication Program across Five Consecutive Commercial Broiler Flocks," *Journal of Applied Poultry Research* 18, no. 2 (2009): 165-171; J. MacDonald and S. Wang, "Foregoing Sub-Therapeutic Antibiotics: The Impact on Broiler Grow-Out Operations," *Applied Economic Perspectives and Policy* 33, no. 1 (2011): 79-98.
12. W. McBride, N. Key, and K. Mathews, "Subtherapeutic Antibiotics and Productivity in US Hog Production," *Applied Economic Perspectives and Policy* 30, no. 2 (2008): 270-288.
  13. F. Aarestrup, V. Jensen, and H.D. Emborg et al., "Changes in the Use of Antimicrobials and the Effects on Productivity of Swine Farms in Denmark," *American Journal of Veterinary Research* 71, no. 7 (2010): 726-733.
  14. S. Levy, "Reduced Antibiotic Use in Livestock: How Denmark Tackled Resistance," *Environmental Health Perspectives* 122, no. 6 (2014): A160-A165.
  15. M. Wierup, "The Swedish Experience of the 1986 Year Ban of AGPs, with Special Reference to Animal Health, Disease Prevention, Productivity, and Usage of Antimicrobials," *Microbial Drug Resistance* 7, no. 2 (2001): 183-190.
  16. C. Coglian, H. Goossens, and C. Greko, "Restricting Antimicrobial Use in Food Animals: Lessons from Europe," *Microbe* 6, no. 6 (2011): 274-279.
  17. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, "Sales of Veterinary Antimicrobial Agents in 26 EU/EEA Countries in 2012," Fourth EVSAC Report (2014); H. Wegener, F. Aarestrup, L. Jensen, A. Hammerum, and F. Bager, "Use of AGPs in Food Animals and Enterococcus Faecium Resistance to Therapeutic Antimicrobial Drugs in Europe," *Emerging Infectious Diseases* 5, no. 3 (1999): 329-335.
  18. D. Maron, T. Smith, and K. Nachman, "Restrictions on Antimicrobial Use in Food Animal Production: An International Regulatory and Economic Survey," *Globalization and Health* 9:48, (2013): 1-11.
  19. U.S. Food and Drug Administration, "Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209," Center for Veterinary Medicine (2013).
  20. K. Nachman, T. Smith, and R. Martin, "Antibiotics: Call for Real Change," *Science* 343, no. 6167 (2014): 140.
  21. F. Diaz, "OIE Initiative to Collect Quantitative Data on the Use of Antimicrobial Agents in Animals to Establish a Global Database," European Surveillance of Veterinary Antimicrobial Consumption Stakeholders meeting, London, UK, 2014.
  22. S. Le Hello, R. Hendricksen, and B. Doublet et al., "International Spread of an Epidemic Population of Salmonella Enterica Serotype Kentucky ST198 Resistant to Ciprofloxacin," *Journal of Infectious Diseases* 204, no. 5 (2011): 675-684.
  23. World Health Organization, *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food* (2000).
  24. WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, *Integrated Surveillance of Antimicrobial Resistance* (2013): 1-93.
  25. Codex Alimentarius Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance CAC/GL 77-2011, 4; D. Adams, R. Cooper, M. Hahn, and J. Kahan, eds., *Food and Drug Law and Regulation* (Washington, D.C.: FDLI, 2011): at 911-918.
  26. World Organization for Animal Health, *Factsheet on Antimicrobial Resistance* (2013).
  27. World Trade Organization, *Understanding the WTO Agreement on Sanitary and Phytosanitary Measures* (1998).
  28. World Trade Organization, "Article 5: Assessment of Risk and Determination of the Appropriate Level of SPS Protection," *WTO SPS Agreement*, 5, no. 6 (1998).
  29. Russia Federal Veterinary and Phytosanitary Surveillance Service Press Release (December 5, 2014), Translated by USDA; FDA Import Alert, "Detention without Physical Examination of Aquacultured Catfish, Basa, Shrimp, Dace, and Eel from China-Presence of New Animal Drugs and/or Unsafe Food Additives," (2015).
  30. World Health Organization, *AMR: Global Report on Surveillance* (2014): at 61.
  31. See Diaz, *supra* note 21.
  32. President's Council of Advisors in Science and Technology, *Report to the President on Combating Antibiotic Resistance*, Executive Office of the President (2014); see World Organization for Animal Health, *supra* note 26.
  33. A. Hammerum, O. Heuer, and H.-D. Emborg et al., "Danish Integrated Antimicrobial Resistance Monitoring and Research Program," *Emerging Infectious Diseases* 13, no. 11 (2007): 1633-1639.
  34. F. Bager et al., "Glycopeptide Resistance in Enterococcus Faecium from Broilers and Pigs Following Discontinued Use of Avoparcin," *Microbial Drug Resistance* 5, no. 1 (1999): 53-56.
  35. K. Grave et al., "Usage of Veterinary Therapeutic Antimicrobials in Denmark, Norway and Sweden Following Termination of AGP Use," *Preventive Veterinary Medicine* 75, no. 1 (2006): 123-132.
  36. F. Aarestrup, "Sustainable Farming: Get Pigs off Antibiotics," *Nature* 486, no. 7404 (2012): 465-466.
  37. H. Korsgaard, Y. Agersø, A. Hammerum, and L. Skjøl-Rasmussen, eds., *DANMAP Annual Report: Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark* (2013).
  38. J. Kates and R. Katz, "The Role of Treaties, Agreements, Conventions, and Other International Instruments in Global Health," *Infectious Disease Clinics of North America* 25, no. 2 (2011): 455-475.
  39. L. Gostin and D. Sridhar, "Global Health and the Law," *New England Journal of Medicine* 37, no. 18 (2014): 1732-1740.
  40. S. Murphy, "Concentrated Market Power and Agricultural Trade," *EcoFair Trade Dialogue* (2006).
  41. Analysis based on UN Comtrade data from International Trade Center Statistics.
  42. Codex Alimentarius, *Code of Practice to Minimize and Contain Antimicrobial Resistance*, CAC/RCP 61-2005.
  43. D. Fidler and L. Gostin, "The WHO Pandemic Influenza Preparedness Framework: A Milestone in Global Governance for Health," *JAMA* 306, no. 2 (2011): 200-201.
  44. A. Hollis and Z. Ahmed, "The Path of Least Resistance: Paying for Antibiotics in Non-human Uses," *Health Policy* 118 no. 2 (2014): 264-270.

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# Much Can Be Learned about Addressing Antibiotic Resistance from Multilateral Environmental Agreements

*Steinar Andresen and Steven J. Hoffman*

## Introduction

Antibiotic resistance (ABR) is a common-pool resource challenge like those that global environmental scholars have been addressing for decades. Just like clean air, fish stocks, and oceans, antibiotic effectiveness shares the two defining qualities of a common good: it is rivalrous in that it is limited or subtractable upon use, and it is non-excludable in that it is very difficult to stop people from abusing them inappropriately.<sup>1</sup> This is because each use of antibiotics increases the likelihood that affected bacteria will adapt and evolve in ways that makes them less susceptible to these bacteria-harming antibiotics. The natural development of resistance is what separates antibiotics from most other medicines — the use of which do not affect the effectiveness of these medicines for others.

In this sense, ABR is a global ecological problem and a tragedy of the commons.<sup>2</sup> This means that any attempt to address the global threat of ABR can glean lessons from the environmental sector, at the core of which lies many global collective action problems like ABR and attempts to correct them. Much can be learned from what has worked in global environmental governance and the many areas where there has been failure.<sup>3</sup> This article identifies a few lessons for addressing ABR to inform research and policy directions going forward.

## Global Governance of the Environment

The backbone of global environmental governance is made up of almost 1,200 international treaties known as “multilateral environmental agreements” (MEAs). Most of these MEAs are bilateral — between two states — but a significant number are regional and global.<sup>4</sup> Over the past decades there has been significant progress in terms of the approach and sophistication of MEAs, such that they can be grouped into different “generations” of treaties.<sup>5</sup> In the 1970s, government negotiators of MEAs generally limited themselves to just identifying the existence of a problem and did not specify how they would address it. In these MEAs, such as the North Sea environmental regime, there were few tangible commitments and actions — if any. In the 1980s and 1990s, MEAs started including both targets and timetables. For example, a particular emissions target might be set for a certain calendar year. This generation of MEAs allowed state parties to the agreement and other stakeholders to measure progress, or lack thereof. In the 1990s differentiation was added as a feature of MEAs because it became evident that equal targets and timetables for all countries — rich and poor alike — was too simple and infeasible. This was also needed for reasons of global justice as developing countries could not reasonably be expected to reach the same goals within

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the same time period. Finally, most recently, market-based mechanisms have been added to some MEAs to give states incentives to reduce emissions. The most prominent example is the flexible mechanisms of the Kyoto Protocol to the United Nations (UN) Framework Convention on Climate Change (FCCC), which allowed for carbon credits, joint implementation and “cap-and-trade” solutions according to each country’s own preference.

States are necessarily the main actors involved in MEAs: only states can negotiate and be parties to international legal agreements, with a few minor exceptions such as United Nations (UN) entities and regional bodies like the European Union. Yet since the UN’s Rio Earth Summit in 1992, civil society organi-

environmental summits and have been integrated into global decision-making processes. Scientific and technical advisory groups have become an increasing mainstay of MEA negotiations as the complexity and scientific uncertainty of global environmental issues increased. The advice of these bodies is heeded more frequently than when such bodies do not exist; their influence increases when their advice is consistent and represents a broad consensus among scientists. Still, despite its increasingly central role, science has remained only one among many legitimate concerns and considerations in MEA negotiations. Political decisions are seldom taken directly from scientific advice.<sup>6</sup>

Although MEAs are the backbone of global environmental governance, they do not represent the sole way through which the world has governed the environment. Non-legal approaches abound. The most visible non-legal strategy is the convening of global summits, some of which have served as the focal point for MEA negotiations but others not. Particularly high-level summits have been arranged nearly every decade (i.e., 1972, 1992, 2002, and 2012). These summits have been important for facilitating cross-country learning, global agenda-setting, and the adoption of new approaches and principles. Their real-world significance, however, is probably diminished by the dense institutional networks that exist in global environmental governance and that already facilitate this “learning” function.<sup>7</sup>

Perhaps the most innovative dimension of global environmental governance is how legal and non-legal approaches have been combined with promising outcomes.<sup>8</sup> One example is the way that some ambitious actors develop and adopt non-binding commitments, advocate for them, and then encourage their uptake by states over time — eventually becoming part of MEAs and legally binding on all state parties. Another example is the emergence of many partnerships over the last 10-15 years, both public-private as well as purely private ones. These partnerships have often been established upon the failure of states to agree on an MEA, such as in the case of the international management of forests.<sup>9</sup> In this sense, partnerships have served as both alternatives to and supplements for MEAs.

**It is clear that global environmental governance has become more sophisticated over the decades. But has this progress in the development of increasingly complex institutional arrangements translated into more effective governance? This question is vital to understand and answer before global health researchers and decision-makers should draw lessons from the environmental sector for ABR — as the relationship between sophisticated governance and effectiveness is not straightforward.**

zations (CSOs) have had a strong presence at environmental meetings and have been important participants. Businesses joined the fray in a major way ten years later starting with the Johannesburg Earth Summit in 2002. Both of these groups are now considered legitimate participants; they lobby actively in the making of MEAs to achieve a diplomatic and legal outcome that aligns with their interests. CSOs are plentiful — now far outnumbering governmental representatives at most environmental summits — but their influence is limited as it is national governments, especially the most powerful ones, that tend to call the final shots. Businesses have been less visible but also probably more influential on MEA negotiations as they tend to advocate core national economic interests.

Scientists and scientific organizations represent a third group of non-state actors who have played an increasingly important role in the making of MEAs. Initially it was natural scientists who dominated, but more recently social scientists have also attended global



### Evaluating Global Governance Arrangements

It is clear that global environmental governance has become more sophisticated over the decades. But has this progress in the development of increasingly complex institutional arrangements translated into more effective governance? This question is vital to understand and answer before global health researchers and decision-makers should draw lessons from the environmental sector for ABR — as the relationship between sophisticated governance and effectiveness is not straightforward.

Studies evaluating the effectiveness of global environmental governance have been conducted for at least two decades by scholars of international relations.<sup>10</sup> There is now general agreement among these scholars that effectiveness is best studied in terms of outputs, outcomes and impacts. *Outputs* are most often the metric of interest among international lawyers; they deal with the ambition, specificity and stringency of rules emanating from a particular regime. In theory, the more ambitious, specific and stringent the rules, the greater the effectiveness that observers can expect to see. However, in reality, any output metric deals only with potential effectiveness; this is because rules — no matter how perfect — are not always followed. *Outcomes* bring us one conceptual step deeper by setting out to establish a causal link between the regime that was established and the resulting actions that are taken by target groups, including state parties but also others like CSOs, businesses, and scientific organizations. *Impact*, finally, is about the actual problem-solving capacity of the regime; in other words, to what extent has the regime been able to solve the problem it was set up to address. This final metric is of course the most important of the three possibilities, but methodologically it is also the most difficult to identify, evaluate or quantify due to interference from a host of intervening variables. For example, it is difficult to know whether adoption of the World Health Organization's Framework Convention on Tobacco Control (FCTC) in 2003 caused a decrease in global tobacco consumption or whether such a decline in consumption (if there has even been one) was caused by greater global awareness of tobacco harms which allowed both the adoption of this international treaty and the decline in tobacco use.<sup>11</sup>

When evaluating what makes some regimes effective and others not, there is relatively broad agreement among global environmental scholars that what matters is both the design of institutions within the regime as well as external factors beyond global decision-makers' control. These factors have been

conceived of in terms of *problem structure* and the regime's *problem-solving capacity*.<sup>12</sup>

Specifically, some problems are intrinsically more difficult to resolve than others due to competing interests, scientific uncertainty and/or political disagreement. Both climate change and biodiversity are examples of problems that, by their nature, are difficult to resolve. Ozone layer depletion — the problem addressed by the much-celebrated Montreal Protocol on Substances that Deplete the Ozone Layer — is far more benign and easier to resolve. ABR probably falls somewhere in the middle between these opposing examples because there are many competing interests at play but there is relative scientific consensus about the problem, its causes, and actions required to resolve it.

Likewise, the regime's problem-solving capacity is a function of power, leadership and institutional design. If there are powerful states taking strong leadership roles within a well-designed regime, then the chances of effective problem-solving capacity are much higher. While power and leadership are naturally hard for most decision-makers to muster, institutional design is relatively easier to shape as it represents a necessary political choice that is often subject to open political contestation among negotiating parties. There must be an institutional design of some sort; the only questions are what that design looks like and how effective it will be at achieving the desired impact (see Panel 1).

### How Effective Is Global Environmental Governance?

The story of global environmental governance is one of dramatic successes and disappointments. On the one hand, it has been documented that MEAs and other institutions have achieved a net positive effect in that global environmental problems would be worse in their absence. On the other hand, most observers of environmental challenges — both experts and the general public alike — know that few, if any, have been fully resolved. According to the most recent UN Environment Programme's Global Environmental Outlook in 2012, only a handful of some 90 global environmental goals investigated were given a high effectiveness score.<sup>13</sup> Some regimes received a medium score while others did not score well at all, which indicates there are many environmental problems for which little progress has been achieved.

Perhaps the most interesting feature of the UN's Global Environmental Outlook evaluation is the wide variation in effectiveness scores given to different regimes. This reveals quite starkly how the environment is a sector in which some problems have

Panel I

**Determinants of Regime Effectiveness**

	<b>Determinants</b>	<b>More Effective</b>	<b>Less Effective</b>
<b>Problem Structure</b>	<b>1. Political consensus</b>	<i>High levels of political consensus can make it easier to find common ground and craft creative solutions that work for most actors</i>	<i>Low levels of political consensus can lead to polarization, hostile disputes, and deadlock that can prevent agreement on pathways forward</i>
	<b>2. Scientific certainty</b>	<i>High levels of scientific certainty and consensus can contribute to a better understanding of the problem and potential solutions for addressing it.</i>	<i>Low levels of scientific certainty and consensus can prevent knowing what needs to be done and casts doubt on the value of intervention</i>
<b>Problem-Solving Capacity</b>	<b>3. Power</b>	<i>Presence of powerful actors supporting the regime increases the likelihood of an effective regime and high rates of compliance</i>	<i>Absence of powerful actors makes problem-solving difficult given key parties are not committed so needed resources may also not be available</i>
	<b>4. Leadership</b>	<i>Strong leadership can provide direction to the regime, support coordination, and rally key parties around solutions for implementation</i>	<i>Weak leadership can lead to chaotic decision-making environments and no clear sense of what is needed to resolve problems</i>
	<b>5. Institutional design</b>	<i>Robust institutional designs can facilitate good decision-making, financing, transparency, oversight, dispute resolution and enforcement</i>	<i>Fragile institutional designs can lead to indecision, insufficient financing, poor coordination, and a lack of accountability</i>

While the factors related to problem structure are probably the most important determinants of regime effectiveness, institutional design is relatively easier to shape as it represents a necessary political choice that is usually subject to open political contestation among negotiating parties.

been quite effectively resolved whereas others represent near-total failures of collective action. The most important factors explaining this variation are those related to the underlying problem structure. This lesson can be illustrated by contrasting experiences with two particularly prominent MEAs that were mentioned earlier: the Montreal Protocol (including later additions) and the FCCC (including the Kyoto Protocol).

The Montreal Protocol, for its part, is hailed as one of the few true successes in global environmental governance. To some extent this is the result of good institutional design such as creation of a Multilateral Fund for the Implementation of the Montreal Protocol that has disbursed over \$3 billion USD since its 1991 creation. But primarily the success of this protocol is attributable to the benign problem that it addressed. Ozone depletion can be considered a benign environmental problem because effective substitutions existed

to replace the harmful chlorofluorocarbon gases that caused it. In other words, a quick technological fix already existed, and the number of producers and consumers of these gases that needed to adopt the technological fix were relatively limited. The effectiveness of this regime has been aided by strong involvement of American industry and American government negotiators who saw it in their strategic self-interest to push for a robust international agreement.<sup>14</sup>

In contrast, climate change implicates virtually all economic activity globally. The challenge raises deep-seated conflicts between developed and developing countries, the powerful United States has dragged its feet, and unfortunately there are no quick technological fixes — at least not yet. All of this makes climate change an exceedingly difficult problem to solve. Thus, we should not necessarily consider the negotiators of the “successful” ozone treaty as more proficient than those negotiators behind the “failed” climate change

treaty; instead, the best lesson learned is probably about the varying nature of different types of problems faced and their corresponding difficulty in resolving them.

When considering ABR, these contrasting cases of environmental challenges show there is no universally successful approach to designing effective international agreements. But two concrete lessons can be drawn. The first is how vital it will be to always keep the problem structure of ABR in mind when setting

First, an international ABR agreement should contain robust reporting and verification procedures for tracking actions, inputs, processes, outputs, outcomes and/or impacts.<sup>17</sup> Such basic transparency and oversight mechanisms are often neglected in diplomatic negotiations; they tend to be seen as “technical” matters and therefore less important than commitments, goals and principles. However, reporting procedures are crucial for understanding the nature of the problem, evaluating progress toward addressing it, celebrat-

**When considering ABR, these contrasting cases of environmental challenges show there is no universally successful approach to designing effective international agreements. But two concrete lessons can be drawn. The first is how vital it will be to always keep the problem structure of ABR in mind when setting ambitions for and crafting changes to the global antibiotics regime. The institutional design of any international ABR agreement should ideally reflect its underlying problem structure to maximize its potential for impact. The second lesson is that efforts that can be undertaken to change the problem structure may be just as important — if not even more important — than the design of any new global policy solutions. International agreements or ad-hoc efforts that could change the problem structure of ABR would include developing better diagnostics, infection control strategies, and alternatives to antibiotic use in animals as key components.**

ambitions for and crafting changes to the global antibiotics regime.<sup>15</sup> The institutional design of any international ABR agreement should ideally reflect its underlying problem structure to maximize its potential for impact. The second lesson is that efforts that can be undertaken to change the problem structure may be just as important — if not even more important — than the design of any new global policy solutions. International agreements or ad-hoc efforts that could change the problem structure of ABR would include developing better diagnostics, infection control strategies, and alternatives to antibiotic use in animals as key components.<sup>16</sup>

### **Global Institutional Design for Addressing Antibiotic Resistance**

While it may not be the most important determinant of regime effectiveness, there are some institutional design features that boost the chances of international agreements being more effective. Five were selected on the basis of their perceived relevance for addressing the global threat of ABR.

ing any successes, and holding state parties and other stakeholders to account for any failures.<sup>18</sup> To the extent that these procedures do currently exist in MEAs, they usually rely on states submitting self-reports on their own progress to a coordinating secretariat, which are then synthesized in databases and made publicly available. The challenge is that states often fail to submit their required reports (usually due to limited bureaucratic capacity in developing countries) and may paint a rosier picture of progress than is actually deserved (usually to safeguard their reputations). This points to the importance of supporting countries to meet their reporting requirements and independently verifying the veracity of self-reported data. In some MEAs this function is served by the Global Environmental Facility. Although no central information clearinghouse is perfect: a review of the World Health Organization's FCTC implementation database in 2012 found that the secretariat had misreported 32.7% of entries.<sup>19</sup> The experience with MEAs shows that self-reporting is perhaps the weakest of transparency mechanisms but

that it is a good starting point. Negotiators of international agreements should aim higher.

Second, an international ABR agreement should include both sanctions for non-compliance and assistance for implementation. This reflects the wisdom of two different schools of thought within international relations: the “enforcement school” and the “managerial school.”<sup>20</sup> To simplify, the enforcement school believes that states will try to free ride and cheat such that strong compliance procedures and the possibility of sanctions are needed. The managerial school believes that states want to comply with international agreements — whether by coincidence or by consequence of the agreements — such that non-compliance is evidence of inability or incapacity which should be remedied with financial and technical assistance. Empirical evidence lends support to both assumptions.<sup>21</sup> Politically, sanctions can be quite difficult to negotiate and employ, but they have proven quite impactful for those agreements that manage to incorporate and apply them.<sup>22</sup> Assistance is less difficult politically to negotiate, but just because support is written into an agreement does not mean that it is ever delivered.<sup>23</sup> This points to the potential value of a global pooled fund for addressing ABR that could finance access, conservation and innovation efforts, particular in resource-poor settings. The existence of this kind of fund is partially responsible for the Montreal Protocol’s success in protecting the ozone layer. A similar mechanism is currently being developed to address climate change. For ABR, a pooled fund with differentiated contributions based on gross national income could help ensure that necessary assistance is actually delivered to support compliance and implementation.

Third, an international ABR agreement should be designed in such a way that allows maximally ambitious content.<sup>24</sup> Decision-making rules play an important role here. Indeed, one of the most obvious weaknesses of many MEAs is their frequent reliance on consensus-based decision-making which often leads to a “race to the bottom” or a “law of the least ambitious program.”<sup>25</sup> In short, with a consensus decision-making rule, the state that is least willing to act is most decisive. A majority vote decision-making rule is better even though it may polarize states.<sup>26</sup> It may also be helpful to start negotiations with a smaller or more homogenous group of states — fewer actors to compromise and fewer interest groups to accommodate — but ABR’s need for near-universal action on access, conservation and innovation imperatives means this approach may not be possible.<sup>27</sup>

Fourth, an international ABR agreement should include implementation mechanisms for strengthening political decision-making and securing independent scientific advice.<sup>28</sup> Experience with MEAs sug-

gests that strong and competent secretariats improve the effectiveness of international agreements.<sup>29</sup> They are important for creating knowledge, disseminating it, shaping discourse on how problems are understood, and facilitating negotiation of collective solutions through sharing their ideas and expertise. Although, realistically, their influence varies considerably, depending on the problem structure they are addressing, the resources available to them, the quality of their staff, and the dynamism and strategic foresight of their leaders.<sup>30</sup> For ABR, the World Health Organization secretariat is a most obvious choice for supporting intergovernmental decision-making; though the UN agency’s recent financial, governance and human resource challenges may make this additional responsibility both burdensome and infeasible.<sup>31</sup> Either way, a separate and independent scientific panel on ABR should be created by the agreement to continually synthesize the evolving research evidence, recommend updates to the agreement, and inform its implementation. The chances of science influencing policy are greater when that science is communicated in a reader-friendly way from an authoritative and independent panel that is free from apprehensions of bias.<sup>32</sup> Like with secretariats, the nature of the problem also matters: scientific panels will be most influential when offering advice on benign problems, characterized by a high degree of scientific certainty and low levels of political conflict.

Fifth, an international ABR agreement should contain provisions, obligations, and targets that are as specific, precise, and clear as possible. Specificity makes it easier to evaluate whether the agreement is being followed. Precision helps facilitate positive competition among state parties regarding who is the best performer. Clarity minimizes the risk of future disputes caused by different interpretations of the same text. Overall, MEAs have shown considerable progress across generations of agreements in slowly moving away from vague rules. However, this has been possible to different extents among different environmental challenges. While it may be fairly easy to specify quantitative targets for atmospheric emissions, for example, it proved much harder to do so for biodiversity — which makes the Convention on Biological Diversity an illustrative example of generality and vagueness. As far as possible, negotiators of an international ABR agreement should aim to maximize the specificity, precision and clarity of the text they adopt. Different parts of the ABR challenge may allow for different levels of these virtues — which should be expected given the very different political-economy problems preventing access, conservation and innovation for antibiotics.



## References

1. A. Hollis and P. Maybarduk, "Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
2. *Id.*
3. K. Sandberg, S. J. Hoffman, and M. Pearcey, *Lessons for Global Health from Global Environmental Governance* (London, UK: Chatham House, 2015): at 9-12.
4. R. Mitchell, "International Agreement Database Project 2002-2015," available at <<http://iea.uoregon.edu/page.php?file=home.htm&query=static>> (last visited June 1, 2015).
5. S. Andresen, E. L. Boasson, and G. Hønneland, eds., *International Environmental Agreements: An Introduction* (New York and London: Routledge, Taylor and Francis Group, 2012).
6. A. Underdal, "Science and Politics: The Anatomy of an Uneasy Partnership," in S. Andresen, T. Skodvin, A. Underdal, and J. Wettestad, *Science and Politics in International Environmental Regimes: Between Integrity and Involvement* (Manchester, UK: Manchester University Press, 2000): at 1-22; S. Andresen, "The Role of Scientific Expertise in Multilateral Environmental Agreements: Influence and Effectiveness," in M. Abrus, K. Arts, E. Hey, and H. Raulus, eds., *The Role of Experts in International and European Decision Making Processes: Advisors, Decision-Makers or Irrelevant Actors?* (Cambridge, UK: Cambridge University Press, 2014): at 105-125.
7. S. Andresen, "Do We Need More Sustainability Conferences?" in P. Dauverge, ed., *Handbook of Global Environmental Politics: Second Edition* (Cheltenham, UK: Edward Elgar Publishers, 2012): at 87-97.
8. J. B. Skjærseth, O. S. Stokke, and J. Wettestad, "Soft Law, Hard Law and Effective Implementation of International Environmental Norms," *Global Environmental Politics* 6, no. 3 (2006): 104-121.
9. L. Gulbrandsen, *Transnational Environmental Governance: The Emergence and Effects of the Certification of Forests and Fisheries* (Cheltenham and Northampton, UK: Edward Elgar, 2010).
10. E. Miles, S. Andresen, E. Carlin, J. B. Skjærseth, A. Underdal, and J. Wettestad, *Environmental Regime Effectiveness: Confronting Theory with Evidence* (Cambridge, MA: MIT Press, 2002); H. Breitmeier, O. R. Young, and M. Zürn, *Analyzing International Environmental Regimes: From Case Study to Database* (Cambridge, MA: MIT Press, 2006).
11. S. J. Hoffman and J.-A. Røttingen, "Assessing the Expected Impact of Global Health Treaties: Evidence from 90 Quantitative Evaluations," *American Journal of Public Health* 105, no. 1 (2015): 26-40; S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "Assessing Proposals for New Global Health Treaties: An Analytic Framework," *American Journal of Public Health* (2015): e1-e8.
12. E. Miles, A. Underdal, S. Andresen, J. Wettestad, J. B. Skjærseth, and E. Carlin, *Environmental Regime Effectiveness: Confronting Theory with Evidence* (Cambridge, MA: MIT Press, 2002).
13. United Nations Environment Programme. *Global Environment Outlook 5: Environment for the Future We Want* (Nairobi, Kenya: United Nations Environment Program, 2012).
14. J. B. Skjærseth, "International Ozone Policies: Effective Environmental Cooperation," in S. Andresen, E. Boasson, and G. Hønneland, eds., *International Environmental Agreements: An Introduction* (London and New York: Routledge, 2012): at 38-49.
15. S. J. Hoffman, B. McGrady, G. M. Caleo, N. Daulair, S. Elbe, and D. L. F. Wong et al., "Achieving Global Collective Action For Improving Access to Antimicrobials and Sustaining Their Effectiveness," in preparation.
16. A. Behdinan, S. J. Hoffman, and M. Pearcey, "Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
17. S. J. Hoffman and T. Ottersen, "Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).
18. *Id.*
19. Z. Rizvi and S. J. Hoffman, "WHO's Undermining Tobacco Control," *The Lancet* 380, no. 9843 (2012): 727-728.
20. A. Chayes and A. H. Chayes, *The New Sovereignty Compliance with International Regulatory Agreements* (Cambridge, MA: Harvard University Press, 1998).
21. E. Brown-Weiss and H. Jacobsen, eds., *Engaging Countries Strengthening Compliance with International Environmental Accords* (Cambridge, MA: MIT Press, 1998).
22. See Hoffman and Ottersen, *supra* note 17.
23. S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "International Law Has a Role to Play in Addressing Antibiotic Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only; S. J. Hoffman and J.-A. Røttingen, "Dark Sides of the Proposed Framework Convention on Global Health's Many Virtues: A Systematic Review and Critical Analysis," *Health & Human Rights Journal* 15, no. 1 (2013): 117-134.
24. S. J. Hoffman and J. A. Røttingen, "Assessing Implementation Mechanisms for an International Agreement on Research and Development for Health Products," *Bulletin of the World Health Organization* 90, no. 11 (2012): 854-863.
25. A. Underdal, *The Politics of International Fisheries Management: The Case of the Northeast Atlantic* (Oslo, Norway: Universitetsforlaget, 1980).
26. A. Steinar, "The Whaling Regime: Good Institutions but Bad Politics?" in R. Friedheim, ed., *Toward A Sustainable Whaling Regime* (Seattle and London: University of Washington Press, 2000): at 235-265.
27. Z. Rizvi and S. J. Hoffman, "Effective Global Action on Antibiotic Resistance Requires Careful Consideration of Convening Forums," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).
28. S. J. Hoffman and J.-A. Røttingen, "Split WHO in Two: Strengthening Political Decision-Making and Securing Independent Scientific Advice," *Public Health* 128, no. 2 (2014): 188-194.
29. F. Biermann and B. Siebenhüner, eds., *Managers of Global Change: The Influence of International Environmental Bureaucracies* (Cambridge, MA: The MIT Press, 2009).
30. *Id.*
31. See Rizvi and Hoffman, *supra* note 19.
32. See Sandberg, Hoffman, and Pearcey, *supra* note 3, at 9-12.

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# Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms

*Steven J. Hoffman and Trygve Ottersen*

## Introduction

Most proposals for new international agreements aim to address important global challenges. If the goal is to solve problems, then the value of these agreements depends on their ability to influence the world — to shape norms, constrain behavior, facilitate cooperation, and mobilize action. A recent review of empirical studies has suggested that many international agreements fail to achieve their aspirations.<sup>1</sup> The review indicates that the form in which states make commitments to each other — through an international legal agreement or through other means — may not be as important as commonly thought. It is the content of the commitments and how these are supported by mechanisms to encourage implementation that matter the most. When developing proposals for new international agreements, like the one that has recently been proposed to address antibiotic resistance (ABR),<sup>2</sup> attention to implementation mechanisms should therefore be equal to if not greater than the attention paid to its form.

The key to implementation is *accountability*.<sup>3</sup> To avoid purely symbolic agreements and to achieve real-world impact, accountability must be at the core of agreements and their development. This is as true for an agreement on ABR as it is for any other international agreement.

Definitions of “accountability” vary widely. In the present context, accountability best refers to a relationship involving answerability and enforceability.<sup>4</sup> According to one leading definition in this vein, accountability “implies that some actors have the right to hold other actors to a set of standards, to judge whether they have fulfilled their responsibilities in light of these standards, and to impose sanctions if they determine that these responsibilities have not been met.”<sup>5</sup> Another much-cited definition describes accountability as “a relationship between an actor and a forum, in which the actor has an obligation to explain and to justify his or her conduct, the forum can pose questions and pass judgement, and the actor may face consequences.”<sup>6</sup>

An accountability relationship can be characterized along three dimensions and by answering three basic questions. *Among whom* is accountability owed? *For what* are the actors accountable? And *how* are accountability relationships built and secured?

This article examines these questions and explores opportunities to strengthen accountability in the context of international agreements, with specific reference to the proposed international agreement on ABR. We provide a menu of accountability mechanisms addressing transparency, oversight, complaint, and enforcement, describe how these mechanisms can

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promote compliance, and identify key considerations for an ABR agreement.

### **Parties to Accountability Relationships (“Among Whom?”)**

Accountability can be difficult to understand, partly because in most settings there are multiple relevant accountability relationships. These form an interconnected network among different actors. State parties

access to appropriate antibiotics, adopt regulations banning inappropriate use of antibiotics in livestock, or provide funding for research and development relevant to ABR. With regard to process, state parties may be expected to ensure that all districts, hospitals, and pharmacies have adequate reporting systems for the sale and use of antibiotics. For outcomes, states may be expected to achieve a particular level of affordability for antibiotics (e.g., course of treatment not

to exceed one day’s wage of lowest-paid government worker), usage in animals (e.g., less than a certain amount per livestock raised), or investment in antibiotic innovation (e.g., more than a certain percentage of public health expenditures).<sup>8</sup>

Less frequently discussed, but no less important, is accountability for fair process. As part of an international agreement, state parties may be held accountable for ensuring processes for public participation and engagement at the national level, as well as for

facilitating inclusive processes at the international level. State parties could also be expected to systematically measure inequalities — including inequalities in access to antibiotics — and to systematically assess whether these are addressed in a fair and effective way.

**This article explores opportunities to strengthen accountability in the context of international agreements, with specific reference to the proposed international agreement on ABR. We provide a menu of accountability mechanisms addressing transparency, oversight, complaint, and enforcement, describe how these mechanisms can promote compliance, and identify key considerations for an ABR agreement.**

to an international agreement are accountable to each other, but also to their domestic constituencies and often to one or more supra- or transnational entities. Four types of entities are particularly important in this context (see Appendix). One is collective bodies of the state parties to the agreement, such as a governing council, conference, or assembly. Another type is independent oversight bodies whose mandate is specifically linked to the agreement in question. Examples include designated committees, panels, courts, and secretariats. A third type of entity is general fora whose broad mandate covers matters pertaining to the agreement. These entities may include the United Nations (UN) General Assembly, the World Health Assembly, and, for its members, the G7, G20, and G77.<sup>7</sup> Fourth, there are entities such as non-governmental organizations (NGOs) and civil society organizations (CSOs) that represent different constituencies, interests, and perspectives.

### **Object of Accountability Relationships (“For What?”)**

The objects for which actors in accountability relationships are answerable vary across relationships. These can include taking certain actions, instituting certain processes, or achieving certain outcomes. For example, state parties to an international ABR agreement may be expected to enact policies that promote

### **Mechanisms for Building and Securing Accountability Relationships (“How?”)**

Accountability relationships depend on formal or informal mechanisms for their establishment and for being sustained over time. Four types of accountability mechanisms are particularly important in the context of international agreements: (1) transparency mechanisms, (2) oversight mechanisms, (3) complaint mechanisms, and (4) enforcement mechanisms (see Table 1).

#### *1) Transparency Mechanisms*

Transparency mechanisms make information about actors available to observers.<sup>9</sup> In the context of an international agreement, the key actors are state parties, and the key observers are other state parties, plus supra- and transnational entities and the general public. For an international agreement on ABR, relevant information pertains to the epidemiology of infectious diseases, data on resistance, indicators of access to antibiotics, sales and use of antibiotics, financial flows, and government action to improve access, conserva-

Table 1

**Mechanisms for Promoting Accountability**

- |   |
|---|
| <ol style="list-style-type: none"> <li>1. Transparency mechanisms <ol style="list-style-type: none"> <li>a. Information aggregation</li> <li>b. Publicity</li> <li>c. Regular reporting</li> <li>d. Access-to-information requests</li> </ol> </li> <li>2. Oversight mechanisms <ol style="list-style-type: none"> <li>a. Standard-setting</li> <li>b. Data collection</li> <li>c. Implementation review</li> <li>d. Impact assessment</li> </ol> </li> <li>3. Complaint mechanisms <ol style="list-style-type: none"> <li>a. State complaints</li> <li>b. Secretariat complaints</li> <li>c. Non-state-actor complaints</li> <li>d. Appeals of decisions</li> </ol> </li> <li>4. Enforcement mechanisms <ol style="list-style-type: none"> <li>a. Public disapproval</li> <li>b. Loss of privileges</li> <li>c. Economic punishment</li> <li>d. Military intervention</li> </ol> </li> </ol> |
|---|

tion, and innovation. To be effective, transparency mechanisms must make it possible for observers to easily understand and verify the information provided.

Many existing international agreements incorporate transparency mechanisms, including mechanisms that promote and make possible (a) information aggregation, (b) publicity, (c) regular reporting, and/or (d) access-to-information requests (see Appendix). One example is the Minamata Convention on Mercury. It requires each state party to report on the measures it has taken to implement the Convention and on the effectiveness of those measures.

The benefits from more transparency are potentially transformative. Transparency is considered a prerequisite for accountability and is expected to improve legitimacy, compliance, and learning — thereby enhancing the real-world impact of agreements. Although these expectations have not yet been matched by empirical evidence, as impact evaluations of transparency mechanisms in international agreements appear to be non-existent.<sup>10</sup>

## 2) Oversight Mechanisms

Oversight mechanisms involve active monitoring and evaluation of actors, actions, inputs, processes, outputs, or outcomes.<sup>11</sup> These mechanisms build on transparency, but go further by involving active col-

lection and processing of information and comparison of findings against some normative or technical standard. In the context of ABR, potential oversight bodies include designated committees, panels, courts, and secretariats, and the other supra- or transnational entities described above can also have an oversight role. Oversight mechanisms can monitor and assess the extent to which state parties comply with the agreement, as well as the situation with regard to access, conservation, and innovation of antibiotics at global and national levels. Even basic monitoring of antibiotics sales and use would be a major step forward, as indicated by how even the United States does not yet systematically collect such data.<sup>12</sup> Oversight mechanisms can also track state parties' compliance with decisions made through complaint mechanisms.

Many different oversight mechanisms are embedded in existing agreements, and these mechanisms involve to various degrees (a) standard-setting, (b) data collection, (c) implementation review, and/or (d) impact assessment (see Appendix). For example, the Kyoto Protocol to the UN Framework Convention on Climate Change requires that its 43 "Annex 1" state parties, those with industrialized or transitioning economies, report a national inventory of greenhouse gas emissions and sinks, and convey information on their implementation of the Protocol. Each report is assessed by an international expert review team, which forwards its own assessment of these reports to the Compliance Committee for consideration.

The potential benefits from oversight mechanisms are similar to those from transparency mechanisms. These benefits include improvements in legitimacy, compliance, and learning. However, as for transparency mechanisms, little empirical evidence is available to directly evaluate this widely held belief in their benefits.<sup>13</sup>

## 3) Complaint Mechanisms

Complaint mechanisms process and adjudicate grievances about actions, inputs, processes, outputs, or outcomes attributable to an actor.<sup>14</sup> In the context of international agreements, the impugned actors are typically state parties. Complainants are usually other state parties, sometimes oversight bodies created by the agreements, and less often individuals, NGOs/CSOs, or corporations. For an ABR agreement, non-fulfillment of the agreement's obligations is likely to be the most common complaint. These mechanisms can be institutionalized as separate bodies or be incorporated as part of existing entities, such as an existing international court, tribunal, or organization.



Complaint mechanisms are usefully categorized according to whether they are available to (a) states, (b) secretariats, (c) non-state actors without international legal personality (e.g., individuals, NGOs/CSOs, corporations), and/or for (d) appeals of decisions (see Appendix). The International Health Regulations (IHR) provides an example of a complaint mechanism that is open to states; an example that also illustrates how these mechanisms can be designed as multi-step processes. In the IHR's ideal process, state parties "shall seek in the first instance to settle the dispute through negotiation or any other peaceful means of their own choice, including good offices, mediation or conciliation." If not resolved, the state parties may agree to refer the dispute to the World Health Organization's Director-General for mediation. If the issue is still unresolved, binding arbitration is theoretically possible if the dispute is among states that have voluntarily accepted arbitration "as compulsory with regard to all disputes concerning the interpretation or application of these Regulations" (although no state has voluntarily accepted binding arbitration to date). Ultimately, states can refer the matter to the International Court of Justice.

Other agreements allow non-state actors to access complaint mechanisms (see Appendix). One example is the Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters ("Aarhus Convention"). This Convention grants individuals "access to a review procedure before a court of law or another independent and impartial body established by law" when they believe their requests for information have not been adequately addressed by state parties. On the basis of this provision, a Compliance Committee has been established, and one of the ways a review can be triggered is by communications from individuals or NGOs/CSOs.

Complaint mechanisms can improve the effectiveness of agreements when they encourage or compel state parties to confront, explain, and resolve their non-compliance. There is some empirical evidence to support this widely held view.<sup>15</sup>

#### 4) *Enforcement Mechanisms*

Enforcement mechanisms impose sanctions on non-compliant actors.<sup>16</sup> These sanctions can be formal or informal, real or reputational. They include (a) public disapproval, (b) loss of privileges, (c) economic punishment, and/or (d) military intervention (although this last sub-category is not appropriate for addressing ABR). The non-provision of benefits that otherwise would have been provided can be a form of sanction. Sanctions thus relate to both applying "sticks" and withdrawing "carrots."

Transparency, oversight, and complaint mechanisms can facilitate some enforcement on their own. They can identify and publicize non-compliant behavior and thus facilitate "naming and shaming" of non-compliant actors. They are also important for more specific enforcement mechanisms, as they can help determine whether sanctions are appropriate. In the context of international legal agreements, this decision will most often be made by a conference of parties, a separate supranational assembly (like the UN Security Council), or a dispute resolution body. Conversely, enforcement mechanisms can help strengthen transparency, oversight, and complaint mechanisms. Even where agreements include clear provisions for such mechanisms, realization of their full potential usually requires ancillary enforcement mechanisms. The weakness of the theoretically robust IHR complaint mechanism, for example, is that every step is voluntary without pre-acceptance of binding arbitration, and no party has accepted binding arbitration to date.<sup>17</sup>

A dearth of formal enforcement mechanisms is often seen as a hallmark of international agreements, including international law.<sup>18</sup> However, negotiators of an international agreement addressing ABR can learn from notable exceptions (see Appendix). One example is the Marrakesh Agreement establishing the World Trade Organization (WTO). Under this agreement, a state party can request authorization of countermeasures from WTO's Dispute Settlement Body if WTO rules are breached and if other steps have been unsuccessful. If granted, the winning state party is authorized to impose trade sanctions vis-à-vis the losing state party. The UN Charter provides several other examples, including how failure to pay UN membership fees results in loss of voting privileges in UN assemblies.

Enforcement mechanisms promote effective implementation by incentivizing compliance, disincentivizing non-compliance, and strengthening other accountability mechanisms. Many studies have found sanctions to be effective in promoting implementation.<sup>19</sup>

#### **Discussion**

This article has reviewed the central aspects of accountability relationships and outlined ways to build and secure these relationships in the context of international agreements. Specifically, the article provided a menu of accountability mechanisms from which negotiators of international agreements can mix-and-match to facilitate transparency, oversight, complaint, and enforcement. It is clear that there are many options available for strengthening accountability and ensuring that international agreements

have a fighting chance of achieving their progenitors' aspirations.

No international agreement should incorporate every accountability mechanism described in this article, but most — if not all — agreements should incorporate at least one mechanism from each category. States that are serious about addressing global challenges through international legal agreements should particularly insist on including effective transparency, oversight, complaint, and enforcement mechanisms. This is plausibly the best way of ensuring that negotiated legal texts have the effects they are intended to procure.

Accountability is often championed as an unequivocal good, but more is not always better. A shift in accountability can alter power dynamics in undesir-

forces, and armies — and the public consternation that even international legal agreements “aren’t really binding” or “don’t matter.”<sup>23</sup> However, this does not mean that much more cannot be done internationally. Experience from certain regimes like the international trade sector shows there is potential for stronger international agreements and more effective institutions.

Governmental capacity is another challenge for accountability and for compliance with international agreements — even in the presence of strong institutional mechanisms. While dissemination of data and documents that governments have readily available may sound quite simple, in reality, most of the mechanisms described require significant bureaucratic capacity. For example, some oversight mechanisms require sophisticated data collection systems and technical expertise for conducting data analyses.

This capacity varies tremendously across countries. In response, international agreements can differentiate accountability requirements according to capacity or require that high-capacity countries assist countries with lower capacity. Again, weak institutions and limited governmental capacity do not mean that much more cannot be done.

Formal accountability mechanisms are neither necessary nor sufficient for building and securing accountability relationships. Actors can also hold each other accountable through informal mechanisms. For example, the United States unilaterally reviews countries' compliance with the WTO's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and sometimes imposes sanctions on countries it judges to be non-compliant.<sup>24</sup> Formal accountability mechanisms also do not automatically translate into real-world changes, although institutionalizing them may be the best way to strengthen accountability in the short term and to promote a culture of accountability in the longer term.

The issues raised here are all important areas for future inquiry, especially given how empirical evidence is scant across the board. This research agenda should be pursued alongside efforts to intelligently craft new international agreements so that theory and practice can learn from each other.

## Conclusion

International agreements without accountability do not work. To promote accountability, mechanisms for transparency, oversight, complaint, and enforcement should all be considered when agreements are sought. As available evidence cannot single out an optimal set of mechanisms for each context, this article has pro-

**International agreements without accountability do not work. To promote accountability, mechanisms for transparency, oversight, complaint, and enforcement should all be considered when agreements are sought.**

able ways, especially in undemocratic settings.<sup>20</sup> In all settings, strengthening one accountability relationship can weaken another. The balance between different accountability relationships is also important. It has been argued, for example, that the Global Fund to Fight AIDS, Tuberculosis & Malaria fails to hold donors accountable for delivering their promised financial contributions in the way it holds recipients accountable for achieving results.<sup>21</sup>

The Appendix shows considerable variation in the specific mechanisms utilized by existing international legal agreements, which are themselves only one type of international agreement. The optimal mechanism in each category and the optimal combination of mechanisms for an agreement are likely to vary across settings. For future agreements, it is important to evaluate each set as a whole, since individual mechanisms interact in multiple ways and can be mutually synergistic or antagonistic. These sets should also be carefully assessed against widely shared values, including those pertaining to effectiveness, fairness, and legitimacy.<sup>22</sup>

Today, most international agreements lack effective mechanisms for transparency, oversight, complaint, and enforcement. Enforcement mechanisms are in particular short supply. This reflects the general incapacity for enforcement at the global level — compared with the national level that has powerful courts, police

Agreement	Transparency Mechanisms	Oversight Mechanisms	Complaint Mechanisms	Enforcement Mechanisms
Health 1) International Health Regulations	State Parties and the Director-General of the World Health Organization (WHO) are to report to the World Health Assembly (WHA) on the implementations of the Regulations.	WHO is to periodically conduct studies to review and evaluate the Regulations, particularly provisions regarding health surveillance, and submit its findings to the WHA. The WHA is to periodically review implementation of the Regulations and can request the advice of a Review Committee; an expert committee appointed by the Director-General. The Review Committee is to meet periodically to make recommendations to the Director-General about the functioning of the Regulations. The Director-General is then to communicate the recommendations to the WHA.	Disputes between Parties about the interpretation or application of the Regulations are to be settled first through negotiation or any other peaceful means of their choice, including good offices, mediation, or conciliation. Unresolved disputes can be mediated by the Director-General, or adjudicated through binding arbitration if among states that have voluntarily accepted arbitration as compulsory with regard to all disputes concerning the interpretation or application of the Regulations. Parties may refer intractable disputes to the International Court of Justice.	None.
2) WHO Framework Convention on Tobacco Control	Each Party is required to submit to the Conference of the Parties periodic reports on its implementation of the Convention, which are to include information on: legislative, executive, administrative, or other measures taken to implement the Convention; any constraints or barriers encountered, and measures taken to overcome these barriers; financial and technical assistance provided or received for tobacco control; tobacco research and surveillance; tobacco taxation rates; tobacco consumption trends; data on tobacco trade, storage, and distribution.	The Conference of the Parties is to consider reports submitted by the Parties and adopt regular reports on the overall implementation of the Convention.	Disputes between Parties regarding the interpretation or application of the Convention are first to be settled through negotiation or any other peaceful means of their choice, including good offices, mediation, or conciliation. Unresolved disputes can be resolved through ad hoc arbitration in accordance to procedures adopted by the Conference of the Parties.	None.

Agreement	Transparency Mechanisms	Oversight Mechanisms	Complaint Mechanisms	Enforcement Mechanisms
<p><b>Human Rights</b></p> <p>3) International Covenant on Economic, Social and Cultural Rights</p>	<p>State Parties are to report to the United Nations (UN) Secretary-General on the measures adopted and progress made in achieving the observance of the rights described in the Covenant. The Secretary-General is then to transmit the reports to the UN Economic and Social Council and other specialized agencies.</p>	<p>The UN Economic and Social Council is to review reports from State Parties and can submit reports to the UN General Assembly with a summary of the information received and general recommendations.</p> <p>UN specialized agencies may report to the Economic and Social Council about progress made in achieving the observance of the provisions falling within the scope of their activities and may provide recommendations.</p> <p>The UN Economic and Social Council may transmit the reports from the State Parties and specialized agencies to the Human Rights Council.</p> <p>Under the Optional Protocol, if the Committee receives reliable information indicating grave or systematic violations by a State Party of any of the rights set forth in the Covenant, the Committee shall invite that State Party to cooperate in the examination of the information. The Committee may designate one or more of its Members to conduct an inquiry and to report urgently to the Committee. After examining the findings of such an inquiry, the Committee shall transmit these findings to the State Party concerned together with any comments and recommendations. The State Party concerned shall, within six months, submit its observations to the Committee.</p>	<p>Under the Optional Protocol, communications may be submitted by or on behalf of individuals or groups of individuals claiming to be victims of a violation of any of the rights set forth in the Covenant. The Committee is to bring the communication to the attention of the State Party concerned. Within six months, the receiving State Party is to explain or clarify the matter and the remedy, if any. The Committee is to make available its good offices to the Parties concerned with a view to reaching a friendly settlement of the matter. If unsuccessful, the Committee shall continue to examine the communications received and shall transmit its views on the communications, together with its recommendations, if any, to the Parties concerned. The State Party shall give due consideration to the views and recommendations of the Committee and shall submit to the Committee, within six months, a written response, including information on any action taken in the light of the views and recommendations of the Committee.</p> <p>Under the Optional Protocol, a State Party that considers that another State Party is not fulfilling its obligations can initiate a process resembling the process described above.</p>	<p>None.</p>



Agreement	Transparency Mechanisms	Oversight Mechanisms	Complaint Mechanisms	Enforcement Mechanisms
4) Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment	State Parties are to report to the Committee against Torture on measures taken to implement the Convention at least every four years. The Committee consists of ten experts. The UN Secretary-General shall transmit the report to all State Parties.	Reports from State Parties are to be reviewed by the Committee against Torture, which can make comments and suggestions to the State Parties. The Committee is to submit an annual report on its activities to the State Parties and the UN General Assembly. If the Committee has evidence suggesting that torture is being systematically practiced in the territory of a State Party, the Committee can designate its Members to make an inquiry into the issue. The Committee is then to report its findings and suggestions to the State Party concerned. The process is to be confidential, but after consultations with the State Party, a summary account can be included in the Committee's annual report.	If a State Party notifies another State Party that the former considers that the latter is not giving effect to the provisions of the Convention, the receiving State is to reply with an explanation or clarification. If the matter is not settled within six months, either State can refer the matter to the Committee against Torture. The Committee is to make available its good offices to the State Parties concerned with a view to a friendly solution of the matter. The Committee is to submit a report to the State Parties summarizing the facts and any solution reached within 12 months. Communications from or behalf of individuals can be submitted to the Committee against Torture about alleged violation of any provision of the Convention. The Committee is to bring this communication to the attention of the State Party concerned, and the receiving State is to submit an explanation or clarification to the Committee within six months. The Committee is to examine the matter and forward its views to the individual and State Party concerned. Disputes between State Parties about the interpretation or application of the Convention are first to be sought settled through negotiation and then arbitration. If no agreement is reached on the organization of the arbitration, any one of the Parties may refer the dispute to the International Court of Justice.	None.

Agreement	Transparency Mechanisms	Oversight Mechanisms	Complaint Mechanisms	Enforcement Mechanisms
5) Convention on the Rights of Persons with Disabilities	<p>Each State Party is to collect statistics and research data to help implement policies related to the Convention, and to disseminate this to the public and ensure accessibility to persons with disabilities and others.</p> <p>Each State Party is to submit to the Committee on the Rights of Persons with Disabilities a comprehensive report on measures taken and progress made at least every four years or whenever the Committee requests.</p> <p>Each report is to be made widely available to the public and all State Parties.</p>	<p>The Committee is to consider reports from each State Party, make suggestions and recommendations, and can request further information.</p> <p>The Committee can itself examine a State Party's implementation of the Convention if submission of a report is significantly overdue.</p> <p>The Committee is to report every two years to the UN General Assembly and the UN Economic and Social Council and make suggestions and recommendations based on the State Parties' reports.</p>	None.	None.
<b>Environment</b>	<p>Each Party is to periodically communicate to the Conference of the Parties a national inventory of anthropogenic emissions and removals. The 43 "Annex I" State Parties, those with industrialized or transitioning economies, are to submit annual inventories. Each Party is also to communicate the measures taken to implement the Convention. Parties to the Kyoto Protocol are to include information related to its implementation. The Secretariat is to make communications publicly available.</p>	<p>National communications and greenhouse gas inventories from Annex I Parties are to be reviewed by international teams of independent experts. The results of their work are to be made publicly available. For Parties to the Kyoto Protocol, each Parties' report is to be reviewed by an expert review team. All review reports are to be forwarded to the Compliance Committee for consideration. Expert review teams are also to prepare a report for the Conference of Parties.</p> <p>The Conference of Parties is to regularly review implementation by the Parties and the overall effects of the measures taken. The Conference of the Parties serving as the meeting of the Parties to the Kyoto Protocol has a similar role with regard to that Protocol.</p>	<p>The Compliance Committee of the Kyoto Protocol is to consider questions of implementation, which can be raised by expert review teams or a Party to the Protocol. The Facilitative Branch is to provide advice and facilitation to Parties in implementing requirements. Disputes concerning interpretation or application of the Convention is first to be settled through negotiation or other peaceful means. Unsettled disputes can be referred to the International Court of Justice or arbitration if the Parties have declared one or both of these means as compulsory. If unsuccessful, the dispute is to be submitted to a conciliation commission. The Kyoto Protocol contains similar provisions.</p>	<p>The Enforcement Branch of the Kyoto Protocol's Compliance Committee is responsible for overseeing a Party's implementation of its reporting requirements where its accounting of emissions is concerned. The Branch has the authority to suspend and reinstate a Party's eligibility to participate in the Kyoto mechanisms.</p> <p>The Enforcement Branch is also to determine whether a Party is non-compliant with its emissions commitment. If a Party's emissions exceed its holdings of Kyoto Protocol units at the end of the commitment period, it must make up the difference, plus a penalty of 30% in the next commitment period. The Party must also develop a compliance action plan, and its eligibility to "sell" credits under emissions trading will be suspended.</p>

Agreement	Transparency Mechanisms	Oversight Mechanisms	Complaint Mechanisms	Enforcement Mechanisms
7) Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters ("Aarhus Convention")	Each Party is to report regularly to the Meeting of the Parties on their achievements.	<p>The Compliance Committee is to prepare, at the request of the Meeting of Parties, a report on compliance with or implementation of the Convention.</p> <p>The Compliance Committee is to monitor, assess, and facilitate the implementation of and compliance with the Parties' reporting requirements.</p> <p>The Meeting of the Parties is to keep under continuous review the implementation of the Convention.</p> <p>The Meeting of the Parties is to review the policies for and legal and methodological approaches to access to information, public participation in decision-making, and access to justice, with a view of further improving them.</p>	<p>The Compliance Committee can review a Party's compliance, and this process can be triggered by a Party to the Convention, the Secretariat, members of the public or non-governmental organizations (NGOs), or the Committee's own initiative. The Committee can make recommendations to the Meeting of the Parties or directly to individual Parties.</p> <p>Disputes between Parties on the interpretation or application of the Convention are first to be solved through negotiation or by any other means acceptable to the Parties. Unresolved disputes are to be submitted to either the International Court of Justice or an arbitration tribunal.</p>	<p>The Meeting of the Parties can, upon consideration of a report and any recommendations of the Compliance Committee, decide upon appropriate measures to bring about full compliance with the Convention. These measures may include to provide advice and facilitate assistance, issue declarations of non-compliance, issue cautions, or suspend special rights and privileges accorded to the Party under the Convention.</p>
8) Minamata Convention on Mercury	<p>Each Party is to facilitate the exchange of information, including epidemiological information concerning health impacts associated with exposure to mercury and mercury compounds.</p> <p>Each Party is to provide public information on epidemiology, results of monitoring activities, and activities to meet the obligations under the Convention.</p> <p>Each Party is to report to the Conference of the Parties on the measures it has taken to implement the Convention, the effectiveness of those measures, and possible challenges.</p>	<p>The Implementation and Compliance Committee is to review compliance with the Convention.</p> <p>The Conference of the Parties is to keep under continuous review and evaluation the implementation of the Convention and to consider any recommendations from the Committee.</p> <p>The Conference of the Parties is to evaluate the effectiveness of the Convention periodically, based on reports from the Parties and other available information.</p>	<p>Disputes concerning interpretation or application of the Convention is first to be sought settled through negotiation or other peaceful means. If unsuccessful, the dispute can be sought settled through arbitration or the International Court of Justice if the Parties have declared one or both of these means as compulsory. If unsuccessful or if the Parties have not accepted the same means of dispute settlement, the dispute is to be submitted to a conciliation commission.</p>	None.

Agreement	Transparency Mechanisms	Oversight Mechanisms	Complaint Mechanisms	Enforcement Mechanisms
Trade 9) Marrakesh Agreement establishing the World Trade Organization	<p>Each Member is to notify other Members, through the appropriate body, of changes in relevant laws, regulations, policy statements, and public notices. A consolidated notification is to be provided to the Secretariat annually.</p> <p>Each Member is to periodically report to the Trade Policy Review Body (TPRB) on their trade policies and practices. The Secretariat is also to provide a report to the TPRB on the trade policies and practices of Members under review. The Secretariat is to periodically report to the TPRB on the implementation of the Agreement.</p> <p>The reports by the Member under review and by the Secretariat, together with the TPRB meeting minutes, are to be published and forwarded to the Ministerial Conference.</p>	<p>Based on reports from Members and the Secretariat, the TPRB is to periodically review the trade policies and practices of Members.</p> <p>Following adoption of a panel or Appellate Body report, the Party is to notify its intentions on implementation of the recommendations. The Dispute Settlement Body (DSB) is to keep the intended implementation under regular surveillance by keeping it in its meeting agenda until the issue is resolved. The Member concerned is to provide DSB with a status report on its implementation of the recommendations or rulings at least 10 days before each DSB meeting.</p>	<p>In the event of a dispute, the complaining Member can request another Member to enter into consultations. The Member to which the request is made shall do so within 30 days.</p> <p>If the consultations fail to settle the dispute within 60 days, the complaining Party may request the DSB to establish a panel. The panel is to be composed of three or five well-qualified individuals. Panel reports are to be completed within three or six months, depending on urgency of the matter. Panel reports are to be adopted within 60 days of issuance, unless the DSB decides against it or a Party decides to appeal.</p> <p>During all stages, the Parties can request other means of dispute settlement, such as good offices, conciliation, mediation, and arbitration.</p> <p>If one or both Parties appeal to the panel's decision, the Appellate Body is to conduct a review within 60 or 90 days. The resulting report is to be unconditionally accepted by the Parties to the dispute within 30 days, unless the DSB decides otherwise.</p> <p>If the DSB authorizes the complaining Party to suspend application of concessions or other obligations, disagreements on the level of suspension or principles of retaliation can be referred to arbitration.</p>	<p>If the Member concerned fails to bring the measure found to be inconsistent with a covered agreement into compliance therewith or otherwise comply with the recommendations and rulings within the reasonable period of time, the Member shall, if so requested, enter into negotiations with any Party having invoked the dispute settlement procedures, with a view to developing mutually acceptable compensation.</p> <p>If no satisfactory compensation is agreed upon within 20 days, any Party having invoked the dispute settlement procedures may request from the DSB authorization to suspend application of concessions or other obligations (i.e., to impose trade sanctions).</p>



vided a menu of options and highlighted key considerations for choosing among them. This can be useful for bringing about the revolutionary changes that new international agreements aspire to achieve.

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# References

1. S. J. Hoffman and J.-A. Røttingen, "Assessing the Expected Impact of Global Health Treaties: Evidence from 90 Quantitative Evaluations," *American Journal of Public Health* 105, no. 1 (2015): 26-40.
2. S. J. Hoffman, K. Outtersen, J.-A. Røttingen, O. Cars, C. Clift, Z. Rizvi, F. Rotberg, G. Tomson, and A. Zorzet, "An International Legal Framework to Address Antimicrobial Resistance," *Bulletin of the World Health Organization* 93, no. 2 (2015): 66; S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "International Law Has a Role to Play in Addressing Antibiotic Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).
3. See Hoffman and Røttingen, *supra* note 1; S. J. Hoffman and J.-A. Røttingen, "Assessing Implementation Mechanisms for an International Agreement on Research and Development for Health Products," *Bulletin of the World Health Organization* 90, no. 11 (2012): 854-863; S. J. Hoffman, "Making the International Health Regulations Matter: Promoting Compliance through Effective Dispute Resolution," in S. Rushton and J. Youde, eds., *Routledge Handbook on Global Health Security* (Oxford: Routledge, 2014): at 239-252.
4. A. Schedler, "Conceptualizing Accountability," in A. Schedler, L. Diamond, and M. F. Plattner, eds., *The Self-Restraining State: Power and Accountability in New Democracies* (Boulder, CO: Lynne Rienner, 1999): at 13-28.
5. R. W. Grant and R. O. Koehane, "Accountability and Abuses of Power in World Politics," *American Political Science Review* 99, no. 1 (2005): 29-43.
6. M. Bovens, "Analysing and Assessing Accountability: A Conceptual Framework," *European Law Journal* 4, no. 13 (2007): 447-468.
7. Z. Rizvi and S. J. Hoffman, "Effective Global Action on Antibiotic Resistance Requires Careful Consideration of Convening Forums," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).
8. A. Behdinan, S. J. Hoffman, and M. Pearcey, "Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
9. R. B. Mitchell, "Sources of Transparency: Information Systems in International Regimes," *International Studies Quarterly* 42, no. 1 (1998): 109-130.
10. See Hoffman and Røttingen, *supra* note 1.
11. See Hoffman and Røttingen, *supra* note 3; D. G. Victor, O. Greene, J. Lanchbery, J.C. di Primio, and A. Korula, "Review Mechanisms in the Effective Implementation of International Environmental Agreements," IIASA Working Paper WP-94-114 (Laxenburg, Austria: International Institute for Applied Systems Analysis, 1994).
12. Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2013* (2013).
13. See Hoffman and Røttingen, *supra* note 1.
14. See Hoffman, *supra* note 3; C. J. Menkel-Meadow, "Dispute Resolution," in P. Cane and H. Kritzer, eds., *The Oxford Handbook of Empirical Legal Research* (Oxford: Oxford University Press, 2010): at 596-624.
15. See Hoffman, *supra* note 3.
16. T. Yang, "International Treaty Enforcement as a Public Good: Institutional Deterrent Sanctions in International Environmental Agreements," *Michigan Journal of International Law* 27 (2006): 1131-1184.
17. See Hoffman, *supra* note 3.
18. S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "Assessing Proposals for New Global Health Treaties: An Analytic Framework," *American Journal of Public Health* (2015): e1-e8, doi:10.2105/AJPH.2015.302726.
19. See Hoffman and Røttingen, *supra* note 1.
20. S. J. Hoffman, "Mitigating Inequalities of Influence among States in Global Decision Making," *Global Policy* 3, no. 4 (2012): 421-432.
21. A. Barnes and G. W. Brown, "The Global Fund to Fight AIDS, Tuberculosis and Malaria: Expertise, Accountability and the Depoliticisation of Global Health Governance," in O. D. Williams and S. Rushton, eds., *Partnerships and Foundations in Global Health Governance* (Basingstoke: Palgrave Macmillan, 2011): at 53-75.
22. D. C. Esty, "Rethinking Global Environmental Governance to Deal with Climate Change: The Multiple Logics of Global Collective Action," *American Economic Review: Papers & Proceedings* 98, no. 2 (2008): 116-121.
23. See Hoffman, *supra* note 3.
24. S. Flynn, "Special 301 and Global Administrative Law," in R. C. Dreyfuss and C. R. Garavito, eds., *Balancing Wealth and Health* (Oxford: Oxford University Press, 2014): at 225-246.

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# International Law Has a Role to Play in Addressing Antibiotic Resistance

*Steven J. Hoffman, John-Arne Røttingen, and Julio Frenk*

## Introduction

Adopting international legal agreements for every global health challenge is not a good idea. Such an enterprise would require unprecedented political mobilization and resources that are impossible to sustain, and it would lead to further fragmentation in global health governance. International legalization also has its costs and trade-offs, including potentially devastating dark sides that we have tallied elsewhere.<sup>1</sup>

Yet we believe that calls for an international legal agreement on antibiotic resistance (ABR) are important and that such an agreement is in fact much needed for the future of global health.<sup>2</sup> We came to this conclusion based on a reasoned assessment of the facts before us — the potential benefits, costs, and trade-offs of an ABR legal agreement — and consideration of four criteria we previously proposed for prospectively evaluating proposals for new global health treaties.<sup>3</sup> We came to this conclusion despite previously expressing concerns about adopting new international legal agreements on global health issues.

Why are we so supportive of an international legal agreement on ABR?

## Weighing Benefits, Costs, and Trade-Offs

For potential benefits, we are not under the illusion that international legal agreements always yield positive outcomes. We know the empirical research literature is actually quite mixed: our recent review of 90 quantitative impact evaluations of international legal agreements across domains found that some agreements produced desired effects and others did not.<sup>4</sup> Some impact evaluations even found that international legal agreements were counterproductive to their aims and possibly caused harm.<sup>5</sup> The only two studies evaluating international legal agreements' health effects found structural adjustment agreements worsened basic literacy, infant mortality, and life expectancy at age one,<sup>6</sup> and that international human rights agreements did not improve life expectancy, infant mortality, child mortality, or maternal mortality.<sup>7</sup> Yet we also know that the global collective action problems preventing action on ABR require strong interdependent commitments from states to be overcome, and that international legal agreements formally represent the strongest possible way through which states can make commitments to each other.<sup>8</sup>

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For potential costs, we know first-hand that crafting international legal agreements involves many millions of dollars for numerous meetings, lawyer salaries, negotiator per diems, long-haul flights, and hotel accommodation, and then many more millions are needed for maintenance costs of new governance structures like conferences of parties, annual reporting by states, and diplomatic staff from all participating countries. There are also opportunity costs associated with devoting limited resources, political capital, and rhetorical space to one strategy, effectively shelving other important initiatives with similar objectives and possibly higher impact.<sup>9</sup> Yet we also know that these costs are dwarfed by the costs of inaction that are already being incurred. This includes the estimated 700,000 deaths currently caused each year by

may encourage bolder legal provisions than are often agreed, and that ABR requires cross-sectoral collaboration that will not come even with the most coherent governance of traditional global health actors.<sup>12</sup>

### ABR Satisfies Four Criteria for New International Legal Agreements

Given the uncertain benefits, costs, and trade-offs of an international legal agreement on ABR, we would argue that one should not be adopted unless at least four criteria are met.<sup>13</sup> First, the nature of the problem should have a *significant transnational dimension*, meaning it involves multiple states, transcends national borders, and transfers risks of harm or benefit across countries. Second, the nature of the solution should *justify the use of an instrument with coercive*

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resistance to all kinds of antimicrobials (including antibiotics and also antifungals, antiparasitics, and antivirals), the 10 million deaths per year expected from antimicrobial resistance in 2050, and the \$100 trillion USD cumulative global costs anticipated from it over the next 35 years.<sup>10</sup>

For potential trade-offs, we know the international legalization of ABR policies may prioritize process over outcomes, consensus over plurality, homogeneity over diversity, generality over specificity, stability over flexibility, precedent over evidence, states over non-state actors, ministries of foreign affairs over ministries of health, and lawyers over health professionals. International legal agreements are often ambiguous and lack specific commitments as states settle for the lowest common denominator. They are also often slow to be implemented, challenging to enforce, and difficult to modify. An international legal agreement on ABR could crowd out alternative approaches, limit future action in the area, and further exacerbate challenges in global health governance by promoting a piecemeal, issue-specific approach.<sup>11</sup> Yet we also know that ABR will not be solved by doctors and health professionals by themselves, that the common threat posed by ABR

*features*, such as if the international legal agreement's provisions (a) address multilateral challenges that cannot practically be addressed by any one state alone; (b) resolve collective action problems where benefits are only accrued if multiple states cooperate or coordinate their responses; or (c) advance superordinate norms that embody humanity and reflect near-universal values. Third, the international legal agreement should have a *reasonable chance of achieving benefits*, which means it incentivizes those with power to act, institutionalizes accountability mechanisms designed to bring rules into reality, and/or activates interest groups to advocate for its full implementation. Fourth, an international legal agreement should represent the *best commitment mechanism* for global collective action on the challenge and be projected to achieve greater benefit for its costs than competing alternative mechanisms like political declarations, codes of practices, funding contracts, and institutional reforms.<sup>14</sup>

The proposal for an international legal agreement on ABR satisfies these four criteria. ABR is one of the greatest global risks spreading unabated across state boundaries,<sup>15</sup> a multilateral challenge involving the exploitation of an essential common-pool resource,<sup>16</sup>

and a global public good challenge for ensuring universal access to existing antibiotics (which benefits people beyond the individual consumer) and progress in innovation towards new antibiotics (which also benefits all).<sup>17</sup> It has a reasonable chance of achieving benefits by incentivizing those with power to act, and alternative commitment mechanisms have thus far proven ineffective – including WHO’s ABR strategy from 2001 and follow-on World Health Assembly resolutions.<sup>18</sup> The linchpin is that ABR depends on near-*universal* collective action for it to be tackled, as well as coordinated interdependent action across sectors on access, conservation and innovation for antibiotics.<sup>19</sup>

## Conclusion

An international legal agreement that promotes access, conservation, and innovation for antibiotics represents an excellent candidate for the use of international law. Nonetheless, ultimately, the actual utility of such an agreement will depend largely on whether these global common good and public good challenges persist, and states’ willingness to address them by adopting an agreement with sufficiently ambitious content and robust accountability mechanisms for the whole undertaking to be worthwhile.<sup>20</sup>

## References

1. S. J. Hoffman and J. A. Röttingen, “A Framework Convention on Obesity Control?” *The Lancet* 378, no. 9809 (2011): 2068; S. J. Hoffman and J. A. Röttingen, “Alcohol Control: Be Sparring with International Laws,” *Nature* 483, no. 7389 (2012): 275; S. J. Hoffman, J. A. Röttingen, and J. Frenk, “Assessing Proposals for New Global Health Treaties: An Analytic Framework,” *American Journal of Public Health* (2015): e1-e8, doi:10.2105/AJPH.2015.302726;; S. J. Hoffman and J. A. Röttingen, “Assessing Implementation Mechanisms for an International Agreement on Research and Development for Health Products,” *Bulletin of the World Health Organization* 90, no. 11 (2012): 854-863; S. J. Hoffman and J. A. Röttingen, “Dark Sides of the Proposed Framework Convention on Global Health’s Many Virtues: A Systematic Review and Critical Analysis,” *Health and Human Rights* 15, no. 1 (2013): E117-E1134; S. J. Hoffman and J. A. Röttingen, “Assessing the Expected Impact of Global Health Treaties: Evidence from 90 Quantitative Evaluations,” *American Journal of Public Health* 105, no. 1 (2015): 26-40.
2. S. J. Hoffman, K. Outterson, J. A. Röttingen, O. Cars, C. Clift, Z. Rizvi, F. Rotberg, G. Tomson, and A. Zorzet, “An International Legal Framework to Address Antimicrobial Resistance,” *Bulletin of the World Health Organization* 93, no. 2 (2015): 66; J. A. Röttingen, “Regulating Antimicrobials,” in J. Frenk and S. J. Hoffman, eds., “*To Save Humanity: What Matters Most for a Healthy Future*” (New York: Oxford University Press, 2015): at 297-299.
3. See Hoffman, Röttingen, and Frenk, *supra* note 1.
4. See Hoffman and Röttingen (2015), *supra* note 1.
5. *Id.*
6. M. R. Abouharb and D. Cingranelli, *Human Rights and Structural Adjustment* (New York: Cambridge University Press, 2007).
7. A. Palmer, J. Tomkinson, C. Phung, N. Ford, M. Joffres, K.A. Fernandes, L. Zeng, V. Lima, J. S. Montaner, G. H. Guyatt, and E. J. Mills, “Does Ratification of Human-Rights Treaties Have Effects on Population Health?” *The Lancet* 373, no. 9689 (2009): 1987-1992.
8. See Hoffman and Röttingen (2012, “Assessing Implementation”), *supra* note 1.
9. See Hoffman and Röttingen (2011), *supra* note 1.
10. Review on Antimicrobial Resistance, “Tackling Drug-Resistant Infections Globally,” available at <<http://amr-review.org/home>> (last visited April 18, 2015).
11. See Hoffman and Röttingen (2012, “Alcohol Control”), *supra* note 1.
12. A. Behdinan, S. J. Hoffman, and M. Pearcey, “Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments,” *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
13. See Hoffman, Röttingen, and Frenk, *supra* note 1.
14. *Id.*
15. See Review on Antimicrobial Resistance, *supra* note 10.
16. E. Ostrom, *Governing the Commons: The Evolution of Institutions for Collective Action* (New York: Cambridge University Press, 1990); A. Hollis and P. Maybarduk, “Antibiotic Resistance Is a Tragedy of the Commons That Necessitates Global Cooperation,” *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
17. N. Daulaire, A. Bang, G. Tomson, J. N. Kalyango, and O. Cars, “Universal Access to Effective Antimicrobials: An Essential Feature of Global Collective Action against Antimicrobial Resistance,” *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only; M. Balasegaram, C. Clift, and J.-A. Röttingen, “A Pathway towards an Alternative Business Model for Antibiotic Innovation: A Framework, Fund and Institutional Mechanism,” *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).
18. WHA 67.25, *Resolutions of the Sixty-Seventh World Health Assembly: Antimicrobial Resistance*, World Health Organization, available at <[http://apps.who.int/gb/ebwha/pdf\\_files/WHA67/A67\\_R25-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf)> (last visited May 20, 2015); World Health Organization, *The Evolving Threat of Antimicrobial Resistance: Options for Action* (Geneva: WHO Press, 2012); World Health Organization, *WHO Global Strategy for Containment of Antimicrobial Resistance*, available at <[http://www.who.int/drugresistance/WHO\\_Global\\_Strategy\\_English.pdf](http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf)> (last visited May 20, 2015); World Health Organization, *Antimicrobial Resistance: Global Report on Surveillance* (Geneva: WHO Press, 2014); WHA 58.27, *Resolutions of the Fifty-Eighth World Health Assembly: Improving the Containment of Antimicrobial Resistance*, World Health Organization available at <<http://apps.who.int/medicinedocs/documents/s16340e/s16340e.pdf>> (last visited May 20, 2015).
19. See Hoffman et al., *supra* note 2.
20. S. J. Hoffman and T. Ottersen, “Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms,” *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).



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# Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments

*Asha Behdinan, Steven J. Hoffman, and Mark Pearcey*

## Introduction

This article assesses which policies for addressing antibiotic resistance (ABR) as part of a multi-pronged approach would benefit from legalization through an international legal agreement. Ten candidate policies were identified based on a review of existing literature, especially *The Lancet Series on Antimicrobial Resistance (AMR)*,<sup>1</sup> *The Lancet Infectious Diseases Commission on AMR*,<sup>2</sup> and the World Health Organization (WHO) Global Action Plan for AMR.<sup>3</sup> These policies were then grouped under the headings of access, conservation, and innovation.<sup>4</sup>

Each of the ten policies were assessed using four criteria developed by Hoffman, Røttingen, and Frenk to help consider why their legalization may be helpful, necessary and/or justified.<sup>5</sup> These criteria are: (1) the problem has a significant transnational dimension; (2) the goal justifies the coercive nature of law; (3) the outcome is likely to be beneficial; and (4) legalization represents the best commitment mechanism among competing alternatives.<sup>6</sup>

Using these criteria as analytic benchmarks, we explore how several global policies for ABR depend on legally binding and enforceable commitments, how additional policies would benefit from legalization, and how other policies could helpfully contribute to a

grand bargain that galvanizes support for the implementation of these provisions. Of course, international law can also helpfully articulate principles or recommend national policies for states to consider adopting, but such use of international legal agreements is not the focus of this article.

## Global Access Policies

Two policies fall under the access pillar; both address the underprovision of antibiotics, diagnostic tools, and infection control practices.

### *1. Mobilizing Financial Resources for Laboratory, Surveillance, and Health System Infrastructure in Resource-Poor Countries*

Development assistance is still necessary for health systems strengthening in many low- and middle-income countries (LMICs). Strong health systems are the backbone of reducing the global threat of ABR. For example, stronger laboratory and surveillance systems and infection prevention programs would lower the prevalence of infectious disease and improve the quality of information on the spread of ABR. The inclusion of this policy in an international legal agreement could ensure that resource-poor countries have access to the finan-

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Table I

**Global Policies for ABR**

		Significant transnational dimension	Justifies coercive nature of treaties	Reasonable chance of achieving benefits	Best commitment mechanism
<b>Access Policies</b>	1. <b>Mobilizing financial resources</b> for infrastructure	•	•	•	
	2. <b>Funding</b> for access	•	•	•	
<b>Conservation Policies</b>	3. <b>Prohibiting use</b> of antibiotics for growth promotion or routine prevention	•	•	•	•
	4. Designating <b>human-only classes</b> of antibiotics	•	•	•	•
	5. Regulating antibiotic <b>prescription</b> and <b>availability</b> for humans	•	•	•	•
	6. <b>Educating</b> on effective use		•	•	
	7. Strengthening <b>infection control practices</b>	•	•	•	
	8. Strengthening and coordination of <b>surveillance</b>	•	•	•	•
	9. Prohibiting the <b>marketing</b> and promotion of antibiotics	•		•	
<b>Innovation Policies</b>	10. <b>Funding and incentives</b> for antibiotic technologies	•	•	•	

cial capacity necessary to ensure appropriate access to antibiotics and implement antibiotic conservation efforts. While this policy could also be pursued effectively outside an international legal agreement, such as through bilateral arrangements or existing pooled funding mechanisms, it is a key component of a global response to ABR and could therefore benefit from legalization. This financing could be used to incentivize states to implement crucial conservation ABR policies – by either providing the funds needed to be compliant (the approach adopted in Article 44 of the International Health Regulations) or by conditioning the availability of these funds on implementation of ABR conservation policies (an approach used controversially yet regularly by the International Monetary Fund).

*2. Funding for Access to Appropriate Antibiotics, Diagnostics, and Related Technologies in Resource-Poor Countries*

When pursued in conjunction with conservation measures, policies for increasing appropriate access to antibiotics, diagnostics and related technologies could reduce the rate of ABR in a just and equitable manner

by diminishing the transmission of resistant bacteria.<sup>7</sup> The broad and ambitious scope of this policy could be too vast to include as part of an international legal agreement; its equity focus and redistribution consequences would also be nearly unprecedented in international law. There could also be potential harms and trade-offs, including how inappropriate access quickens resistance, and there may be better alternative commitment mechanisms through which states and non-state actors could advance this policy (e.g., development goals, codes of practice, global funds).<sup>8</sup> However, like financing for health systems and infrastructure, this policy on funding access to antibiotics could be helpful in an ABR legal agreement to address vital equity imperatives and incentivize states to implement conservation policies. In this instance, an international legal agreement that creates (or that references external) pooled funding mechanisms could ensure adequate financing needed for access and conservation goals.

## Global Conservation Policies

Seven policies fall under the conservation pillar, which together aim to reduce the incidence and spread of ABR and ensure appropriate antibiotic use.

### *3. Prohibiting Antibiotics for Growth Promotion and Routine Prevention in Animals*

Overuse, misuse, and abuse of antibiotics in the agriculture industry facilitate the spread of ABR.<sup>9</sup> An international legal agreement that encourages and enforces minimum national regulatory standards could ensure action in all states to mitigate ABR and conserve the effectiveness of existing antibiotics. Antibiotic use in animal husbandry amounts to 80% of all use in the United States, and is projected to increase by 67% worldwide.<sup>10</sup> There is therefore danger that resistance in animals may spread to humans without global implementation of rational use regulations in agriculture.<sup>11</sup> Global rules could also minimize any competitive disadvantages that would be experienced by livestock industries within states that adopted regulations on their own. In order to effectively reduce the negative effects of irrational antibiotic use, where individual private benefits do not offset total social costs, this policy is exactly of the kind that most benefits from international legalization.

### *4. Designating Human-Only Classes of Antibiotics*

There is a clear tension between the potential for private gains in using antibiotics in the agriculture sector and the negative impacts this may have on public health. Using international law to restrict the use of certain antibiotics could slow the development of resistance to these medicines and promote the use of alternative therapies and preventive measures — closing the gap between the private and public costs of this enterprise. Including this policy in an international legal agreement could help promote its adoption since countries would only benefit from it if implemented by all countries simultaneously. The key factor that points towards the need for international law to support this policy is that near-complete global compliance is needed for it to be effective. This is the result of high levels of trade and travel that facilitate the international spread of resistant bacteria. International law — the strongest way through which states can make commitments to each other — lessens concerns about non-compliance and free ridership compared with alternative commitment mechanisms (albeit not fully eliminating them).<sup>12</sup>

### *5. Regulating Antibiotic Prescription and Availability for Humans*

Currently, there is a lack of accepted global guidance and context-specific guidelines for the prescription of antibiotics by health professionals. In fact, two-thirds of antibiotics sold have not been prescribed by a physician.<sup>13</sup> The establishment of best practice guidelines that are adaptable and differentiated to each particular country context is necessary to mitigate the potential negative effects of antibiotic misuse and overuse by humans. For countries with an adequate supply of physicians and strong health system infrastructure, antibiotic prescription guidelines can be put in place or strengthened to discourage their irrational use. For the many LMICs where drug prescription systems are infeasible, alternative regulations can be pursued, such as antibiotic use legislation, monitoring and surveillance efforts, pharmacist training, and public awareness campaigns.<sup>14</sup> Including an adaptable and differentiated regulation on antibiotic availability in an international legal agreement could encourage countries to do their part toward collective responsible use without unduly limiting access to these life-saving medicines. An international legal agreement that required all countries to have one particular system for limiting antibiotic availability — such as a prescription system — would be inappropriate and could have disastrous health consequences.

### *6. Providing Education on Effective Antibiotic Use to Health Professionals and Patients*

To reduce unnecessary use and prescription of antibiotics, effective education needs to be offered to both health professionals and patients. Professional training and awareness campaigns can be effective demand-reduction measures,<sup>15</sup> especially in countries where one can obtain antibiotics without a prescription.<sup>16</sup> This policy supports the goal of conservation, as it could work alongside other policies for reducing irresponsible antibiotic use at both the individual and systems levels. Funds mobilized through an international legal agreement or external pooled funding mechanisms could aid in the implementation of ABR education measures. Including this policy in an international legal agreement could help encourage global negotiation of regulatory standards, development of clinical and public health guidelines, and sharing of best practices for optimizing education efforts.

### 7. Strengthening Infection Control Practices

Infection control is an important public health strategy that is costly and that yields significant benefits for parties other than the payer. Neighboring countries, for example, may collectively benefit more from strong infection control practices than the implementing country. This positive externality results in underutilization of infection control practices given the local benefits to implementers may not exceed their costs — even when the global benefits surely would exceed

likelihood that other states will be able to benefit from them too.

### 9. Prohibiting the Marketing and Promotion of Antibiotics

Along with public awareness campaigns, a further demand-side policy that could be included in an international legal agreement is imposing marketing bans on antibiotics worldwide. This policy includes provisions such as banning industry and retailers from advertising antibiotics, restrictions on using price or

**An international legal agreement could effectively support global collective action towards several ABR goals. Of the ten candidate policies examined, each could benefit to a certain extent if included in an international legal agreement. It is clear that while some policies may only be effective if internationally legalized, other policies would be more effective if legalized, and still other policies would benefit at least marginally from inclusion in an international legal agreement. Yet even when expected benefits from international legalization are marginal, including such policies may be useful anyway in supporting implementation of the other policies, changing norms, or incentivizing states to participate.**

costs. Requiring infection control practices as part of an international legal agreement could help ensure states implement these policies for the betterment of all (and in turn benefit from other countries' implementation of these policies). If the burden of costs could be shared equitably among state parties, the international legalization of this policy could also aid in the striking of a grand bargain.<sup>17</sup>

### 8. Strengthening and Coordination of Surveillance Systems and Laboratory Capacity

National ABR surveillance systems remain fragmented and lack regional and global coordination. The lack of global standards for laboratory methodologies has reduced the ability to collect, analyze, and compare data, inhibiting the potential impact of this data in improving evidence-informed policies everywhere.<sup>18</sup> This dearth of data and coordination from many countries affects the ability of all countries to address ABR effectively — especially considering how much of the ABR threat comes from the unknown transmission of resistant bacteria from other countries. Creating international legal obligations to gather and share data could help ensure that states actually undertake these responsibilities, and it maximizes the

packaging for promotions, and regulating the location, size, and type of drug retailers.<sup>19</sup> This approach has been used to some degree of success in the Framework Convention on Tobacco Control, with more than 50% of ratifying countries having restricted these marketing measures for cigarettes to some extent.<sup>20</sup> Globally accepted marketing bans could be especially helpful in today's age of the Internet and advanced mobile communications technologies given that many forms of media spread seamlessly across national borders. The international legalization of this policy could therefore decrease harmful antibiotic marketing messages and help protect states that have banned antibiotic promotion efforts from being subjected to cross-border promotion efforts.

### Global Innovation Policies

One policy falls under the innovation pillar, which involves research and development for antibiotics, diagnostics, and related technologies for the detection, prevention, and treatment of infectious diseases.

### 10. Funding and Incentives for Developing New Technologies Addressing ABR



Currently there is insufficient funding and incentives for developing new antibiotics and other related technologies. However, most existing funding allocations by states across issues are voluntary; there are very few instances where states legally bind themselves to funding requirements (with membership dues to international organizations representing an important exception).

That being said, if states were ambitious, internationally legalizing this policy – or at least the principles underlying it, such as increasing funding, universal participation, and differentiating state contributions by development status – could be used to change norms about global responsibilities of high-income countries in this area and mobilize participation among LMICs in any international legal agreement. The latter might be especially effective if LMICs were promised access to research funding and the fruits of new innovations at-cost if they comply with conservation provisions.

While the dearth of funding and incentives for new ABR technologies could be solved outside of an international legal agreement through the concerted efforts of a few wealthy states,<sup>21</sup> including it would solidify interconnections and commitment across the access, conservation, and innovation imperatives and help solve the political-economy challenges facing the global antibiotics regime.<sup>22</sup>

## Conclusion

An international legal agreement could effectively support global collective action towards several ABR goals. Of the ten candidate policies examined, each could benefit to a certain extent if included in an international legal agreement. It is clear that while some policies may only be effective if internationally legalized, other policies would be more effective if legalized, and still other policies would benefit at least marginally from inclusion in an international legal agreement. Yet even when expected benefits from international legalization are marginal, including such policies may be useful anyway in supporting implementation of the other policies, changing norms, or incentivizing states to participate.<sup>23</sup> States can theoretically include every possible ABR policy in an international legal agreement as recommended actions; but some of the policies depend on legally binding and enforceable commitments, whereas others can have an impact without such a high level of obligation.

By legalizing the necessary policies, effective action is more likely to be undertaken to meet the access, conservation, and innovation imperatives needed to fully address the global threat of ABR. An international legal agreement is most helpful for promoting

universal implementation of needed conservation policies, with access provisions supporting them, and innovation requirements helping mold a delicate grand bargain.

## References

1. C. Ardal, K. Outtersen, S. J. Hoffman, A. Ghafur, M. Sharland, and N. Ranganathan et al., "International Collaboration to Improve Access to and Sustain Effectiveness of Antimicrobials," *The Lancet* (in press).
2. R. Laxminarayan, A. Duse, C. Wattal, A. K. M. Zaidi, H. F. L. Wertheim, N. Sumpradit et al., "Antibiotic Resistance - The Need for Global Solutions," *The Lancet Infectious Diseases* 13, no. 12 (2013): 1057-1098.
3. World Health Organization: Draft Global Action Plan on Antimicrobial Resistance, World Health Organization, *available at* <[http://www.who.int/drugresistance/AMR\\_DRAFT\\_GAP\\_1\\_Oct\\_2014\\_for\\_MS\\_consultation.pdf](http://www.who.int/drugresistance/AMR_DRAFT_GAP_1_Oct_2014_for_MS_consultation.pdf)> (last visited May 29, 2015).
4. S. J. Hoffman, K. Outtersen, J.-A. Røttingen, O. Cars, C. Clift, and Z. Rizvi et al., "An International Legal Framework to Address Antimicrobial Resistance," *Bulletin of the World Health Organization* 93, no. 2 (2015): 66.
5. S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "International Law Has a Role to Play in Addressing Antibiotic Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
6. S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "Assessing Proposals for New Global Health Treaties: An Analytic Framework," *American Journal of Public Health* (2015): e1-e8.
7. See WHO, *supra* note 3.
8. S. J. Hoffman, B. McGrady, G. M. Caleo, N. Daulair, S. Elbe, and D. L. F. Wong et al., "Achieving Global Collective Action For Improving Access to Antimicrobials and Sustaining Their Effectiveness," in preparation; J. S. Edge and S. J. Hoffman, "Empirical Impact Evaluation of the WHO Global Code of Practice on the International Recruitment of Health Personnel in Australia, Canada, UK and USA," *Globalization & Health* 9, no. 60 (2013): 1-10.
9. B. Spellberg, J. G. Bartlett, and D. N. Gilbert, "The Future of Antibiotics and Resistance," *New England Journal of Medicine* 368, no. 4 (2013): 299-302.
10. A. Huttner, S. Harbarth, J. Carlet, S. Cosgrove, H. Goossens, and A. Holmes et al., "Antimicrobial Resistance: A Global View From the 2013 World Healthcare-Associated Infections Forum," *Antimicrobial Resistance and Infection Control* 2, no. 31 (2013): 1-13; T. P. Van Boeckel, C. Brower, M. Gilbert, B. T. Grenfell, S. A. Levin, and T. P. Robinson et al., "Global Trends in Antimicrobial Use in Foods," *Proceedings of the National Academy of Sciences of the United States of America* 112, no. 18 (2013): 5649-5654.
11. World Health Organization, *The Evolving Threat of Antimicrobial Resistance*, (2012), *available at* <<http://www.who.int/patientsafety/implementation/amr/publication/en/>> (last visited June 1, 2015).
12. S. J. Hoffman and J.-A. Røttingen, "Be Sparing With International Laws," *Nature* 483, no. 7389 (2012): 275; S. J. Hoffman and J.-A. Røttingen, "Assessing Implementation Mechanisms For an International Agreement On Research and Development For Health Products," *Bulletin of the World Health Organization* 90 (2012): 854-863; S. J. Hoffman and T. Ottersen, "Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
13. K. Le Doare, C. I. S. Barker, A. Irwin, and M. Sharland, "Improving Antibiotic Prescribing for Children in the Resource-Poor Setting," *British Journal of Clinical Pharmacology* 79, no. 3, (2015): 446-455.
14. *Id.*

15. E. Leung, D. E. Weil, M. Raviglione, and H. Nakatani, "Policy Package to Combat Antimicrobial Resistance," World Health Organization World Health Day Antimicrobial Resistance Technical Working Group, *available at* <<http://www.react-group.org/uploads/publications/other-publications/WHO-Policy-Package-to-Combat-Antimicrobial-Resistance.pdf>> (last visited June 1, 2015).
16. See Hoffman and Röttingen ("Assessing Implementation"), *supra* note 12.
17. See Leung et al., *supra* note 15.
18. G. Vernet, C. Mary, D. M. Altmann, O. Doumbo, S. Morpeth, and Z. A. Bhutta et al., "Surveillance for Antimicrobial Drug Resistance in Under-Resourced Countries," *Emerging Infectious Diseases* 20, no. 3 (2014): 434-441.
19. L. Henriksen, "Comprehensive Tobacco Marketing Restrictions: Promotion, Packaging, Price, and Place," *Tobacco Control* 21, no. 2 (2012): 147-153.
20. *Id.*
21. J.-A. Röttingen and C. Chamas, "A New Deal for Global Health R&D? The Recommendations of the Consultative Expert Working Group on Research and Development," *PLOS Medicine* 9, no. 5 (2012): e1001219.
22. WHO Consultative Expert Working Group on Research and Development, "Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination," WHO, *available at* <[http://www.who.int/phi/cewg\\_report/en/](http://www.who.int/phi/cewg_report/en/)> (last visited June 1, 2015); Z. Rizvi and S. J. Hoffman, "Effective Global Action on Antibiotic Resistance Requires Careful Consideration of Convening Forums," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via [aslme.org](http://aslme.org).
23. S. J. Hoffman and J.-A. Röttingen, "Assessing the Expected Impact of Global Health Treaties: Evidence from 90 Quantitative Evaluations," *American Journal of Public Health* 105, no. 1 (2015): 26-40.

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# Effective Global Action on Antibiotic Resistance Requires Careful Consideration of Convening Forums

*Zain Rizvi and Steven J. Hoffman*

## Introduction

The nature and effectiveness of any international legal agreement is heavily shaped by the forum in which it is negotiated and implemented.<sup>1</sup> This includes both the substantive content that global policymakers agree upon and the subsequent state compliance with those provisions. Forums differ in their institutional characteristics, thereby providing unique opportunities and costs for participating actors. Forums may have different mandates, capacities, cultures, members, and legal processes — all of which ultimately affect distributions of power and influence.<sup>2</sup> These differences then shape how issues are framed, the content of agreements as they are negotiated, and the incentives states have to comply with any obligations.

Academics and policymakers have called for global collective action to address the transnational challenge of antibiotic resistance (ABR), including the adoption of an international legal agreement to facilitate it.<sup>3</sup> The use of international law — which formally represents the strongest possible mechanism through which states can commit to each other — is justified by the interdependencies across countries and needed actions on access, conservation, and innovation for antibiotics.<sup>4</sup>

But through which forum should such a law be negotiated and implemented? While much has been written about *what* must be done to address ABR, far less work has analyzed *how* or *where* such collective action should be facilitated — even though the success of any international agreement on ABR depends greatly on how negotiations are convened and where the agreement is adopted.

This article evaluates the strengths and weaknesses of different global political forums that may be used to develop an international legal agreement for ABR. Based on existing mandates and legal authority, at least four forums seem plausible for developing such an agreement: (1) a self-organized venue; (2) the World Health Organization (WHO); (3) the World Trade Organization (WTO); and (4) the United Nations General Assembly (UNGA).

Of course, if adopted, any international legal agreement could be complemented by non-legal initiatives pursued through other institutions. These could include the development of an analogous institution to the Global Fund to Fight AIDS, Tuberculosis & Malaria, specifically for funding antibiotic access, conservation, and innovation initiatives. With this in mind, this article focuses on one component of the broader global response needed for ABR — that of an international legal agreement.

## Forum 1: Self-Organized Venue

One route available to states is the adoption of an independent multilateral legal agreement, without the involvement of any formally constituted intergovernmental organizations. For example, the G7 or the Oslo-7 Foreign Policy and Global Health countries represent groupings that could perhaps act together, coordinating efforts using an international legal agree-

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ment. Indeed, ABR was identified as a “key issue” for the 2015 G7 summit in Schloss Elmau, Germany and featured prominently in the communiqué.<sup>5</sup>

The flexibility afforded by an independent agreement is a key strength: by organizing a smaller group of like-minded states, conveners can ensure that provisions are meaningful, comprehensive, and not watered down to the lowest common denominator due to a need for consensus across scores of countries. The success of any early agreement with a smaller

## Forum 2: World Health Organization

WHO could serve as a forum for an international legal agreement on ABR, either through the modification of its existing International Health Regulations (IHR) or the adoption of a new international legal agreement.

### *Revising the International Health Regulations*

Binding on 196 states,<sup>6</sup> the IHR could be a legal mechanism for states to promote collective action on ABR. As proposed, the emergence of resistant bac-

While much has been written about *what* must be done to address ABR, far less work has analyzed *how* or *where* such collective action should be facilitated — even though the success of any international agreement on ABR depends greatly on how negotiations are convened and where the agreement is adopted. This article evaluates the strengths and weaknesses of different global political forums that may be used to develop an international legal agreement for ABR. Based on existing mandates and legal authority, at least four forums seem plausible for developing such an agreement: (1) a self-organized venue; (2) the World Health Organization (WHO); (3) the World Trade Organization (WTO); and (4) the United Nations General Assembly (UNGA).

group of states could also generate momentum for greater global action among larger groups of states. Bold efforts by the G7, for example, could lead to further mobilization by the G20, G77, regional bodies, and/or other groups. Additionally, independent action by the G7 could significantly address at least one part of the ABR challenge — the innovation deficit — given that their collective contributions to health research and development (R&D) represent such a large proportion of the world’s total investment in the area. Although admittedly, focused action on innovation (to the exclusion of action on access to and conservation of antibiotics) would not require an international legal agreement.

A self-organized international legal agreement may be promising, but without early institutional buy-in and support, it may be difficult to mobilize a wide cross-section of states towards collective action. There may be questions of legitimacy, particularly given the sensitive nature of an ABR agreement. In the long run, addressing gaps in antibiotic access, conservation, and innovation probably require a near-universal effort, such that an independent multilateral legal agreement could only be a stepping-stone at best. Nonetheless, robust efforts of a small group of states like the G7 could provide a strong catalyst for broader global action.

teria could be considered a public health emergency of international concern, which would require states to notify WHO of its occurrence.<sup>7</sup> More ambitiously, the IHR could be revised to require additional state actions that address the threat of ABR.

The primary advantage with this option is that the IHR already exists; reinterpreting or revising it would not require the approval of domestic parliaments and congresses. The disadvantage is that the IHR was primarily crafted to support disease surveillance and response.<sup>8</sup> Issues of access, conservation, and innovation — all vital to a global ABR strategy — would effectively remain unaddressed within this limited framework. Although the IHR could be used to bolster surveillance and response capacities as part of a broader, multi-pronged effort, state compliance with the IHR has thus far been relatively poor,<sup>9</sup> limiting its potential as an implementation vehicle. Most disconcerting is the political challenge: the recent IHR revisions in 2005 were highly contentious and resulted in a delicately balanced agreement; revising the agreement may result in states wanting to renegotiate a host of complex and divisive issues.



### *Adopting a New Legal Agreement*

Alternatively, the World Health Assembly (WHA) could develop one of two types of legal agreements. The first, enabled by Article 21 of WHO's constitution, allows the WHA to enact regulations on certain matters that become automatically binding on all WHO member states, unless a state affirmatively chooses to opt-out.<sup>10</sup> Second, the WHA can develop a new international legal agreement under Article 19 of the organization's constitution, which enables the adoption of conventions with a two-thirds vote.<sup>11</sup> These conventions become binding once states ratify them through their respective national processes. This approach was used for WHO's Framework Convention on Tobacco Control (FCTC).<sup>12</sup>

An Article 21 WHO regulation has many of the same advantages and disadvantages as a WHO convention under Article 19; the forum is effectively the same. However, unlike a convention, the WHA can only enact regulations on specific issues. The most relevant in this case are regulations on "sanitary and quarantine requirements and other procedures designed to prevent the international spread of disease."<sup>13</sup> Regulations on ABR could be construed as "other procedures." However, the WHA has historically been reluctant to introduce new regulations, choosing instead to issue non-binding recommendations to address topics such as quality control of medicines, breast-milk substitutes, and malaria control.<sup>14</sup> If introduced, an ABR regulation would have the advantage of legislating without positive consent, binding states unless they take action to opt-out.

As a whole, WHO's strength as a forum is based on its mandate of promoting human health. It intuitively makes sense to convene an agreement with significant consequences for human health under the auspices of the coordinating authority on global health. WHO is controlled by member states, it is generally regarded as a legitimate entity, and it may appeal to states as a natural forum for taking action on ABR.

But WHO has also recently faced difficulty in fulfilling its existing mandate due to resource-constraints, a situation which seems unlikely to change in the near future given the intractability of its governance challenges.<sup>15</sup> ABR is also vitally linked to issues strictly beyond human health, including agriculture and trade. These limitations become acute when considering the political capital required to push for a new international legal agreement through WHO, an organization historically averse to utilizing international law. Moreover, even if the negotiation process was initiated, the institutional culture of WHO could make drafting a meaningful instrument difficult. Effective legal instruments require strong compliance mecha-

nisms.<sup>16</sup> WHO's primary legal instruments — the IHR and FCTC — contain weak accountability mechanisms that rely on the willingness of states to comply.<sup>17</sup>

### **Forum 3: World Trade Organization**

WTO could also serve as a forum for the development of an international legal agreement addressing ABR. Two avenues could be pursued.

First, the WTO Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) — which sets rules for food safety and animal health standards — could be used to bolster conservation efforts.<sup>18</sup> In fact, certain states have already imposed unilateral trade restrictions over concerns about levels of antibiotic residues on products.<sup>19</sup> A more global effort would likely require strengthening of the standards set by the Codex Alimentarius Commission, which establish the normative platform for the SPS Agreement.<sup>20</sup>

Second, WTO could develop a new international legal agreement specific to ABR. Issues involving agriculture, innovation, and trade are all within the purview of WTO's mandate.

Using WTO as a forum could benefit from the organization's culture of compliance and the strength of its existing dispute resolution mechanisms.<sup>21</sup> WTO is widely heralded as an institution in which international law actually matters. Moreover, some momentum for collective action on ABR has been generated by the unilateral actions already taken by some states.

However, WTO's narrow mandate as it relates to ABR would pose challenges. Focused on agriculture, innovation, and trade, states may have different understandings of ABR, leading to uncomfortable trade-offs and compromises that would not be taken in less politically charged forums (e.g., issues surrounding access to medicines). This is particularly concerning given the history of prominent power differentials and inequalities of political influence among states at the WTO.<sup>22</sup>

### **Forum 4: United Nations General Assembly**

States could alternatively choose UNGA as a convening forum for a new international ABR legal agreement. The primary strength of UNGA is that it is a senior, high-profile, general jurisdiction intergovernmental forum. The negotiation of an ABR legal agreement at UNGA could place it higher on the global political agenda. This increased attention and engagement by global policymakers could increase the prioritization of ABR within domestic settings, increasing the likelihood that the agreement will be implemented.

The senior status of UNGA also extends across the UN system and other IGOs. It could be easier to facili-

tate collaboration on ABR among sister agencies with the leadership of UNGA. Though WHO is nominally the UN's coordinating health authority, the creation of both UNAIDS and the UN Mission for Ebola Emergency Response — and the expansion of health activities at UNICEF, UNFPA and others — demonstrate that this capability is often limited in practice. UNGA

drivers of ABR and appropriate responses — often raised by the agriculture sector — could also be marginalized given the minimal representation of those sectors.<sup>23</sup>

But the measure of success for an international legal agreement is not only the strength of the text as written, but also how its provisions are implemented

at a national level and how they actually influence state behavior.<sup>24</sup> Exclusively empowering the human health sector at the global level would likely fail to influence state behavior sufficiently to address ABR, primarily because it would not engender the type of multisectoral response that is needed.<sup>25</sup> It would fail to engage the national agricultural and trade sectors, which may have vastly different worldviews and priorities (e.g., food security and economic development). Convincing only Ministers of Health would probably not be enough. Ministers of Health often hold little influ-

ence in national political systems such that it can be difficult for them to persuade other officials, like Heads of Government and Ministers of Trade. And as was demonstrated in the early response to HIV/AIDS and the current response to non-communicable diseases, Ministers of Health are often “wary that multisectoralism [will] take power and money away from them.”<sup>26</sup>

Engaging all relevant stakeholders at the global level — or at least having their concerns represented — is thus imperative to the success of an international legal agreement addressing ABR. A self-organized coalition of states (e.g., G7), WTO and UNGA could all facilitate inclusive discussions with a range of actors from agriculture, trade, and health, potentially leading to greater policy coherence and a more effective multisectoral response. UNGA has the added advantage of greater legitimacy, higher visibility, and broader participation. Including a range of stakeholders in the negotiating process may help avoid making the proposed international ABR legal agreement a document that is not a reflection of actual state interests and legal commitments but of aspirations — as some have claimed of WHO's FCTC.<sup>27</sup> Indeed, some state delegations made commitments during the FCTC negotiation process that went against the official positions of their national governments.<sup>28</sup>

**he complexity of both the issue of ABR and the institutional landscape suggest that an effective response may best be coordinated through multiple fora. Many of the particular challenges associated with each forum could be addressed by harnessing linkages between them. An analysis of the different permutations of forums that are possible is beyond the scope of this article, but it seems at first glance that pursuing an international legal agreement simultaneously through both WHO and UNGA represents a promising strategy.**

has acted before on health matters, including convening special sessions on HIV/AIDS (2001, 2006, 2011), non-communicable diseases (2011, 2014), and Ebola (2014).

But an increased role for UNGA in adopting international legal agreements on health issues might also lead to fragmentation and duplication. Overlapping authority may result in inefficiencies and a lack of accountability. Furthermore, although UNGA has increasingly responded to health issues, ABR might be seen as a technical “Geneva issue,” falling within WHO's mandate, rather than a “New York issue” that may be addressed at UNGA. ABR would also have to compete with the traditional concerns tabled at UNGA related to peace, security and development, perhaps making it difficult to get traction.

## Discussion

These four different forums for implementing an international ABR legal agreement present unique opportunities and challenges, particularly because of the multisectoral nature of the issue. Nonetheless, due to ABR's significant consequences for human health, many in the global health community see WHO as the natural convener. Indeed, with human health as the primary focus, like-minded Ministers of Health may make more ambitious legal commitments at WHO. Difficult questions regarding the

Still, WHO possesses both an inherent legitimacy and technical expertise that could be leveraged to coordinate the world's response to ABR. Its power of enacting binding regulations without positive consent is also unique among forums.

## Conclusion

The complexity of both the issue of ABR and the institutional landscape suggest that an effective response may best be coordinated through multiple fora. Many of the particular challenges associated with each forum could be addressed by harnessing linkages between them. An analysis of the different permutations of forums that are possible is beyond the scope of this article, but it seems at first glance that pursuing an international legal agreement simultaneously through both WHO and UNGA represents a promising strategy. For example, UNGA could be used to develop momentum and gain higher-level political attention for a WHO regulation; or alternatively, UNGA could develop an international ABR legal agreement that delegated technical responsibilities to WHO, addressing claims of fragmentation and potentially enabling greater prioritization of health concerns. Such references would not be unprecedented: the UN-organized Single Convention on Narcotic Drugs (1961) requires that any changes to the list of narcotic substances be made upon WHO's recommendation.<sup>29</sup>

Ultimately, an effective international legal agreement on ABR will require bold, creative action, along with careful consideration of the competing advantages and disadvantages of potential forums through which it could be pursued.

## References

- Note that for the purposes of this paper, we assume that compliance is equivalent to effectiveness (i.e., if the states agreed to enact the policies contained within the instrument, they would reduce the threat of ABR).
- H. Murphy and A. Kellow, "Forum Shopping in Global Governance: Understanding States, Business and NGOs in Multiple Arenas," *Global Policy* 4, no. 2 (2013): 139-149.
- S. J. Hoffman, K. Outtersson, J.-A. Røttingen, O. Cars, C. Clift, Z. Rizvi, F. Rotberg, G. Tomson, and A. Zorzet, "An International Legal Framework to Address Antibiotic Resistance," *Bulletin of the World Health Organization* 93, no. 2 (2015): 66; J.-A. Røttingen, "Regulating Antibiotics and Resistance," in J. Frenk and S. J. Hoffman, *To Save Humanity: What Matters Most for a Healthy Future* (New York: Oxford University Press, 2015).
- S. J. Hoffman, J.-A. Røttingen, and J. Frenk, "International Law Has a Role to Play in Addressing Antibiotic Resistance," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
- Federal Government of Germany, "German G7 Presidency: Key Topics for the Summit Announced," available at <http://www.g7germany.de/Content/EN/Artikel/2014/11\_en/2014-11-18-g7-themen\_en.html> (last visited May 22, 2015); G7, "Leaders' Declaration G7 Summit, 7-8 June 2015," available at <https://www.g7germany.de/Content/EN/\_Anlagen/G7/2015-06-08-g7-abschluss-eng\_en.pdf> (last visited June 15, 2015).
- World Health Organization (WHO), "International Health Regulations," 2015, available at <http://www.who.int/topics/international\_health\_regulations/en/> (last visited May 22, 2015).
- D. Wernli, T. Hausteiner, J. Conly, and Y. Carmeli, "A Call for Action: The Application of the International Health Regulations to the Global Threat of Antibiotic Resistance," *PLoS Medicine* 8, no. 4 (2011): e1001022.
- See WHO, *International Health Regulations*, 2005.
- WHO, *Implementation of the International Health Regulations: Report by the Director-General*, 2013.
- WHO, *Constitution of the World Health Organization* (1948).
- Id.*
- WHO, *Framework Convention on Tobacco Control* (2003).
- See WHO, *supra* note 10.
- A. Lakin, "The Legal Powers of the World Health Organization," *Medical Law International* 3, no. 3 (1997): 23-49.
- S. J. Hoffman and J.-A. Røttingen, "Split WHO in Two: Strengthening Political Decision-Making and Securing Independent Scientific Advice," *Public Health* 128, no. 2 (2014): 188-194.
- S. J. Hoffman and J.-A. Røttingen, "Assessing the Expected Impact of Global Health Treaties: Evidence from 90 Quantitative Evaluations," *American Journal of Public Health* 105, no. 1 (2015): 26-40; S. J. Hoffman and T. Ottersen, "Addressing Antibiotic Resistance Requires Robust International Accountability Mechanisms," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
- See WHO, *supra* notes 8 and 12.
- WTO, *The WTO Agreement on the Application of Sanitary and Phytosanitary Measures* (1995).
- A. So, T. J. Shah, S. Roach, Y. L. Chee, and K. E. Nachman, "International Agreement to Address the Contribution of Animal Agriculture to Antibiotic Resistance: A One Health Approach," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): available via aslme.org.
- See WTO, *supra* note 18.
- WTO, "Understanding the WTO: Settling Disputes," available at <https://www.wto.org/english/thewto\_e/whatis\_e/tif\_e/displ\_e.htm> (last visited May 27, 2015).
- S. J. Hoffman, "Mitigating Inequalities of Influence among States in Global Decision Making," *Global Policy* 3, no. 4 (2012): 421-432.
- J. Rushton, P. Ferreira, and K. Stärk, "Antibiotic Resistance: The Use of Antibiotics in the Livestock Sector," OECD Food, Agriculture and Fisheries Papers, No. 68 (Paris: OECD Publishing, 2014); S. P. Oliver, S. E. Murinda, and B. M. Jayarao, "Impact of Antibiotic Use in Adult Dairy Cows on Antibiotic Resistance of Veterinary and Human Pathogens: A Comprehensive Review," *Foodborne Pathogens and Disease* 8, no. 3 (2011): 337-355.
- S. Andresen and S. J. Hoffman, "Much Can Be Learned About Addressing Antibiotic Resistance from Multilateral Environmental Agreements," *Journal of Law, Medicine & Ethics* 43, no. 2, Supp. (2015): online only.
- See So et al., *supra* note 19.
- UNAIDS, *The First 10 Years* (2008).
- G. Jacob, "Without Reservation," *Chicago Journal of International Law* 5, no. 1 (2004): 287-302.
- Id.*
- United Nations, *Single Convention on Narcotic Drugs* (1961).