



CENTER
FOR
GLOBAL
DEVELOPMENT

A NEW GRAND BARGAIN TO IMPROVE THE ANTIMICROBIAL MARKET FOR HUMAN HEALTH



A CGD Working
Group Report

Anthony McDonnell,
Katherine Klemperer,
Morgan Pincombe, Rachel
Silverman Bonnifield,
Prashant Yadav, and Javier
Guzman

Anthony McDonnell, Katherine Klemperer, Morgan Pincombe, Rachel Silverman Bonnifield, Prashant Yadav, and Javier Guzman. 2023. "A New Grand Bargain to Improve the Antimicrobial Market for Human Health, Final Report of the CGD Working Group." Washington, DC, and London, UK: Center for Global Development www.cgdev.org/amr.

CENTER FOR GLOBAL DEVELOPMENT

2055 L Street, NW Fifth Floor
Washington, DC 20036
www.cgdev.org

1 Abbey Gardens
Great College Street
SW1P 3SE London

Center for Global Development. 2023.
Creative Commons Attribution-NonCommercial 4.0



CENTER
FOR
GLOBAL
DEVELOPMENT



A NEW GRAND BARGAIN TO IMPROVE THE ANTIMICROBIAL MARKET FOR HUMAN HEALTH

A CGD Working Group Report

Anthony McDonnell,
Katherine Klemperer,
Morgan Pincombe,
Rachel Silverman Bonnifield,
Prashant Yadav, and
Javier Guzman

Contents

- Foreword iii**
- Acronyms..... iv**
- The Working Group, the Center for Global Development, and this Report v**
- Executive Summary vii**
- 1. Problems with the Antimicrobial Market1**
 - 1.1 Key challenges..... 1
 - Insufficient global action2
 - The three pillars of sustainability: innovation, access, and stewardship 3
 - 1.2 Innovation challenges in the market for antimicrobials 4
 - Overview of innovation problems 4
 - Processes needed to set a more equitable antimicrobial innovation agenda 8
 - The inadequacy of regulation of antimicrobials, including of clinical trials 9
 - New methods needed to assess the value of antimicrobial innovation10
 - 1.3 Access challenges in the market for antimicrobials.....12
 - Inadequate access to off-patent medicines13
 - Inadequate access to on-patent medicines15
 - Some current solutions to access challenges.....16
 - Ensuring that antibiotics reach the people who need them19
 - 1.4 Stewardship challenges in the market for antimicrobials19
 - The fine balance of strengthening stewardship while ensuring access20
 - Targets for stewardship and the appropriate use of antimicrobials22
 - Current targets for stewardship and appropriate use22
- 2. Recommendations..... 27**
 - 2.1 Political recommendation 27
 - Recommendation 1: Establish a new “Grand Bargain” to improve the antimicrobial market for human health..... 27
 - 2.2 Operational recommendations..... 29
 - Recommendation 2: Implement a sustainable access hub for antimicrobials..... 29
 - Recommendation 3: Ensure that innovation is properly valued and meets the needs of LMICs 32
 - Recommendation 4: Strengthen regional regulatory processes 33
 - Recommendation 5: Enact systems to track access and control and measure the unnecessary use of antimicrobials..... 34

Recommendation 6: Set targets to track progress on innovation, access, and stewardship goals.....	35
Acknowledgments	37
References	42
Annex A. Research Projects Undertaken as Part of the Working Group	46
Annex B. Policy Recommendations Included in the Case Studies of India and Brazil	48
Annex C. Illustrative Example of the Text of a Grand Bargain.....	49

Figures

Figure ES.1. Overview of the proposed Grand Bargain to Improve the Antimicrobial Market for Human Health....	ix
Figure ES.2. Overarching aim and proposed benefits of a sustainable access hub for antimicrobials.....	x
Figure 1. Rates of resistance of key antibiotics, 2002–20	2
Figure 2. Three factors needed for a sustainable antimicrobial market: innovation, access, and stewardship.....	3
Figure 3. Mismatch between share of clinical trials and global burden of disease for bacterial infections.....	5
Figure 4. Relative use of Access antibiotics	24
Figure 5. Global distribution of medical staff	25
Figure 6. Overview of recommendations of the CGD’s Working Group A New Grand Bargain to Improve the Antimicrobial Market for Human Health.....	27
Figure 7. Overview of the proposed Grand Bargain for Antimicrobial Innovation, Access, and Stewardship	28
Figure 8. Overarching aim and proposed benefits of a sustainable access hub for antimicrobials	30

Tables

Table 1. Annual burden of antimicrobial resistance.....	1
Table 2. Estimated number of lives saved and return on investment from a pull mechanism for new antimicrobials in selected countries	7
Table 3. Global costs and benefits of a subscription model after 10 and 30 years	8
Table 4. The STEDI framework for valuing antimicrobials.....	10
Table 5. Attributes of antibiotic value to be used in the Methods, Attributes, Procedures, and Social Preferences (MAPS) tool	11
Table 6. Number of antimicrobials in each AWaRe category.....	13

Boxes

Box 1. Key features of reimbursement systems in the United Kingdom and Sweden.....	6
Box 2. Health technology assessments in the United Kingdom’s subscription model.....	11
Box 3. The AWaRe classification.....	12
Box 4. Lack of access to antimicrobials in low-income countries.....	13
Box 5. The Shionogi, GARDP, and CHAI partnership for the rollout of cefiderocol	16
Box 6. Supporting treatment for tuberculosis through the Global Drug Facility.....	17
Box 7. Strategically stockpiling selected antibiotics.....	18
Box 8. Delinking payments from sales volume in out-of-pocket payment systems.....	21
Box 9. Lessons from the international control of opioids.....	23
Box 10. Using a model to assess the need for antimicrobials.....	25

Foreword

The Center for Global Development (CGD) established its first working group on antimicrobial resistance in 2007, with the final report published in 2010. In her preface to the report, my predecessor, Nancy Birdsall, wrote that “as with climate change, we now understand the science of drug resistance well enough to act, but the policy response has eluded us.” Rereading that report, it is striking both how much has changed and how much remains the same. All four of the report’s recommendations could be reissued today to address the glaring inequalities that still exist, but progress has been made. The supply chain for drugs is more secure, and the standards of drugs have improved. There is far greater government funding for clinical research, and many countries are exploring innovative ways to purchase crucial drugs. Most strikingly, improvements in surveillance mean we now know the catastrophic consequences of antimicrobial resistance, with 5 million people dying each year with a drug-resistant infection.

When that work started, 16 years ago, so many of the policy problems had no obvious solutions. Today, many workable solutions have been found for issues including reducing antibiotic use in agriculture, incentivizing new drugs without incentivizing unnecessary use, and rolling out diagnostics and setting targets for appropriate use. More important still, the problem can no longer be said to be an “extremely serious problem... that does not receive serious attention.” Antimicrobial resistance was discussed in most G7 and G20 communiqués in the last decade, and in 2016, it became the fourth health topic to be addressed at a UN General Assembly High-Level Meeting.

Yet despite all of this progress, the fundamental point remains the same: Not enough is being done to stop the relentless advance of drug resistance. Collective action problems have hampered implementation of many proposals that would reduce the dangers of resistance. And insufficient progress has been made in identifying policy solutions to the problems faced by low- and middle-income countries (LMICs). In response, in early 2022, CGD convened a working group—*A New Grand Bargain to Improve the Antimicrobial Market for Human*

Health—that brought together key figures from governments, international organizations, civil society, and industry.

The working group’s final report highlights the stark disparity in research on policy issues relevant to LMICs when compared with high-income countries (HICs), with less than 10 percent of the academic literature examined focusing on the former group. Different stakeholders have very different policy priorities, with those in HICs more inclined to emphasize the need for innovative new drugs while LMIC policymakers view access as a much greater priority. Countries often think it is not in their interest to implement policies that most agree all countries would benefit from. Global cooperation is needed to overcome collective action problems.

Thankfully, the experts’ consensus view is a mutually beneficial deal - or Grand Bargain - to solve this problem is possible. Any agreement should seek to fund the innovation of new antimicrobials that meet all countries’ needs, facilitate access for people across the world, and protect the treatments from inappropriate use. A healthy market for antimicrobials relies on delivering on and balancing three objectives: innovation, access, and stewardship. The report highlights five steps to operationalize the goals in the Grand Bargain. Governments and international organizations should start taking steps immediately to implement these goals.

Next year is an important year in the fight against drug resistant infections, as the United Nations will hold its second High-Level Meeting on antimicrobial resistance. Now is the time to build on the work that CGD and so many others have produced over the last 16 years to create a robust market for antimicrobials that meets the world’s needs.



Masood Ahmed

Center for Global Development
President

Acronyms

aHTA	adaptive health technology assessment
AMR	antimicrobial resistance
AWaRe	Access, Watch, and Reserve
BPPL	Bacterial Priority Pathogen List
CARB-X	Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centers for Disease Control and Prevention
CGD	Center for Global Development
CHAI	Clinton Health Access Initiative
DDD	defined daily dose
EEPRU	Economic Evaluation of Health and Care Interventions
ESO	eco-system orchestrator
GARDP	Global Antibiotic Research and Development Partnership
GDF	Global Drug Facility
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GRAM	Global Research on Antimicrobial Resistance
HIC	high-income country
HTA	health technology assessment
LIC	low-income country
LMICs	low- and middle-income countries
MAPS	Methods, Attributes, Procedures, and Social Preferences Framework
NAP	National Action Plan
PAHO	Pan American Health Organization
PASTEUR	Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act
QALY	Quality-Adjusted Life Year
R&D	research and development
TB	tuberculosis
TPP	target product profile
WHO	World Health Organization

The Working Group, the Center for Global Development, and this Report

This report outlines the findings of the Center for Global Development's (CGD) working group on *A New Grand Bargain to Improve the Antimicrobial Market for Human Health*. This working group, convened in 2022, builds on CGD's previous research and analysis on antimicrobial resistance (AMR) and health product markets to examine policy options for improving antimicrobial innovation, access, and stewardship in low- and middle-income countries (LMICs) and driving global action against AMR.

Working group members:

- ▶ **Javier Guzman**, Center for Global Development (Chair)
- ▶ **Anthony McDonnell**, Center for Global Development (Technical lead)
- ▶ **Manica Balasegaram**, the Global Antibiotic Research and Development Partnership (GARDP)
- ▶ **Siddhartha Bhattacharya**, NATHEALTH
- ▶ **Thomas Cueni**, International Federation of Pharmaceutical Manufacturers and Associations
- ▶ **Austen Davis**, Norwegian Agency for Development Cooperation
- ▶ **Steve Isaacs**, Aduro BioTech
- ▶ **Mahlet Kifle Habtemariam**, Africa Centres for Disease Control and Prevention
- ▶ **Jayasree Iyer**, Access to Medicine Foundation
- ▶ **Jeremy Knox**, Wellcome Trust
- ▶ **Mirfin Mpundu**
- ▶ **Badri Narayanan**, National Institution for Transforming India
- ▶ **Tochi Okwor**, Nigeria Centre for Disease Control
- ▶ **Kevin Outtersson**, Boston University and the Combating

Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

- ▶ **Milton Ozorio Moraes**¹, Fiocruz
- ▶ **Naomi Rupasinghe**, World Bank
- ▶ **Rachel Silverman Bonnifield**, Center for Global Development
- ▶ **Faisal Sultan**, Former Special Assistant to the Prime Minister of Pakistan
- ▶ **Yot Teerawattananon**, Health Intervention and Technology Assessment Program (HITAP)
- ▶ **Brenda Waning**, Stop TB Partnership, United Nations Office of Project Services (UNOPS)
- ▶ **Prashant Yadav**, Center for Global Development

Katherine Klemperer and **Morgan Pincombe** supported the working group.

This diverse group included global antimicrobial resistance leaders, including government officials, heads of global health institutions, representatives from the pharmaceutical industry, funders, and health care providers from low-, middle-, and high-income countries. Representation spanned a range of countries, including Brazil, Kenya, India, Nigeria, Norway, Thailand, the United Kingdom, the United States, and Zambia.

Many important areas need to be addressed to tackle the AMR challenge. For example, improved infection prevention and control, including expanding access to vaccines and clean water, is needed to stop resistant pathogens from spreading and reduce the demand for antimicrobials. Investments in human capital are needed so that doctors, nurses, pharmacists, and other health professionals can improve the quality of

¹ CGD mourns the loss of Milton Ozorio Moraes, a wonderful colleague and valued member of this working group who passed away in November 2022

the care they provide. Rather than address all of these issues, the working group focused on improving innovation, access, and stewardship of antimicrobials because finding collective solutions to these issues is likely to yield significant rewards in the fight against AMR and cooperation is likely to result in significant positive synergies.

The working group met three times: a virtual meeting in May 2022, at an in-person meeting in London in January 2023, and at a virtual meeting in July 2023. In advance of these meetings, policy recommendations were shared with working group members and other key stakeholders for comment. The report's content is based on the deliberations of the working group and a range of research pieces and analyses that CGD's research team either conducted or commissioned. Every working group member had the opportunity to view this report and provide feedback, which CGD incorporated.

However, working group members do not necessarily endorse all components of this report, nor do the contents of this report constitute a policy commitment by any party. All errors and omissions are those of the authors.

The report was funded by the Wellcome Trust. CGD is an independent and nonpartisan research institution. There are no conditions or limitations on CGD's independence in research, findings, conclusions, or resulting publications. Where appropriate, CGD may welcome and consider comments or views from funders, but CGD retains total discretion and final decision-making authority over program and project research topics, speakers, participants in activities, and the content of reports. For a list of the many people we would like to thank for supporting this work, please see the acknowledgements section on page 37.

Executive Summary

Every year, antimicrobial resistance (AMR) directly causes 1.27 million deaths and is associated with an additional 3.7 million deaths (Murray et al. 2022). Low- and middle-income countries (LMICs) bear the brunt of this burden, accounting for nearly 90 percent of the direct death toll and over 99.5 percent of AMR-related deaths among children under five (McDonnell and Klemperer 2022). Already, more people die directly from AMR than from HIV/AIDS, malaria, or any one form of cancer other than lung cancer (Murray et al. 2022; Roser and Ritchie 2019). And the problem of AMR is only growing: Without effective antibiotics, it has been estimated that 10 million people a year could die from AMR—equivalent to the annual death toll from all cancers (Review on Antimicrobial Resistance 2016). Some life-saving surgeries and treatments, including transplants will not be possible, because the risks from these procedures will be too high without effective antibiotics (Davies, Grant, and Catchpole 2013).

Tackling AMR requires global consensus and action on many fronts. Creating an antimicrobial market that ensures adequate innovation, access, and stewardship is key to fighting AMR. Improving infection prevention and control, increasing surveillance, and reducing antibiotic use in agriculture are also critical.

Progress has been made to garner political commitment to tackle AMR, including through high-level commitments at the 2015 World Health Assembly and the 2016 UN General Assembly. More than 170 National Action Plans (NAPs) were developed to formalize government responses to AMR (WHO 2023e). New R&D initiatives have been created (such as CARB-X, GARDP, and the AMR Action Fund), and some countries have started to pilot new ways to value and procure antibiotics, including the United Kingdom's subscription model

and Japan's pilot for a revenue guarantee system. Surveillance systems have been improved through the Fleming Fund, and better data for decision making are available via the R&D Hub.

These policies and commitments are laudable, but collective action problems still stand in the way of realizing a new international approach to the antimicrobial market. Fewer than 20 percent of NAPs have been fully funded and implemented (WHO 2022c). The pipeline of innovative antibiotics is insufficient to tackle the challenge of AMR (World Health Organization 2022a), and the funding gap for early-stage product development is at least \$250 million a year (European Commission and Agency 2023).

Building on its previous research and analysis on AMR, in 2022, CGD launched the working group *A New Grand Bargain to Improve the Antimicrobial Market for Human Health* to examine policy options to drive global action against AMR. This report outlines the findings from the working group, which includes the principles of a Grand Bargain that we believe all stakeholders can and should sign up to during the UN General Assembly's High-Level Meeting in 2024.

BALANCING ANTIMICROBIAL INNOVATION, ACCESS, AND STEWARDSHIP

The current market for antimicrobials fails to spur research and development (R&D), ensure access to new and existing products, and protect against overuse. These three objectives—innovation, access, and stewardship—must be balanced to ensure sustainability and equity. Global commitment and action are needed to overcome collective action problems and realize a new market structure for antimicrobials.

Inadequate innovation

The R&D pipeline for antimicrobials is—and for decades has been—dry. The number of new antibiotics approved by the US Food and Drug Administration fell from 16 in 1983–87 to 3 in 2008–12—a decline of 81 percent (Luepke et al. 2017). Resistance buildup is outpacing innovation, and the innovation agenda does not sufficiently reflect the needs of LMICs. Methods to assess the value of antimicrobial treatments fail to adequately value all benefits derived from antimicrobials. As a result, remuneration is insufficient to encourage innovation, and market entry in many countries is limited. Analysis conducted as part of this working group offers a new assessment framework that can integrate LMIC priorities, including affordability, accessibility, ease of administration, heat stability, and wide applicability.

Amidst persistent challenges, some recent positive developments have occurred in antimicrobial innovation. Payouts contingent on R&D success (“pull incentives”) have been piloted in the United Kingdom and Sweden and proposed in the United States, Japan, Canada, and the European Union. Estimates suggest that the domestic return on such investments would be as high as 28:1 (Towse and Silverman Bonni- field 2022). Further implementation of these mechanisms, coupled with higher levels of “push funding” (upfront funding for R&D), are needed to fill the significant remaining gaps in the innovation pipeline (Towse and Silverman Bonni- field 2022).

Inadequate access

Inadequate access to existing and new antimicrobials is a leading cause of death from AMR infections and a key priority in the AMR response in LMICs (McDonnell et al. 2022). Alongside the moral imperative to expand access to essential medicines, widespread availability of essential treatments is needed to help decrease transmission and limit inappropriate use of other antimicrobials used when first-line treatments are inaccessible, reducing the risk of diseases spreading to the whole world.

Most antibiotics are off-patent (Madden and Outtersen 2023). Manufacturers of these drugs face thin margins and minimal

incentives to invest in supply chain flexibility and resiliency. Shortages of amoxicillin—a key off-patent medicine—were recorded in late 2022 and early 2023 in 80 percent of the 35 countries for which the World Health Organization (WHO) had data (Mancini and Kuchler 2022). Greater supply chain resiliency is needed, but collective action problems disincentivize procurers from paying the price.

On-patent antimicrobials are often unavailable (due to high barriers to market entry) and unaffordable. Initiatives such as the partnership created by the pharmaceutical company Shionogi, the Global Antibiotic Research and Development Partnership (GARDP), and the Clinton Health Access Initiative (CHAI) to ensure the successful rollout of their novel antibiotic cefiderocol and efforts by the Global Drug Facility to roll out safe, effective, and affordable tuberculosis treatments provide lessons and potential models for future interventions to address access issues for off-patent and on-patent treatments.

Inadequate stewardship

The current market for antimicrobials contains structural failures and perverse incentives that undermine stewardship, contribute to higher levels of inappropriate use, and drive up resistance rates. Stewardship refers to the appropriate use of antimicrobials to ensure that their efficacy is maintained over time. Adequate stewardship measures must be imposed to support appropriate use of Reserve and Watch category drugs, as defined by the WHO’s AWaRe classification. Prescription policies and reporting databases could be leveraged to strengthen stewardship, but they must allow countries sufficient flexibility to sustain and expand access to antibiotics at a level commensurate with local disease burden. Countries need targets for antimicrobial usage that are measurable (to facilitate accountability) and absolute (so that they can be tailored to national circumstances).

RECOMMENDATIONS

This report presents recommendations on increasing the availability of critically needed drugs, creating incentives to develop new ones, and reducing market pressures to misuse

or oversell the drugs. It provides one political and five operational recommendations. The political recommendation outlines why it is both possible and in everyone's interest to overcome the collective action problems inherent in dealing with market failures in the antimicrobial market through a global agreement. The five operational recommendations describe actions countries could take to begin to implement such a deal.

Political recommendation

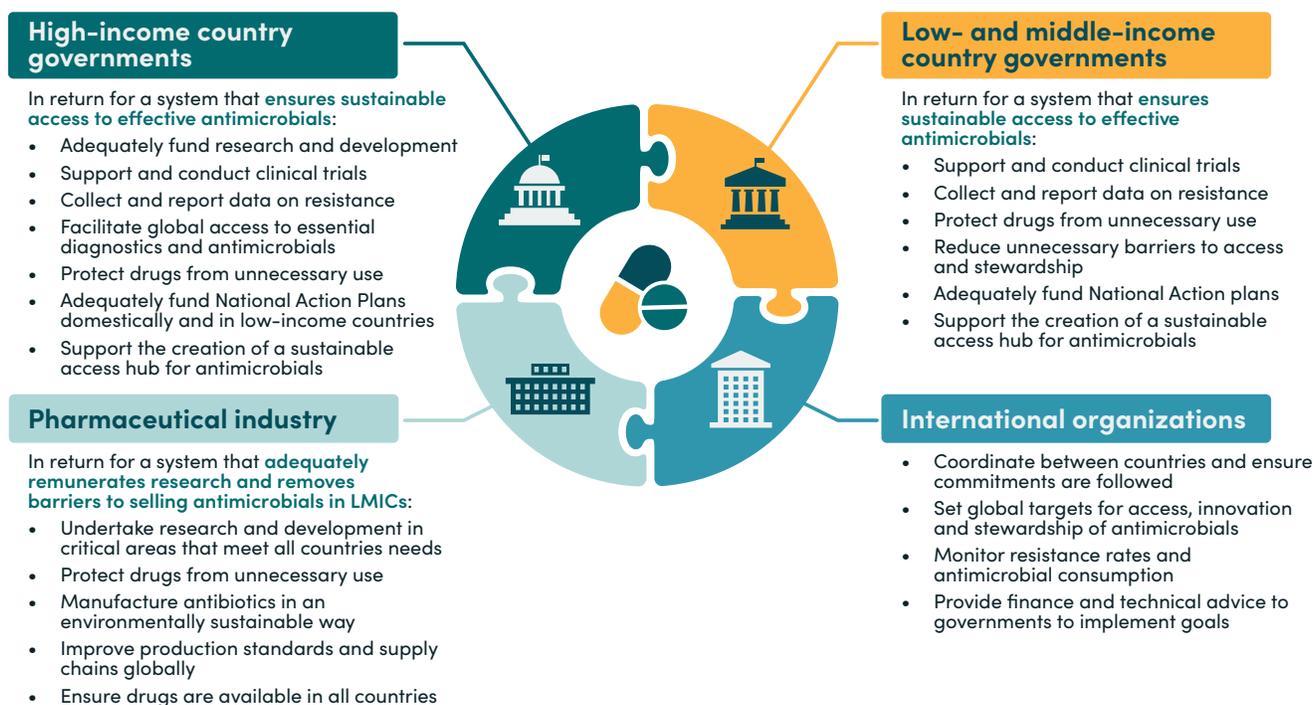


Recommendation 1: Establish a new “Grand Bargain” in the antimicrobial market for human health

Countries should negotiate and agree on a new political understanding (or Grand Bargain) on antimicrobials at the UN General Assembly High-Level Meeting on AMR in 2024. A Grand Bargain is both achievable and in everyone's interest (figure ES.1). It should set out commitments for countries,

international organizations, and the pharmaceutical industry to ensure the adequate functioning of antimicrobial procurement systems. It should ensure that countries protect antimicrobials from unnecessary use, contribute toward R&D for new treatments, and ensure that essential antibiotics reach people who need them, including by creating a system that facilitates the distribution of drugs in countries not well served by current systems. International organizations—which include UN bodies like the WHO, international finance institutions like the World Bank, and regional health organizations like the African Centres for Disease Control and Prevention—have a role to play in coordinating and monitoring the system. Industry should commit to conducting research on new treatments, including those that meet the needs of LMICs, and ensure equitable access to drugs in exchange for a system that engenders adequate remuneration and supports appropriate distribution.

FIGURE ES.1 Overview of the proposed Grand Bargain to Improve the Antimicrobial Market for Human Health



Operational recommendations



Recommendation 2: Implement a sustainable access hub for antimicrobials

A sustainable access hub (or hubs) should be established to address issues in the antimicrobial market, including demand fragmentation and low volumes, that contribute significantly to access challenges, especially in LMICs (figure ES.2). The hub would serve primarily as a backstop to facilitate access to essential antimicrobials and diagnostics in settings where the market is currently failing. It could be a global entity or a series of regional initiatives; its functions could be handled by one organization or divided among and led by several.

Six key functions would help deliver on the hub's goals:

- ▶ supporting procurement of an essential portfolio of antimicrobials and diagnostics
- ▶ facilitating registration and distribution of these products
- ▶ shaping the antimicrobial market as a large procurer
- ▶ improving the tracking of global antimicrobial consumption
- ▶ ensuring that purchasers meet the WHO's stewardship and access standards
- ▶ managing or supporting financial and technical assistance for resource-constrained countries to implement stewardship and surveillance systems.



Recommendation 3: Ensure that innovation is properly valued and meets the needs of LMICs

High-income countries (HICs) should implement funding systems, including push and pull incentives, that attract investment for treatments that meet the needs of all countries. To better guide global innovation, the WHO should employ new methods to determine the Priority Pathogen List and develop target product profiles (TPPs) that better reflect the disease burden in, and priorities of, LMICs. Procurement decisions in all countries should be guided by assessment frameworks that adequately assess the value of antimicrobial innovation. This report outlines an assessment framework designed to be flexible enough to accommodate local contexts, needs, and preferences.



Recommendation 4: Strengthen regional regulatory processes

Robust regional approaches to regulating antimicrobials could streamline the approval of clinical trials; reduce the time to issue marketing authorization while guaranteeing consistent standards for safety, efficacy, and quality; and improve post-marketing vigilance and surveillance. Regional regulatory approaches would enhance resource utilization, especially in low-income countries (LICs), where mature, functional systems and regulatory capacity are limited. In addition to expanding timely access to antimicrobials, regional approaches could support regional procurement.

FIGURE ES.2 Overarching aim and proposed benefits of a sustainable access hub for antimicrobials



Benefits:

- **Ensure access** access to quality assured products by reducing barriers to entry including facilitating product registration
- **Reduce inappropriate use of antimicrobials** by providing diagnostics, financial and technical assistance, and reducing incentives to oversell
- **Help countries track and report** consumption data to WHO's GLASS platform
- **Reduce shortages** by shaping markets and forecasting and aggregating demand, tracking suppliers' capacity, and stockpiling where necessary
- **Reduce prices** of medicines through pooled procurement and multi-year contracts



Recommendation 5: Enact systems to track access and control and measure the unnecessary use of antimicrobials

Countries should enact policies to reduce unnecessary use and develop robust tracking systems to measure the impact of such policies. Control policies should be tailored to the type of antimicrobial and include a prescription policy for Reserve (and where appropriate, Watch) category antimicrobials. These policies should be coupled with a reporting database for Reserve antibiotics and be underpinned by robust data systems and access to diagnostics. Such a system for controlling and tracking antimicrobial usage will be a critical step in the implementation of the Grand Bargain. These systems should also be built with access in mind so that they track when essential antibiotics are not available to treat patients.



Recommendation 6: Set targets to track progress toward innovation, access, and stewardship goals

Specific, measurable, achievable, relevant, and timebound targets are essential to implementing any international agreement on tackling AMR. Countries could set them at the High-Level Meeting on AMR at the 2024 UN General Assembly. These targets could include (a) the percentage of people with justified need who are able to access effective and affordable antimicrobials, (b) the justified level of antimicrobial consumption in each country, and (c) the number of innovative new products in the antimicrobial pipeline. This report identifies methodologies that could be used to set targets. To support implementation, countries could also receive guidance, technical assistance, and, in resource-constrained environments, the funds to help meet the targets.

Problems with the Antimicrobial Market

1.1 KEY CHALLENGES

In 2019, the World Health Organization (WHO) declared antimicrobial resistance (AMR) one of the top 10 global public health threats facing humanity (WHO 2019). The threat is indeed grave: every year, AMR directly leads to 1.27 million deaths, and another 3.7 million people die from a drug-resistant infection that was not considered the primary cause of death (Murray et al. 2022). More people die every year directly from AMR than from HIV/AIDS, malaria, or any one form of cancer other than lung cancer (Murray et al. 2022; Roser and Ritchie 2019).

The majority of this burden falls on low- and middle-income countries (LMICs), where nearly 90 percent of the 1.27

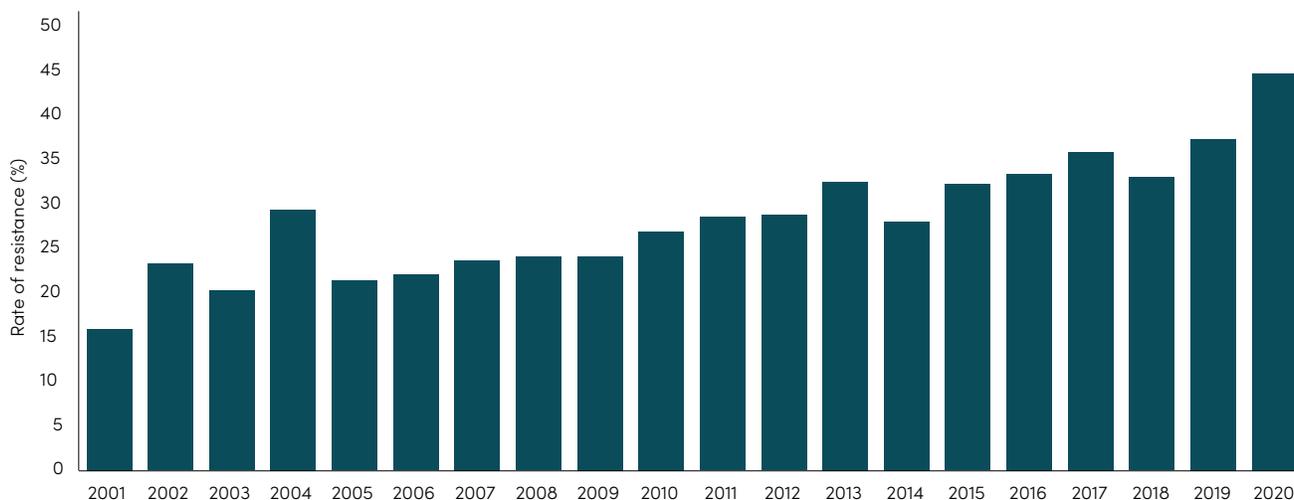
million direct deaths from AMR occur. Each death in an LMIC is responsible for an average of 40 years of life lost. In sub-Saharan Africa, the number is even higher, at 60—compared with 17 in high-income countries (HICs). This contrasting burden is explained to a great extent by the stark inequity affecting children under five, among whom over 99.5 percent of deaths are in LMICs (McDonnell and Klemperer 2022; Murray et al. 2022) (table 1).

The world is already facing a crisis; without concerted action, the situation is projected to worsen. Resistance rates are increasing among many pathogens, and many vital antibiotics are becoming less effective. A systematic literature review of resistance rates to 15 key antibiotics conducted with Boston University as part of this working group shows a clear increase

TABLE 1 Annual burden of antimicrobial resistance

COUNTRY GROUP	TOTAL DIRECT DEATHS FROM AMR		DIRECT DEATHS FROM AMR AMONG CHILDREN UNDER FIVE		
	NUMBER	PERCENTAGE OF DEATHS FROM ALL CAUSES	NUMBER	PER 100,000 CHILDREN UNDER FIVE	AVERAGE NUMBER OF LIFE YEARS LOST PER AMR DEATH
High-income countries	141,000	1.1	893	1.4	17
Low- and middle-income countries	1,129,000	2.7	252,833	40.8	40
Sub-Saharan Africa	317,500	2.4	128,900	75	60

FIGURE 1 Rates of resistance of key antibiotics, 2001–20



Source: McDonnell et al. forthcoming.

Note: The drugs included were amoxicillin, amoxicillin-clavulanic acid, azithromycin, cefalexin, cefotaxime, ceftriaxone, ciprofloxacin, clarithromycin, cloxacillin, doxycycline, flucloxacillin, gentamicin, metronidazole, ofloxacin, and sulfamethoxazole-trimethoprim. The results are averaged across all drug-bug combinations and weighted by the sample size of the study.

in resistance over time (figure 1). Resistance rates increased by an average of 0.84 percent a year when controlling for the study, bacteria, and drug fixed, indicating that changes in resistant rates were not driven by site selection (McDonnell et al. forthcoming). Over 80 percent of experts interviewed as part of this study believed that four essential drugs (amoxicillin, cefalexin, ciprofloxacin, and cloxacillin) will very likely be lost to resistance within the next 15 years and therefore require replacement.

Without effective antibiotics, many people will die from resistant infections. In 2014, the United Kingdom's Independent Review on AMR estimated that by 2050, 10 million people a year could die from AMR—equivalent to the annual death toll from all cancers. Some life-saving surgeries and treatments, including transplants, will not be possible because the risks from these procedures will be too high without effective antibiotics (Davies, Grant, and Catchpole 2013; Hall, McDonnell, and O'Neill 2018).

Insufficient global action

Over the past decade, several stakeholders have taken steps to address the AMR challenge. The 2015 World Health Assembly adopted a landmark Global Action Plan on AMR, harmonizing

and coordinating global commitments to address it. In 2016, AMR featured on the UN General Assembly agenda—only the fourth time a health topic had been included for debate. Its inclusion led to an aspirational political declaration that made few concrete commitments other than echoing the World Health Assembly's call on all countries to create their own National Action Plans (NAPs) to address AMR. In response, 170 governments developed NAPs, acknowledging the threat of AMR and formalizing their policy response (WHO 2023e). The WHO established the Global Antimicrobial Resistance and Use Surveillance System (GLASS) to standardize AMR surveillance and generate data to ultimately inform policies. It also convened the Global Leaders Group, an expert group to advance AMR political commitments and action to address the AMR pandemic. Other high-level commitments to tackle AMR have been issued by the World Health Assembly, the G20, and the G7 (WHA 2019; G20 Leaders 2022; G7 Health Ministers 2022).

As part of these commitments, several stakeholders have developed and implemented policy solutions to increase investment in antimicrobial innovation, secure access to critical drugs, and reduce unnecessary use (to preserve their effectiveness). Examples include a range of “push” incentives that subsidize the cost of R&D through funding or changes in

regulation, and “pull” incentives that help generate revenue for successfully developed products (Cama et al. 2021). A few nonprofit initiatives, such as the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic Research and Development Partnership (GARDP); public-private R&D partnerships, such as the AMR Action Fund; and impact investment funds, such as the REPAIR Impact Fund, contribute the bulk of push funding for antimicrobial innovation. Additional proposed and implemented incentives are positioned to spur further antimicrobial R&D, including pull incentives led by the G7 (G7 Health Ministers 2022).

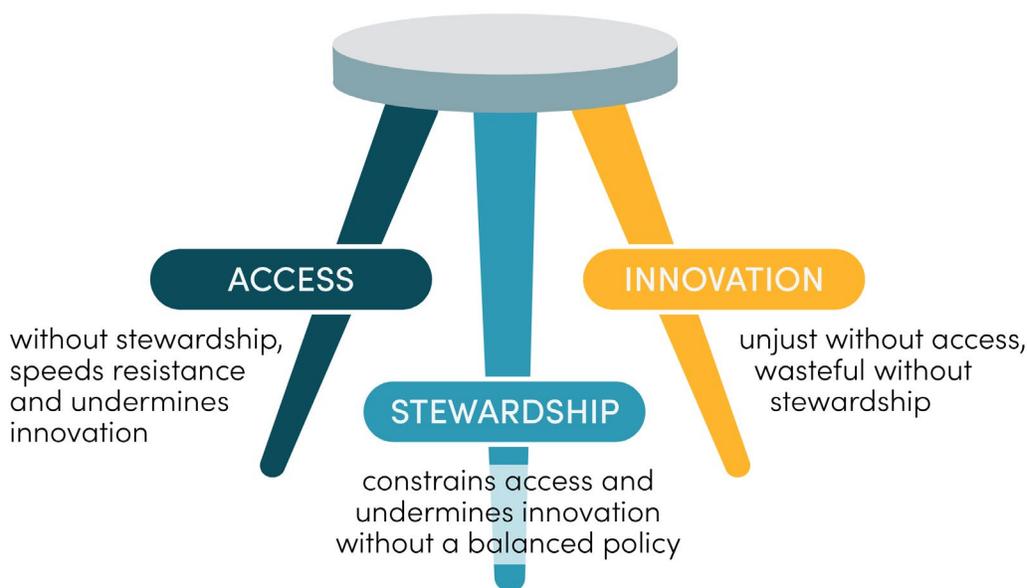
Despite these political commitments, no fundamental change has occurred in the international approach to tackling AMR by spurring innovation, improving access, or reducing unnecessary use. For example, 170 countries now have NAPs, but fewer than 20 percent of them have been fully funded and implemented (WHO 2022c). R&D funding has increased significantly, but it has not reached the levels deemed necessary by most expert panels. Part of the reason for the lack of action

is a collective action problem.² Given that all countries will reap the benefit of any action to tackle AMR, but the costs often fall on the countries that take action, individual countries are insufficiently motivated to act (Weldon et al. 2022). Without clear political benefits for action or penalties for inaction, policymakers often struggle to mobilize support and resources for adequate investment in the AMR response.

The three pillars of sustainability: innovation, access, and stewardship

The current market for antimicrobials fails to adequately incentivize the development of new products and secure sufficient access to new and existing antibiotics, and it incentivizes overuse, by linking profit to the volume of sales. The market falls short on the three key pillars that form the foundation of any sustainable approach: innovation to develop new drugs, access to existing and new antimicrobials, and stewardship to protect drugs from overuse (figure 2). Given the interplay among these three objectives, any system lacking any one of them will not be sustainable. Without innovation, urgently needed new drugs will not be developed; without access, the

FIGURE 2 Three factors needed for a sustainable antimicrobial market: innovation, access, and stewardship



Adapted from: Hoffman and Outtersson 2015.

² A collective action problem arises when multiple parties would benefit from an action but have an incentive to let others do it instead. Individual self-interest prevents action from being taken that would leave all parties better off.

people in greatest need may be unable to obtain the drugs they need, allowing resistant infections to spread; without stewardship, widespread inappropriate and overuse can lead both new and existing drugs to rapidly become ineffective. The problems associated with each of these areas differ for on- and off-patent antimicrobials.

The research on feasible and effective solutions is weak, especially in LMICs, where the burden of AMR is highest. A systematic review of academic and grey literature and interviews with 28 experts conducted for this report highlight the dearth of research on how to effectively and sustainably secure innovation, access, and stewardship of antimicrobials in LMICs (McDonnell et al. 2022). About half (51 percent) of papers mention an LMIC (72 out of 141 papers identified), but most do so in only passing, and less than 10 percent (14 of 141) focus exclusively on LMICs. Just 12.5 percent of papers with listed authors (16 of 128) included any authors based in an LMIC; 95 percent of authors were based in HICs.

Both the interviews and the literature review highlight how LMIC- and HIC-based groups often have very different priorities. Interviewees in LMICs focus more on access to drugs, whereas researchers in HICs are more concerned about innovation. Both groups highlight stewardship as a priority. The landscape analysis found broad agreement that international coordination and new antimicrobial purchasing arrangements are needed to improve antimicrobial procurement in LMICs. Differences in countries' incentives and interests suggest that a negotiated deal, or Grand Bargain, is needed to integrate and balance these different priorities, prevent stakeholders from losing out, and protect the system from collapse (McDonnell et al. 2022; Laxminarayan 2022).

The literature review and interviewees also highlight the significant research gaps that constrain political agreement or policy action. This finding was used to frame the research agenda undertaken as part of the working group, including three country case studies (of Brazil, India, and Kenya) to better understand the local context of antimicrobial markets (see annex A for a list of research projects and annex B for recommendations included in the case studies of Brazil

and India). The rest of this report examines the challenges identified by these research projects and the solutions that come from them. As innovation is the first stage in the life of a new product, followed by ensuring people are able to use it and then protecting it from inappropriate use, we discuss the issues in this order.

The recommendations included in this report come from an array of sources. Ideas were taken from a review of the literature; discussions with working group members, a wide array of stakeholders, and the public; and formal feedback from experts and key stakeholders. We put them forward as ideas that we believe will greatly improve public health, but do not seek any ownership of or monopoly over them.

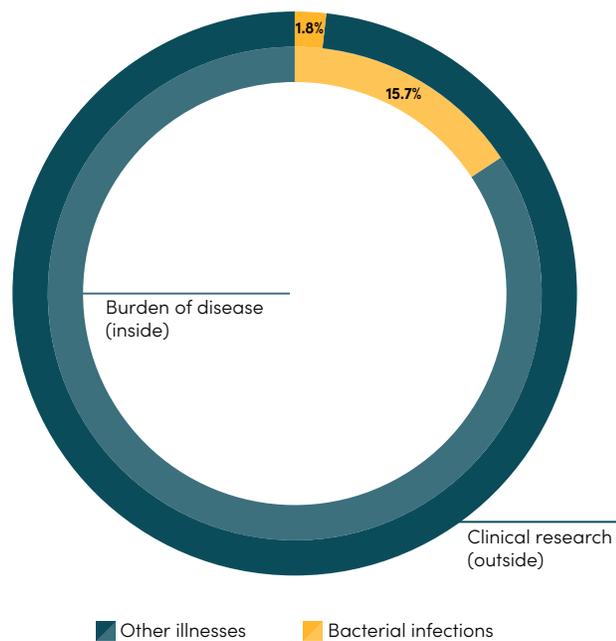
1.2 INNOVATION CHALLENGES IN THE MARKET FOR ANTIMICROBIALS

Problems throughout the R&D and market entry continuum and an overall lack of incentives have resulted in a dearth of antimicrobial innovation. This section examines the overall situation and specific issues at each stage: the lack of adequate R&D financing, difficulties determining what new products are needed, the challenges and shortcomings of the current regulatory system, and the systematic undervaluation of antimicrobials by health technology assessment systems (the systems used to determine the value of a medical intervention, considering medical, economic, social, and ethical issues) (European Commission n.d.).

Overview of innovation problems

Despite the grave threat AMR will pose in the future and the heavy burden it imposes today, efforts to find new treatments have been limited. Fewer than 1.8 percent of the 13,605 Phase II and Phase III clinical trials recruiting patients as of August 21, 2023 relate to bacterial infections (as tracked on clinicaltrials.gov), even though 15.7 percent of global deaths are from bacterial infections, more than half of which are linked to resistance (Ikuta et al. 2022). Figure 3 demonstrates this mismatch between the scale of the problem and the amount of research into potential solutions.

FIGURE 3 Mismatch between share of clinical trials and global burden of disease for bacterial infections



Sources: United States National Library of Medicine n.d.; Institute for Health Metrics and Evaluation (IHME) 2023; Institute for Health Metrics and Evaluation (IHME) and University of Oxford 2023.

Note: The number of Phase II and III clinical trials related to bacterial infections was assessed by inserting the search term bacterial into the condition or disease search box on clinicaltrials.gov and applying four filters to the search: “Phase II” OR “Phase III,” “intervention,” and “recruiting.” The total number of Phase II and III trials was found using the same search terms, without any condition or disease indicated. Searches were conducted August 21, 2023.

The R&D gap for antimicrobials is massive and has grown over time. Over 25 years, the number of new antibiotics approved by the US Food and Drug Administration declined by 81 percent, from 16 in 1983–87 to 3 in 2008–12 (Luepke et al. 2017). No new class of antibiotic has been discovered since 1987 (ReAct n.d.).

The problem is not just the number of new products but also their efficacy. A WHO assessment of the 60 antibiotics in development in 2020 found that these potential products had little benefit over existing drugs, with very few targeting the most critical resistant bacteria. So serious is the inadequacy

of the pipeline of new antimicrobials that the WHO noted that the lack of innovation is “undermining efforts to combat drug-resistant infections” (WHO 2020).

Innovation is urgently needed to develop new antimicrobials to replace those being lost to resistance. However, under the current procurement system, the return on investment is not sufficient to generate the private investments needed. The revenue a company makes on a drug is determined by the price and volume sold. For antimicrobials, any new drug developed would ideally be kept in reserve as a last resort in order to preserve its efficacy—and thus have a low sales volume. Further, health technology assessments do not sufficiently value all of the benefits derived from antimicrobials (see page 10). As a result, prices could be unreasonably low and market entry is limited in various countries.

Governments need to ensure that purchasing systems compensate drug developers sufficiently, even if they are not the direct purchasers. About \$3.1 billion in global pull incentives per antibacterial medicine per decade would be needed to do so (Outtersson 2021).

Some governments have recognized the need for action. At the May 2023 summit, for example, the G7 health ministers continued to “commit to exploring and implementing push and pull incentives that promote investment in R&D of antimicrobials” (G7 Health Ministers 2023).³ However, few HICs have implemented systems that will achieve the innovation goals required. Issues such as free riding further limit policy change.⁴ Despite these challenges, several countries have made progress (box 1).

Some positive developments occurred in recent years. The level of push funding available to pharmaceutical companies engaged in antimicrobial R&D increased significantly. In the first six years after its launch in 2016, for example, the nonprofit CARB-X awarded \$398.2 million dollars to product developers, accelerating 92 R&D projects (CARB-X 2023).

3 Funding for R&D can be categorized as either push funding (which subsidizes research early in the process, helping companies “push” a product to market) or pull funding (which rewards research output and so “pulls” a product to market). Both are crucial for a healthy antimicrobial pipeline.

4 As all countries would benefit from the investment made by one in a purchasing system but only the country funding a pull incentive picks up the cost, the incentive for individual countries to invest without collective action is reduced.

BOX 1. KEY FEATURES OF REIMBURSEMENT SYSTEMS IN THE UNITED KINGDOM AND SWEDEN

The United Kingdom's National Health Service (NHS) offers reimbursement of products via delinked payment contracts for up to £20 million (\$25 million) per year. Each year, in return for the use of its product in the NHS, the manufacturer receives a fixed annual payment, irrespective of the volume of antibiotic used, based on the estimated value of the antibiotic to society. Two drugs were selected during the initial pilot for an initial 3-year period, with the option to extend for up to 10 years.

The Swedish model is intended to secure access to rather than boost R&D on antimicrobials. The model guarantees a small amount of revenue for five antimicrobials active against priority 1 pathogens on the WHO priority pathogen list. The government signed two-year contracts, with the possibility of extension, with four pharmaceutical companies for access to these five products. In return for maintaining a defined security stock in Sweden and

committing to deliver to hospitals within 24 hours of ordering, each pharmaceutical company was guaranteed reimbursement of at least SEK 4 million (approximately \$370,000) per product. The revenue companies received was partially delinked from volume. If revenue from sales was less than the guaranteed amount, the state paid the difference; if revenue was greater than the guaranteed amount, the companies received 10 percent. The Swedish Public Health Agency has recommended that the model be made permanent but acknowledges that the program only facilitates access and does not incentivize innovation.

An analysis found that the model allowed Sweden to gain access to several medicines earlier than similar European countries. During the 2.5-year pilot duration, the state paid over SEK 25 million (\$2.3 million) extra to ensure the availability of the products.

The AMR Action Fund—a global coalition of pharmaceutical industry, philanthropic funders, and multilateral development banks launched in 2020—expects to invest more than \$1 billion in projects by small biotech companies over the next 10 years (AMR Action Fund 2023). New Drugs for Bad Bugs, Europe's largest public-private partnership, invested across the full R&D chain. More than half of the €660 million (\$710 million) in its Innovative Medicines Initiative program (€347 million) came from the pharmaceutical industry (Innovative Medicines Initiative n.d.; Kostyanov et al. 2016). Launched in 2012, with the first projects starting in 2013, the program encompassed eight projects, before finishing in 2021 (Innovative Medicines Initiative n.d.).

Overall, however, experts believe that this push funding is less than \$200 million a year—significantly less than estimates of push funding needs by the AMR Review, Drive-AB, BCG, and the European Observatory on Health Systems and Policies (Anderson, Panteli, and Mossialos 2023; Årdal et al. 2018; Boluarte and Schulze 2022; Review on Antimicrobial

Resistance 2016). A 2023 EU report stated that there is “relative consensus” on the need to provide additional push funding of \$250–\$400 million a year (European Commission and Agency 2023). The most recent report by the WHO and the Global AMR R&D Hub to the G7 Finance and Health Ministers found that “the small biotech companies and research groups developing the most promising pre-clinical antibacterial R&D projects need additional push funding to replenish a weak clinical pipeline” (WHO 2023d).

Since the final reports from the AMR Review and Drive-AB, ideas on pull funding have become mainstream in policy discussions. Many governments and supranational groups, such as the G7, have released reports supporting such incentives. Sweden is piloting a revenue guarantee model; the United Kingdom's National Health Service recently made its subscription model permanent; Japan is developing a pilot pull incentive as part of its 2023 G7 presidency; and Canada recently announced plans to implement a pull incentive.

Pull side proposals with different degrees of ambition are at various stages of implementation across the G7. The European Union is considering its options. In the United States, the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act (PASTEUR) failed to move through Congress in the three years since it was first introduced. This potentially highly impactful legislation for a subscription model with contracts up to \$3 billion was reintroduced in 2023, however, and has the support of the Biden administration.⁵

The benefits of investing in a pull mechanism for new antimicrobials are clear. Silverman Bonnifield and Towse model the 10- and 30-year costs and benefits of government subscription-based pull mechanisms for the G7 countries, from both the domestic and global welfare perspectives (Silverman Bonnifield and Towse 2022a, 2022b, 2022c, 2022d; Towse and Silverman Bonnifield 2022).⁶ The costs for their model are based

on the introduction of 18 new antibiotics over 30 years, with a total commitment of \$4.5 billion for each drug.

According to their analysis, in the G7 and the European Union alone, the creation of new antibiotics would prevent almost 1.2 million deaths (table 2). Returns on investment would be huge in every country, ranging from an 11-fold return in the United Kingdom to an almost 28-fold return in both the United States and Japan over a 30-year period. From the global perspective—considering only the health value of Disability Adjusted Life Years (DALYs) averted—the return on investment grows to 27:1 over a 10-year time horizon and 125:1 over the full 30-year program duration (table 3).

Sensitivity analysis suggests that the high returns are robust under a wide variety of alternative assumptions and scenarios. The evidence is thus clear that it is in the interest of HICs to fund new pull incentives, such as subscription models, for development of novel antibiotics. As most of these gains will

TABLE 2 Estimated number of lives saved and return on investment from a pull mechanism for new antimicrobials in selected countries

COUNTRY OR COUNTRY GROUP	NUMBER OF LIVES SAVED		RETURN ON INVESTMENT (DOLLAR BENEFIT PER DOLLAR INVESTED)	
	OVER 10 YEARS	OVER 30 YEARS	OVER 10 YEARS	OVER 30 YEARS
Canada	2500	48,10	4.5	20.4
European Union	20,000	384,900	3.9	18.2
Japan	14,100	269,700	6.0	27.7
United Kingdom	4,600	88,400	2.5	11.4
United States	20,000	383,000	5.9	27.6
G7	61,300	1,174,100	5.0	23.1

Source: Towse and Silverman Bonnifield 2022.

5 The PASTEUR Act would change how the government buys antimicrobials. Instead of paying per tablet, as in the current model, the US government would pay a fixed amount per antibiotic, based on the quality of the drug. These payments would go to pharmaceutical companies regardless of the volume purchased.

6 These estimates are based on an illustrative subscription program, with parameters drawn (where possible) from the literature and some simplifying and deliberately conservative assumptions about program design and remuneration. The authors assumed that the cost of such a subscription model would be split between G7 and EU countries based on their GDP. They assumed annual growth in antibiotic resistance of 2 percent and a 2 percent rise in mortality in a scenario without new antibiotics. After guaranteed payments, they assumed that antibiotic prices would drop to marginal costs. Once deployed, each antibiotic was projected to reduce AMR-related deaths by 5 percent at its peak. The model used a 1.5 percent discount rate for health benefits and a 3.5 percent rate for costs. Benefits were monetized based on the direct health gains to patients from treatment of drug-resistant infections, calculated based on local Disability Adjusted Life Years (DALY), and averted hospital costs directly associated with drug-resistant infections.

TABLE 3 Global costs and benefits of a subscription model after 10 and 30 years

ITEM	AFTER 10 YEARS	AFTER 30 YEARS
Total (discounted) cost (billions of dollars)	11.7	38.9
Lives saved	518,000	9,933,000
Disability Adjusted Life Years (DALYs) saved (millions)	19.5	374.5
Value of DALYs saved (billions of dollars)	310.6	4,874.2
Benefit: cost ratio	27:1	125:1

Source: Towse and Silverman Bonnifield 2022.

be achieved in LMICs, it is essential that drugs be rolled out across the world.

Interviews and deliberations undertaken as part of this working group reveal consensus that LICs should not contribute toward the R&D costs of new antimicrobials and that HICs should fund the vast majority of R&D (McDonnell et al. 2022). Middle-income countries (MICs)—particularly upper-middle-income countries, which often have large pharmaceutical markets, a high-burden of resistant disease (Murray et al. 2022), and growing R&D-based capabilities—are also expected to increase their financial contributions to the R&D effort.

Deciding where responsibility should lie could help overcome the collective action problems, allowing countries to work together to fund research the entire world would benefit from. Several approaches to dividing R&D costs have been suggested. The UK government based its subscription model on the relative share of its GDP as a percentage of global GDP (see box 1). Towse and Silverman Bonnifield (2022) and Outterson (2021) divide the R&D costs exclusively between the G7 and the European Union. Their results show that it is very much in a country's interest to fund such a system. Deciding which system to use is a political exercise, which will require compromise and negotiations.

R&D requires more than funding. All countries, regardless of financial means, have an important role to play in undertaking and enabling it, including by collecting and sharing surveillance data and resistant isolates and undertaking clinical trials.

Processes needed to set a more equitable antimicrobial innovation agenda

The pipeline for antimicrobials is inadequate, especially for products needed in LMICs. In 2017, the WHO published a priority pathogen list to guide R&D toward urgently needed antimicrobials. The list might not have sufficiently reflected the needs of LMICs, in part because of the lack of data. Data collection on resistance increased in the past six years, particularly in LMICs. The next iteration of the priority pathogen list, which is scheduled to be published in late 2023, should benefit from these data (GlobalData Healthcare 2023).

Broader change is needed to assess and meet the antimicrobial R&D priorities of LMICs, however. For example, the WHO could use the methods piloted under a research project this working group conducted with Boston University.⁷ These methods include meta-analysis of the literature to look at changes in resistance rates when holding the study, bacteria, and drug fixed; correlations between drug resistance; ways

7 This research project proposes a methodology for determining research priorities and identifying the workhorse drugs that are most at risk of becoming ineffective because of resistance. Workhorse drugs were identified using both absolute usage and the number of indications. For usage levels, the study included the top five most used antibiotics in any WHO region. The number of clinical indications for which each antibiotic was suggested in the WHO Essential Medicines List was then summed and weighted by dividing by the number of alternative drug options for each indication. The 10 antibiotics with the highest weighted values were selected. The final list of workhorse drugs includes the 15 drugs that met either of these criteria.

of weighting studies by sample size; and expert elicitation to identify the drugs most at risk from resistance and those for which a rise in resistance would be most catastrophic (McDonnell et al. forthcoming).

Much of the need for antimicrobials in LMICs is for oral, broad-spectrum antimicrobials that are effective against a wide range of targets and that can be used when diagnostics are not available to identify the pathogen causing the infection. These “workhorse drugs” are the backbone of many treatment protocols and the first-line choices for many infections. Workhorse antibiotics are likely to have been on the market for years as generics. According to the research project with Boston University, they are likely to be lost to resistance within the next 15 years: Over 80 percent of experts interviewed as part of this study believed that four workhorse drugs (amoxicillin, cefalexin, ciprofloxacin, and cloxacillin) will very likely be lost to resistance within the next 15 years and therefore require replacement (McDonnell et al. forthcoming). The oral form and broad spectrum of these drugs make them excellent options for empiric treatment in settings outside of regional or national hospitals (WHO 2021).

Since 2000, only 4 of the 40 new antibiotics licensed have completed a neonatal program (Williams et al. 2022). Antibiotic formulations for neonates are far more important in LMICs than elsewhere: among children under five who die from AMR, 99.65 percent are in LMICs (McDonnell and Klemperer 2022). R&D priority-setting under current market conditions favors intravenous hospital drugs over workhorse drugs. Less than 40 percent of products are being explored for oral use, and only 3.6 percent are categorized as broad spectrum. A more robust system is needed for determining the needs of LMICs and integrating them into target product profiles or health technology assessments. Given that the median time from identification of promising target candidates to first approval is 12.5 years (Outtersson 2021), the need to develop replacement drugs is urgent.

In parallel, improvements in both the technology and use of diagnostics would make it easier to treat people with narrower spectrum drugs, reducing the need for replacements for the broad-spectrum drugs on which the world currently relies.

The inadequacy of regulation of antimicrobials, including of clinical trials

National regulatory authorities are crucial for ensuring the safety, efficacy, and quality of medicines like antimicrobials, but only 30 percent of national regulatory authorities in WHO member states can efficiently regulate medical products (WHO 2018). The lack of regulatory capacity poses significant challenges, particularly for antimicrobials. Duplicative approval processes for clinical trials result in wasted resources, inefficiencies, and prolonged timelines for conducting efficacy and safety studies. Cumbersome marketing authorization procedures further discourage pharmaceutical companies from registering their products. Inadequate vigilance and post-marketing surveillance also contribute to AMR, as substandard and falsified products remain undetected and untreated. In some countries, the lack of regulatory enforcement allows antimicrobials, including Watch and Reserve antimicrobials, to be sold without prescription (Belachew, Hall, and Selvey 2021; Saleem et al. 2020).

The current system of regulating clinical trials has limitations. Insufficient comparative studies, lack of information on how new drugs overcome resistance, and reliance on noninferiority trials lead to inadequate information for prescribers and procurers.⁸ Older antimicrobials suffer from a lack of data on optimal dosages and resistance selection. These challenges hamper innovation and effective antimicrobial management, contributing to the growing threat of AMR. Improving regulatory processes could provide crucial safety and efficacy information, enhance drug stewardship, and accurately value the benefits of new treatments (Muller, Theuretzbacher, and Mouton 2015; FDA 2019; GSK 2023; Rex et al. 2019).

⁸ Noninferiority trials are designed to demonstrate that a new treatment is not substantially worse than an established treatment in terms of efficacy rather than proving that the new treatment is superior. Such trials are used in situations in which the new treatment may offer other benefits, such as reduced side effects, cost, or efficacy against antibiotic resistance pathogens (Rex et al. 2019).

New methods needed to assess the value of antimicrobial innovation

Countries can assess the value of new drugs using health technology assessments or target product profiles.

Health technology assessments

A health technology assessment (HTA) is a standardized, multidisciplinary process that systematically evaluates the properties, effects, and/or impacts of a health technology to inform decision-making in healthcare (WHO 2023c). HTAs allow health agencies to compare the benefits and costs of different treatments to determine which to make available. As no health care system can afford to make all medical treatments available to all people, the goal of a decision-making process based on HTA is to try to maximize the health benefits that can be achieved given budget constraints.

For noncommunicable diseases, the benefits of a treatment go predominantly to the person being treated. An HTA therefore evaluates the extent to which an intervention improves a patient's life.

Broader societal benefits come from treating communicable diseases because treating one person quickly may stop the infection from spreading to other people. To capture this dynamic, models of disease patterns are often used. Dynamic modelling is particularly challenging for resistance because these wider health benefits are not well understood, partly

because data are limited and partly because knowledge is lacking on all of the genetic factors that drive resistance and cause disease and transmission (Colson et al. 2021; Niewiadomska et al. 2019), making it very difficult to capture the wider societal benefits that accrue from a new treatment. A 2018 report described capturing the full value of antimicrobials as “challenging but not impossible” (Rothery et al. 2018).

The United Kingdom's HTA agency, the National Institute for Health and Care Excellence (NICE), established a framework to measure benefits of antimicrobials that traditional evaluation tools do not capture well in 2019. This framework—Spectrum, Transmission, Enablement, Diversity, Insurance, known by the acronym STEDI—was used in 2020, to measure the value of two drugs—ceftazidime-avibactam and cefiderocol—included in the United Kingdom's subscription model (table 4 and box 2).

Quantifying the value of these two new antimicrobials with the STEDI framework proved very difficult. Both drugs were estimated to have values that exceeded the maximum contract value of £10 million (\$12.7 million) a year under the United Kingdom's pilot subscription model (recently increased to £20 million) and for both drugs, most of the value came from adjustments to the original modelling work. As a result, the National Health Service and NICE plan to use a simplified multicriteria decision-analysis methodology to calculate the value of antibiotics, building on the understanding gained from

TABLE 4 The STEDI framework for valuing antimicrobials

ITEM	DESCRIPTION
Spectrum	A narrow spectrum antimicrobial will likely generate less resistance than a broad-spectrum antimicrobial because fewer species of bacteria will face selective pressure from it.
Transmission	An antimicrobial that acts quickly reduces the period in which a patient is infectious, limiting transmission.
Enablement	Antimicrobials facilitate other treatments, such as joint replacements, organ transplants, and chemotherapies.
Diversity	Having a range of antimicrobials available reduces the resistance pressure on any one drug.
Insurance	Patients benefit from having an antimicrobial ready to deal with unexpected increases in resistance.

Source: Leonard et al. (2023).

BOX 2. HEALTH TECHNOLOGY ASSESSMENTS IN THE UNITED KINGDOM'S SUBSCRIPTION MODEL

In 2020, NICE evaluated two drugs, ceftazidime–avibactam and cefiderocol, using the STEDI framework established in 2019. An independent group called Economic Evaluation of Health and Care Interventions (EEPRU) was commissioned to model the drug's benefits, and submissions were collected from patient groups, manufacturers, and experts. For cefiderocol, EEPRU was not able to quantify benefits for the spectrum, transmission, or diversity categories and could not fully account for the insurance value of a new drug. It projected 5,400 Quality-Adjusted Life Years (QALYs) over two decades

for the drug. NICE's review committee believed EEPRU missed some drug values and adjusted the estimate to 16,200 QALYs, meaning the majority of the benefit came from expert feedback rather than modelling. A similar size adjustment was made for ceftazidime–avibactam (National Institute for Health and Care Excellence 2022; Schurer et al. 2023; Woods et al. 2022). These adjustments were an implicit recognition that it is very difficult to accurately model the benefits of new antibiotics. NICE will use a light touch review system in the future.

this more detailed work but relying more heavily on expert elicitation. Experts recommend relying more on expert elicitation to quantify these benefits until the science advances and epidemiological models are “developed that allow us to understand the spread of resistance with greater confidence” (Colson et al. 2021, page 4).

The STEDI–based model for AMR struggled to gauge the true value of new antimicrobials, despite an extensive research process. LMICs face similar challenges, but their more limited capacity and differing needs mean that they need to develop their own valuation methods.

Dr. Manuel Espinoza, of the Pontificia Universidad Católica de Chile, and CGD developed a tool called Methods, Attributes, Procedures, and Social Preferences (MAPS), which helps evaluate the comprehensive value of antimicrobials in LMICs. MAPS distinguishes itself from traditional HTA systems by assessing attributes that are more relevant to LMICs. For example, broad-spectrum drugs that can target multiple infections are valued more highly than narrow-spectrum ones in LMICs because the ability to diagnose is more limited. The tool recognizes the societal insurance value of having new antimicrobials available for resistant pathogens, even if they are not immediately used, and puts greater emphasis on qualitative assessment. Table 5 outlines the key attributes to be included in the MAPS tool.

TABLE 5 Attributes of antibiotic value to be used in the Methods, Attributes, Procedures, and Social Preferences (MAPS) tool

ATTRIBUTE	VALUE
Intrinsic property of the technology	<ul style="list-style-type: none"> ▶ Comparative clinical effectiveness ▶ Safety ▶ Novel action value ▶ Spectrum value ▶ Impact on burden of disease of the population
Healthcare system performance/ goals	<ul style="list-style-type: none"> ▶ Efficiency (economic value) ▶ Equity in access ▶ Equity in health outcomes ▶ Diversity value ▶ Enabling value ▶ Transmission value ▶ Insurance value ▶ Stewardship value ▶ Implementation value
Broader social values	<ul style="list-style-type: none"> ▶ Value of hope ▶ Scientific spillovers ▶ Family spillovers ▶ Productivity impact on patients ▶ Productivity impact on careers ▶ Macroeconomic effects

Using target product profiles

A complement to HTAs are target product profiles (TPPs). Under this system, attributes of value are set prospectively for innovative health products that meet different criteria. As these criteria are set before products are developed rather than retrospectively (as in HTAs), this approach may provide better signals of what society values and is willing to reimburse, reducing commercial risk. Earlier HTA value assessments can also be conducted when a drug is early in development, but such assessments are not likely to be available in LMICs.

The proposed PASTEUR Act legislation in the United States would use a TPP-like mechanism, with the US government first undergoing a rule-making process before publishing various attributes and subscription values.

Measuring successful innovation

In order to test whether new financial incentives, changes to HTA systems, and TPPs are having an impact on the pipeline, targets should be set for innovation. They should be based on estimates of the number of antimicrobials needed and coupled with the WHO system to track R&D. The WHO system already tracks the number of antibiotics under development by antibacterial class, route of delivery, stage of development, target pathogen, and in some cases whether the drug is “innovative” (WHO 2023a). This information can be adapted and matched to the bacterial priority pathogen list or a TPP to determine whether innovation needs are being met. Targets should look not only at the number of successful candidates approved but also at different stages in the clinical pipeline, to see whether targets are likely to be met in the future. About 16 percent of antibiotics going into Phase I trials are eventually approved (Outterson 2021b); if a TPP list calls for two products against a particular pathogen and there are only three candidates in the pipeline active against this pathogen, all of which are in early stages of development, it is highly unlikely that this target will be reached. Policymakers need not wait until two of the candidates have failed to react to this shortfall.

1.3 ACCESS CHALLENGES IN THE MARKET FOR ANTIMICROBIALS

It is vital that everyone who needs them is able to access safe and effective antibiotics, including Access, Watch, and Reserve drugs (box 3).

Focusing efforts on expanding access to antimicrobials cross-listed on the Essential Medicine List and the AWaRe classification, especially Access category drugs, can help boost

BOX 3. THE AWaRE CLASSIFICATION

The AWaRe classification, established by the WHO in 2017, groups antibiotics into four categories:

- ▶ **Access** drugs are antibiotics that have a relatively low resistance potential and a good safety profile in terms of side effects. They are usually relatively inexpensive and easy to use and often have a narrow spectrum of activity.
- ▶ **Watch** drugs are antibiotics that tend to have a broader spectrum of activity and are recommended as first-choice options for patients with more severe clinical presentations or for infections for which the causative pathogens are more likely to be resistant to Access drugs.
- ▶ **Reserve** drugs are last-resort options, used for severe circumstances when all other antibiotics have failed.
- ▶ **Not Recommended** drugs are fixed-dose combinations of antibiotics that are not approved by the major regulatory agencies. Some fixed-dose combinations of antibiotics are well evidenced and provide valuable clinical benefits. However, most are not recommended, as they may result in increased toxicity and resistance. The WHO strongly discourages their use.

TABLE 6 Number of antimicrobials in each AWaRe category

DRUG CATEGORY	NUMBER OF DRUGS ON ESSENTIAL MEDICINES LIST*	TOTAL NUMBER OF DRUGS
Access	21	87
Watch	12	139
Reserve	8	29
Not recommended	0	107
Total	41	362

Source: AWaRe book (World Health Organization 2022b).

Note: * List curated by the WHO that enumerates medications deemed to be most necessary for a basic health care system.

appropriate use and limit resistance. Of the 41 cross-listed drugs included in table 6, 17 are oral antibiotics. They are especially useful because they can be administered easily and used interchangeably (WHO 2021). For example, azithromycin and clarithromycin are both macrolides and share the same mechanism of action and similar treatment profiles (Whitman and Tunkel 1992). Although it is important for one of these treatments to be available in all clinics, it may not be necessary to supply both. More information on AWaRe can be found in the AWaRe book (World Health Organization 2022b).

An estimated 5.7 million people die every year from antibiotic-treatable infections, most of whom live in LMICs; improving access to drugs would dramatically help reduce this toll (Daulaire et al. 2015). Antibiotics are such an important part of health treatment that it will never be possible to achieve the Sustainable Development Goal of achieving universal health coverage without access to them. Access is so low in certain low-income settings (box 4) that some experts have argued that increasing the consumption of more common first- and second-line antibiotics in those places may decrease, rather than increase, the AMR burden, by reducing demand for Watch and Reserve drugs (Hellamand, van Gerven, and Rafiqi 2022; Murray et al. 2022).⁹

BOX 4. LACK OF ACCESS TO ANTIMICROBIALS IN LOW-INCOME COUNTRIES

Access to antibiotics has increased in LICs, but significant barriers remain to their appropriate use, including exclusion from essential medicines lists; poor quality assurance; inadequate regulatory systems that make it particularly difficult to regulate imported drugs; and limited availability of narrow-spectrum antibiotics, according to research conducted by Pisani and McDonnell (2023 forthcoming) for the working group. They also found insufficient evidence to support the widely held view that increased antimicrobial use in LICs is disproportionately driving resistance. Better data on resistance patterns and antibiotic use as well as improved laboratory capacity and reporting systems are needed to better track and address issues in the antimicrobial ecosystem in these countries.

Inadequate access to off-patent medicines

Most of the antibiotics sold in the world are off-patent. In the 90—disproportionately wealthy—countries tracked by IQVIA’s MIDAS project, off-patent medicines account for three-quarters of drugs sold by volume and 88 percent by standard

⁹ Recent work by the Global Research on Antimicrobial Resistance Project (Murray et al. 2022) estimating the global burden of AMR highlights the case of Western Sub-Saharan Africa. This region has the highest burden of resistance in terms of mortality, although other parts of the world have higher resistance rates. Increasing consumption of first- and second-line antibiotics there may decrease rather than increase deaths associated with AMR in the region.

treatment unit (Madden and Outterson 2023). They very likely make up a far greater proportion of use in the rest of the world.

The nature of the access problem for off-patent medicines (which include all antibiotics in the Access category of the AWaRe classification) is very different from access issues for Reserve drugs (which includes many on-patent medicines). Demand for Access drugs is very large, and supply chains are often disrupted, for a variety of reasons. Profit margins are very low, which means that manufacturers quickly drop out of the market when production costs rise. Fluctuations in supply and demand can cause prices to fall unpredictably; when prices fall, manufacturers lose out. These market trends apply for most high-volume generic drugs in LMICs but particularly for infectious disease treatments like antimicrobials, for which disease outbreaks can cause demand to rise unexpectedly. In contrast, demand for patented antibiotics tends to be very low and concentrated on hospital care. Resistance rates clash with these market pressures, because antimicrobials must be replaced when effectiveness diminishes rather than when supply and demand are sufficiently aligned.

Challenges accessing Access drugs: Case study on amoxicillin

Amoxicillin is a vital antibiotic. It is recommended by the WHO's AWaRe book as the first-choice treatment for 10 of the 12 most common primary care infections requiring antibiotics (WHO 2022). Resistance to amoxicillin remains low, and it is one of the cheapest antibiotics tracked by international reference prices. Research in Cameroon and the Democratic Republic of Congo found that it had the lowest markup of any antibiotic (Schäfermann et al. 2020).

Despite its importance, amoxicillin is often in short supply, including in HICs. In late 2022 and early 2023, shortages were recorded in 80 percent of the 35 countries on which the WHO had data (including the United States, Canada, the United Kingdom, and 25 of the European Union's 27 member states) (Mancini and Kuchler 2022). Tracking medicine shortages in LMICs can be much more difficult, because of limited data, but these countries usually suffer far more during global shortages (Silverman et al. 2019; McDonnell et al. 2021).

The supply issues with amoxicillin stem from it being an inexpensive, off-patent, generic drug. Low profitability leads to decreased manufacturing investments, rendering the supply chain unstable. More than 1,000 companies manufacture amoxicillin, but most rely heavily on a few active pharmaceutical ingredients, which they import largely from China. The vulnerability of this supply chain also affects other generic medicines, but the problem is more critical for anti-infectives like amoxicillin because changing disease patterns and public health crises can drastically alter demand, as they did in 2022 (Chigome et al. 2019; Cohen et al. 2023). AMR heightens the risk of shortages. Increased production costs can quickly lead to a market exit by manufacturers, creating global shortages (Raghavendran and Christian 2022). Wealthier countries can secure more supplies by out-paying poorer countries; LICs struggle because of structural obstacles, exacerbating their shortages (McDonnell et al. 2021)

Manufacturers have to strike a balance between overproducing and maintaining a steady supply. In a market with already thin margins, overproduction can lead to significant financial losses, which fall on producers. Underproduction can result in shortages, affecting patient care, with society at large rather than producers paying the cost.

The low price of amoxicillin can disincentivize use. The pharmaceutical industry, pharmacies, and in some countries even clinicians are incentivized to promote and prescribe more expensive drugs by fostering the belief that they are more effective (Lu 2014). Lack of confidence in amoxicillin is likely exacerbated by the high levels of substandard product. A review of the literature on the drug between 1992 and 2009 found that amoxicillin was the most commonly identified substandard/falsified antibiotic, detected in 29 countries (Kelesidis and Falagas 2015). The drug's poor quality reflects both criminal activity and poor regulation. Wide variation in thermostability also affects the drug, particularly in the tropics, where temperatures and humidity are high (Robertson et al. 2021).

Under the current global regulatory system, the onus for quality assurance lies with the importing country, which may lack the capacity to ensure that antibiotics acquired at low cost from

other countries are not substandard and kill resistant as well as susceptible bacteria (Eban 2019; Thakur and Reddy 2022). This caveat emptor system does not work well for the large number of LICs that import most of their low-cost generic antibiotics from a handful of producer countries, particularly as these countries are much more likely to have tropical and subtropical climates, in which medicines degrade quickly (Pisani and McDonnell forthcoming).

These problems are well understood, but governments have not taken enough action. In a study undertaken for this working group to assess antibiotic needs and use in LICs, several interviewees expressed concern that the focus on fixing supply issues for Reserve and novel antibiotics detracts from solving supply constraints for more frequently indicated medicines. A primary physician in a LIC said, “We’re using cipro[floxacin] because it’s about to expire, and we don’t have amoxicillin... There’s no point policing cipro if you don’t have access to amoxicillin” (Pisani and McDonnell forthcoming). This situation leads to suboptimal treatments, which are bad for patients and society at large, as less effective medicines can give pathogens an opportunity to develop resistance, posing a danger to the wider population (Hellamand, van Gerven, and Rafiqi 2022).

Several policy options could address the access problems of off-patent medicines such as amoxicillin. Greater resilience needs to be built into the global procurement system to protect people from demand fluctuations (which often means procurers paying more for reliability). Regulatory systems need to be improved to ensure that medicines are produced to a high standard, and much better data are needed on both the supply of and demand for antibiotics. No one knows how many tablets of amoxicillin are consumed annually, how many producers there are, or how many drugs can be produced. Better data would allow improved forecasting of demand surges and supply shocks.

Challenges accessing Reserve drugs

Low-volume antibiotics that are off-patent often suffer from the worst of both worlds. The supply chain is weak because no one organization has a monopoly on the drugs and thus an incentive to manage it. At the same time, sales volumes are

very low, so a low-cost higher-volume business model does not work. As a result, if demand for these drugs increases, there may not be the capacity to meet it. As AMR gets worse, drugs that were once not seen as being very useful may become far more important. Knowledge about “forgotten” antibiotics and how to produce them is being lost, however. The marketing authorization from regulators to sell these drugs may also have lags. When this happens, clinical trials may be needed. Without intellectual property rights, however, there is little incentive for the private sector to undertake these tasks (Pulcini et al. 2012; Morgan et al. 2023).

Inadequate access to on-patent medicines

Access problems for on-patent medicine can stem from unaffordability for low-income populations. Barriers to entry also lead to a lack of availability in many countries (Kållberg et al. 2018). The 2021 Access to Medicine Foundation AMR Benchmark found that of 17 on-patent medicines, only 6 had filed for marketing authorization (the step required by regulatory authorities to grant market access) in 10 or more LMICs, and only 3 companies had registered any of their patented medicines in a LIC (Access to Medicine Foundation 2021).

Research conducted with the Indian School of Business for this working group provides further evidence on the lack of availability and affordability of on-patent antimicrobials in LMICs. The WHO Essential Medicines List includes eight Reserve antibiotics. More than half of Indian states have either none or only one such antibiotic on their essential drug list. Reserve and Watch drugs are far more expensive than Access drugs in India (32 and 9 times more, respectively), making them unaffordable for many people in a system in which 47 percent of health expenditure is out of pocket (Ministry of Health and Family Welfare 2023).

Research conducted by CGD in collaboration with the Access to Medicines Foundation for this working group found that the reason for the lack of availability and affordability of on-patent medicines in LMICs is threefold: lack of a viable market in many LMICs, complexities with introducing drugs into these markets,

and fears of resistance development, which could harm the market in HICs.

The market for selling these drugs in most LMICs is very small because of low and unstable demand. On-patent antibiotics usually fall into the Reserve category, which are intended mainly for use only where indicated by diagnostics. Large LMICs may seem to have large needs and thus a sufficiently large market, but demand in these countries is often hampered by a weak healthcare system, including insufficient diagnostic capabilities to demonstrate a need for Reserve drugs. In addition, fragmented healthcare systems—as in India, for example, where states are responsible for procurement—means there may be insufficient demand in each region. Demand forecasting is difficult in these markets because of opaque systems, lack of data, and the highly variable demand that comes from infectious disease fluctuations. In some instances, pharmaceutical companies withdraw because the market size does not justify the large annual costs of maintaining registration. Indeed, the share of antibiotics pulled from the market because of commercial difficulties is larger than that of other drugs (Luepke et al. 2017).

The limited market and high costs of deploying treatments deter companies from selling in certain regions because of the need for extensive, expensive data collection on local resistant infections, regulations, medical contexts, and diagnostics

use as well as the complex registration processes required for each country, which may include additional requirements and potential backlogs. Antimicrobials present unique challenges because of the need for data on resistance rates and stewardship capabilities, as well as potential delays from novel trial designs.

Antimicrobials are unique among drugs in that excess use in one patient leads to waning efficacy for all patients; use in one location can thus reduce the market in another. Some pharmaceutical companies have expressed concern about stewardship and apprehension about rolling out antimicrobials in regions where profit is low and the potential for misuse is high. These companies sometimes require LMICs to provide assurances or meet specific stewardship conditions before rolling out their drugs (Klemperer, Rafiqi, and McDonnell forthcoming). These requirements can be too complex for countries with poor health infrastructure.

Current solutions to access challenges

Several initiatives have been created to overcome access problems. Boxes 5, 6, and 7 describe essential features that any solution to improve access to existing and new antimicrobials should include.

BOX 5. THE SHIONOGI, GARDP, AND CHAI PARTNERSHIP FOR THE ROLLOUT OF CEFIDEROCOL

Cefiderocol is a new antibiotic developed by Shionogi, a Japanese pharmaceutical company, for the treatment of severe gram-negative infections that are resistant to other medications (Shionogi 2019). In June 2022, Shionogi signed a licensing agreement with the Global Antibiotic Research and Development Partnership (GARDP) and the Clinton Health Access Initiative (CHAI) to accelerate access to this product, especially for LMICs, which might otherwise have enjoyed only delayed (if any) access to a novel antibiotic (Global Antibiotic Research & Development

Partnership 2022). Under this agreement, GARDP can manufacture and commercialize cefiderocol through sub-licensees in 135 countries. This agreement will cover almost 70 percent of countries, including most of the world's population living in areas with the highest burden of antibiotic resistance, most MICs, all LICs, and a few HICs. GARDP and CHAI will use their expertise in shaping markets and introducing medicines worldwide to help overcome the technical, legal, regulatory, and economic barriers that could otherwise hinder rollout.

BOX 5. CONTINUED

The agreement also includes provisions to work with experts and health ministries to improve hospital-based stewardship programs that ensure appropriate use. Such provisions are crucial to prevent the development of resistance and thus preserve the efficacy of cefiderocol. Shionogi received no payment for the rights or for sales in LICs or lower-middle-income countries. It receives royalties of 9 percent for drugs sold in HICs and 5 percent for drugs sold in upper-middle-income

countries. It relies on revenues from HICs to recoup innovation costs.

This license agreement is the first such agreement between a pharmaceutical company and a nonprofit public health organization for a recently approved antibiotic. It was published online (Shionogi and GARDP Foundation 2022) in order to serve as a baseline for future agreements. Although the agreement is promising—and provides a template that could pave the way for future agreements to improve access—time will be needed to assess the rollout and impact of the program.

BOX 6. SUPPORTING TREATMENT FOR TUBERCULOSIS THROUGH THE GLOBAL DRUG FACILITY

The Global Drug Facility (GDF), launched in 2001, is a flagship mechanism that supports access to diagnostics and treatment for tuberculosis (TB). The GDF plays a critical role in the market for TB treatments, including supporting stewardship and market shaping, procuring and distributing products, providing technical assistance, and supporting capacity building for national-level TB programs. It could be leveraged directly or serve as a model for a similar mechanism to carry out a range of market-shaping and procurement functions for other critical antimicrobials in LMICs.

Universal access to TB treatment is critical to curb its spread, especially among vulnerable populations. Before the GDF, low demand led to sparse supply and inflated costs of TB treatments. As the largest TB medicine and diagnostics supplier to the public sector, the GDF delivered TB products to 130 countries in 2022 (Stop TB Partnership 2022). This growth increased the annual value of medicines and diagnostics for drug-resistant TB sold through the GDF from \$69.4 million in 2008 to \$253.1 million in 2021 (Stop TB Partnership 2023). Offering services from pooled procurement to technical assistance, the GDF supports suppliers, facilitates R&D, and streamlines the global TB response.

The GDF model lowers the cost of medicine by consolidating demand across countries; decreasing transactions costs for procurers and suppliers; and de-risking suppliers from wastage by using numerous tools, including packaging in four languages, a strategic rotating stockpile, and the purchase of full batches of low-demand products. It estimates its cost savings between 2020 and 2022 at \$100 million, primarily through price reductions, flexibility to cancel and postpone orders, and downward adjustment of order volumes for unneeded medicines, according to GDF Chief Brenda Waning. International donors and funds derived from a small procurement fee cover the operational costs of the GDF, which is headquartered in Geneva and housed at the Stop TB Partnership. This funding structure ensures that the prices paid by countries for TB medicines and diagnostics procured by the GDF remain low. To incentivize political action against TB, the GDF offers the most affordable prices to countries. Their approach fosters transparency, as the GDF offers the same prices to all participant countries, which are publicly listed. As a result, the lowest prices in the GDF catalogue can be considered benchmark prices for other TB medicine purchasers.

BOX 6. CONTINUED

The GDF model can be applied to other areas of AMR to provide similar market shaping and pooled procurement benefits. The approach is already being considered to procure and distribute cefiderocol through the partnership between GARDP, Shionogi, and CHAI. A similar approach could be considered

for other antimicrobials to ensure stable, predictable demand for suppliers; enable the negotiation of concessionary prices; provide procurement tender expertise and experience; facilitate the management of shortages through strategic rotating stockpiles; support the scaling-up of antimicrobial use in-country; and explore the potential of accelerated introduction of new diagnostic and treatment tools.

BOX 7. STRATEGICALLY STOCKPILING SELECTED ANTIBIOTICS

A strategically managed stockpile of select antibiotics can serve various critical functions, yielding numerous advantages for manufacturers and patients alike. Most medicines are not currently stockpiled. In a literature review undertaken for this working group, five categories of benefits were identified (Yadav forthcoming):

- ▶ **Buffer supply disruption:** Maintaining a reserve stock can safeguard against glitches in the manufacturing process (issues with the active pharmaceutical ingredient or finished product production), manufacturer exits, and logistics disruptions.
- ▶ **Buffer surges in demand surge:** A stockpile can meet short-term spikes in demand while regular production ramps up to match the increased requirements, preventing stockouts during periods of heightened demand.
- ▶ **Play a market-making role:** In markets with products experiencing initially low demand or perpetually low demand, the stockpile can act as a market maker, providing a stable supply to encourage market growth and development.
- ▶ **Stabilize markets:** A stockpile can play an active role in managing supply and demand fluctuations, reducing demand volatility, and creating more stable market conditions for manufacturers to plan production. Providing a predictable

stream of orders prevents manufacturer exits and encourages sustained market participation by manufacturers.

- ▶ **Mitigate routine program stockouts:** A stockpile can help combat poor forecasting, late order placement, and extended lead-times, ensuring a reliable supply during routine operations.

A review of literature on the US Strategic National Stockpile, the GDF Stockpile, the Oral Cholera Vaccine stockpile, the Oseltamivir stockpile, and Health Emergency Preparedness and Response Authority's feasibility studies of an EU stockpile demonstrate that existing and proposed stockpiles play multiple roles. Their design depends on their primary function. Careful evaluation is necessary to determine the appropriate level of stockpiling (active pharmaceutical ingredient or finished product) and identify the entity responsible for holding the stockpile (manufacturer, government agency, or distributor). These decisions should be based on the specific characteristics of the product market.

Creating a stockpile for selected antibiotics could yield substantial benefits. But cost-effectiveness of establishing a stockpile should first be established to see whether these benefits are worth any additional expense, and a detailed operational design should be developed to ensure the stockpile's successful implementation and utilization.

Ensuring that antibiotics reach the people who need them

Very little information is available on antibiotic consumption, particularly in LMICs. Even less is known about whether drugs are reaching the people who need them most, although there is considerable evidence of stockouts and shortages in many LMICs and the lack of registration of many drugs (Pisani and McDonnell forthcoming).

A standard should be created on what access means. It should be an adapted version of the Essential Medicines List, amended to reflect the fact that not every antimicrobial should be available in every setting. For example, it may not make sense to dispense intravenous or Reserve drugs in primary care settings. The standard should also reflect the fact that drugs can sometimes substitute for each other, so that only one of two drugs on the Essential Medicines List might be sufficient in a given location.

1.4 STEWARDSHIP CHALLENGES IN THE MARKET FOR ANTIMICROBIALS

The inappropriate and overuse of antimicrobials is one of the key drivers of resistance. Curbing these practices requires stewardship—the careful and responsible management of antibiotic use to ensure that their efficacy is maintained over time.

Current purchasing systems incentives are inconsistent with good stewardship. In India and Kenya, half of all antibiotic prescriptions in primary health care settings for example were found to be inappropriate (Sulis et al. 2020). In the United States, 30–50 percent of out-patient prescriptions were found to be inappropriate (Centers for Disease Control and Prevention 2022). In the United Kingdom, 20 percent of antibiotics prescribed in 2018 were found to be inappropriate (Public Health England 2018). For some common illnesses, such as respiratory tract infections, the majority of prescriptions are usually deemed inappropriate (Jørgensen et al. 2013; Bianco et al. 2018).

Inappropriate antimicrobial use is the result of structural failures and perverse incentives. Because revenue is directly linked to the volume of sales in current purchasing systems, producers and drug dispensers are incentivized to oversell antimicrobials to increase profits. Some pharmaceutical companies offer prescribers direct financial or nonfinancial incentives, paying doctors and pharmacists and/or providing them with free goods if they prescribe high levels of antimicrobials (Davies, Meesaraganda, and Stockton 2019). Drug prescribers and dispensers can also face pressures from patients to provide drugs. These incentives may be particularly strong for more expensive drugs, which are usually the ones that are most important to protect in countries where regulation does not exist or is not properly enforced.

As of 2020, in 29 countries—all of them LMICs—over half of total health expenditure was out of pocket (World Health Organization Global Health Expenditure database 2023). In these settings, many people rely on private pharmacies and drug shops for access to medicines. Even within hospitals, public and private, it is common for patients to have to obtain necessary medicines from private retail pharmacies and bring them to the facility. Private pharmacies in settings with weak regulatory enforcement dispense antibiotics without prescriptions. One review found a global pooled prevalence of community pharmacies dispensing nonprescription antibiotics of 63.4 percent. The prevalence was significantly higher in LICs than in HICs (Li et al. 2023), with the country's income level one of the factors driving nonprescription dispensing. This finding is not limited to oral Access drugs; it has also been documented for Reserve drugs (Islam et al. 2022; Saleem et al. 2020). In the state of Kerala, India—a state with a relatively well-functioning public provision system—over 68 percent of injectable antibiotics (based on the defined daily dose) are dispensed in the private sector, primarily through retail pharmacies (Fazaludeen Koya et al. forthcoming). Private pharmacies may dispense incomplete courses, increasing the risk of resistance developing.

Governments in countries with strong regulatory capacity are able to use policy tools to align the private pharmacy sector with broader healthcare goals. Doing so is more challenging

for countries with weak regulatory capacity. One reason why it is difficult to regulate the market in these settings is extreme market fragmentation. In the United Kingdom and the United States, pharmacy chains are prevalent. In many other countries, the pharmacy sector is dominated by independently owned shops. Indeed, several LMICs in Asia and Africa have regulations banning chain ownership of pharmacies (Lowe and Montagu 2009). In India, chain pharmacies make up less than 4 percent of the approximately 800,000 pharmacies and drug shops (Miller and Goodman 2016). Enforcing regulations on this vast number of individual pharmacies poses a significant challenge, as it is virtually impossible for inspectors to visit each pharmacy, especially given resource constraints.

Difficulties also arise from the extreme fragmentation of the pharmacy distribution business in many countries. Fragmentation of wholesalers, sub-wholesalers, cleaning and forwarding agents (intermediaries between drug manufacturers and transportation services) and stockists that cover specific states or subregions leads to additional markups in prices, resulting in higher retail prices and posing challenges for regulatory enforcement. Other factors, such as the lack of professional accountability of dispensing staff, are also very important.

Fixing regulation alone will not be sufficient, as it will not address the root cause of the problem: the incentive incompatibility of individual pharmacies regarding the dispensing of antibiotics. Unless the profits from adhering to proper prescribing practices exceed the profits that can be earned by excessive antibiotic dispensing, excessive dispensing will continue. Addressing the problem requires changing the revenue model of the pharmacy, with respect to Access and, in appropriate cases, Watch antibiotics.

New digital technology companies (including mPharma, SwipeRx, Reach52, Maisha Meds, MedSource, Saveo, Biddano, and PharmaRack), which play the role of eco-system orchestrators (ESOs), could help reduce inefficiencies in distribution systems and offer a possible vehicle to delink payments from sales volume in out-of-pocket payment systems (box 8) (Yadav McDonnell forthcoming). By digitizing certain aspects of the

retail pharmacy business, these companies gather information on demand and inventories. Some of these new distribution companies also provide working capital and financial management systems to help improve the operations and efficiency of traditional retail pharmacies. They have a comprehensive view of sales, stocking, and pricing information within their network of pharmacies, enabling greater transparency and visibility.

The fine balance of strengthening stewardship while ensuring access

Balancing stewardship and access is tricky. Methods designed to limit overuse (such as requiring a doctor's prescription for antimicrobial purchases) can limit access in regions with high levels of morbidity and mortality from treatable infectious diseases and where doctors are not easily accessible. These settings—which are largely (though not exclusively) concentrated in LMICs—need both better access to antimicrobials and more appropriate usage, which in some cases may mean lower use.

Stewardship measures also need to avoid imposing too great a burden on already stretched healthcare professionals. Entering prescriptions into a database may be too time consuming, for example, reducing the number of patients providers are able to see. Any policy designed to strengthen stewardship must allow countries sufficient flexibility to sustain and expand access to antibiotics at a level commensurate with the local disease burden.

Several policies have been proposed and implemented to strengthen stewardship and appropriate use well beyond antimicrobials (Silverman Bonnifield and Klemperer 2023). Many drugs are restricted in some way out of concern for side effects, long-term safety issues, psychoactive effects, addiction, social norms, or externalities. One obvious method to regulate use of medicines is through price—using health taxes, limiting insurance eligibility, or simply making drugs prohibitively expensive.

Some methods—such as drug approval and registration requirements, prescription requirements, limited drug pack sizes, and criminalization of possession/distribution—directly

BOX 8. DELINKING PAYMENTS FROM SALES VOLUME IN OUT-OF-POCKET PAYMENT SYSTEMS

Eco-system orchestrators (ESOs) can promote the appropriate dispensing of antimicrobials and the rapid introduction of novel antimicrobials in an interorganizational network consisting of pharmaceutical manufacturers, distributors (digital or conventional), and retail pharmacies. Emerging technology-enabled players could act as ESOs, introducing a volume-delinked payment model to decouple payment from the quantity of products sold. The manufacturer would sell the novel antibiotic on an annual subscription fee basis to an ESO, which would then resell it to retail pharmacies and hospital pharmacies using a two-tier pricing structure in which pharmacies pay less if they provide data demonstrating appropriate use. This mechanism would mitigate the current incentives for overselling and inappropriate use. The system would have to be designed carefully to ensure that the ESO does not have incentives to under- or oversell these drugs.

As part of this scheme, the ESO would also offer attractive pricing and credit terms for other high-profit products, providing the potential for pharmacies to significantly increase their revenue. These terms would incentivize the pharmacy to

comply with ESO rules, even if sales of the novel antibiotic were low, as the overall arrangement is highly beneficial. The ESO would also be responsible for monitoring sales of the new antibiotic to ensure compliance, and collaborating with regulatory agencies to share data on usage.

To ensure the feasibility and potential success of this model, a few elements need to be in place. Manufacturers must be willing to set the subscription fee sufficiently low that ESO risk is not prohibitively high. The potential involvement of a third-party agency to underwrite some of the ESO's risk through a volume guarantee arrangement could help manufacturers do so. The model also requires collection of comprehensive data on sales volumes, specific prescriptions, and specified indications for use. These data are crucial to reduce the vulnerability of the system to manipulation by various actors. Without strong data systems and auditing, any network member might game the system.

This model should be piloted first for Reserve-category injectable antibiotics, which have not yet been widely adopted in LMICs. If pilots are successful, the system could be scaled up and used more widely.

affect the availability of medicines. Other methods seek to improve the behavior of healthcare providers, by, for example, limiting their interactions with industry, imposing legal liability for prescribers, or mandating that information check prescribing databases before dispensing. Other methods to ensure responsible use include requiring appropriate labeling of medicines (including dosage information), patient education, and patient consent. Targets have also been used to address problems of collective action.

This report examines three policy interventions: prescription policy, reporting databases, and the setting and measuring of targets. In calibrating these policy options, the WHO's AWaRe categories offer a useful paradigm for distinguishing

and differentiating levels of controls and regulations across antibiotic drugs/classes.

Prescription policy

Prescription policy refers to the approvals from specific types of health workers patients must obtain before being given a drug. By forcing people to see a medical professional before accessing medication, prescription policies aim to ensure appropriate use.

Five levels of stringency can be distinguished:

- ▶ Anyone can obtain a medication from any shop.
- ▶ Medicines can be dispensed only under the supervision of a pharmacist (Pharmacist-Only Medicines 2013).

- ▶ Only pharmacists or nurses are authorized to write prescriptions.
- ▶ Only doctors are authorized to write prescriptions.
- ▶ Prescriptions are limited to certain in-patient locations, such as tertiary hospitals and specialist treatment centers.¹⁰

Requiring prescriptions can help reduce AMR. There is concern, however, that such requirements may restrict antibiotic access in regions with low density of healthcare providers, low trust in the health system, and prohibitive financial barriers from user fees and the time cost of seeking healthcare (Taber, Leyva, and Persoskie 2015). Prescription policy should therefore not be used as a blunt instrument—particularly when requirements are set and enforced by a supranational body—but instead tailored to the context and the class of antibiotics.

Reporting databases

Another potential method for controlling the use of antibiotics and promoting their responsible use is to require healthcare providers to report and log all prescriptions for specified drugs (CDC 2021).¹¹ The psychological impact of tracking, as well as the time cost of logging the prescription, can motivate prescribers to take extra care to ensure that all prescriptions are appropriate. Analysis of the database can help regulators identify and intervene with prescribers found to be dispensing at unreasonably high levels and allow for better tracking of targets, such as use levels across regions, which can reveal policy-relevant trends and progress against agreed goals and commitments (Islam and McRae 2014).

For antibiotics, this kind of reporting should be limited to Reserve and, where appropriate, Watch antimicrobials that are dispensed from hospitals. Such reporting systems can create challenges, particularly for health systems that are reliant on paper. In recent years, digitization increased in LMICs, accelerated by COVID-19 (Kickbusch et al. 2021). Both

prescriptions and supply chain information are becoming far more likely to be tracked. This trend is likely to continue, creating opportunities to implement reporting databases.

Targets for stewardship and the appropriate use of antimicrobials

Targets are an important way of tracking progress against commitments and highlighting which countries are being good global citizens and which are not. They have been used effectively to address other collective action problems. When targets are binding, however, they can create unintended consequences (box 9).

AMR is a complex and multifaceted problem that does not have a single, easily quantifiable target like temperature for global climate change. However, it is possible to imagine a macro-level target, such as limiting the deaths or the burden of disease from resistance or the incidence of resistance in certain pathogens.

A range of sector-specific targets will likely be needed to reduce AMR. Much could be learned from the transparent system of Nationally Determined Contributions—the climate pledges in which countries outline what they will do to help limit the rise in global temperature to 1.5°C, adapt to climate impacts, and ensure sufficient finance to support these efforts. Creating a similar framework in which national commitments are registered and updated in a transparent way could help ensure accountability.

Current targets for stewardship and appropriate use

The WHO recommends that countries ensure that at least 60 percent of their antibiotic prescriptions be for Access drugs (Zanichelli et al. 2023). This approach has at least three limitations. It measures a relative rather than an absolute quantity, it is not as ambitious as the problem warrants, and it does not take into account local circumstances.

10 For example, the United Kingdom’s National Health Service has a set of “specialist only” medicines that should be dispensed only in secondary or tertiary care and under the supervision of a specialist (NHS 2023).

11 A related approach can be used for nonprescription, pharmacist-dispensed medicines, in which pharmacists must keep a log of purchasers. For example, purchasers of pseudoephedrine in the United States must show photo identification and sign a log before making a purchase (American Addiction Centers Editorial Staff 2022).

BOX 9. LESSONS FROM THE INTERNATIONAL CONTROL OF OPIOIDS

The International Narcotics Control Board (INCB), established by the United Nations, oversees the implementation of international drug control conventions. Its goal is to strike a balance between ensuring the availability of opioids for medical and scientific purposes and preventing their illicit manufacture, trafficking, and use. Countries are required to provide annual estimates of their needs for narcotic drugs to the INCB, which then authorizes the production and distribution of quantities that meet countries' legitimate medical and scientific needs (International Narcotics Control Board 2023). These estimates function as binding quantities of each specific opioid substance that a country can import or manufacture.

There is a significant imbalance in global opioid access. Most of the world's morphine, a key opioid used in pain management, is consumed by a small number of mostly HICs. Many LMICs have limited or no access to morphine, because of several factors, including strict drug control policies and regulations, lack of infrastructure and training in pain management, cost, fears of addiction and misuse, weaker data systems that make it harder to demonstrate additional need, and a bias against poorer countries likely inherent in how decisions are made (Nickerson et al. 2017). The health consequences of this inequity are profound. The richest 10 percent of countries possess 90 percent

of distributed morphine-equivalent opioids. While wealthy countries are dealing with opioid overuse and addiction, poorer countries face a crisis of inadequate pain relief (Burke-Shyne et al. 2017; Knaul et al. 2022).

This imbalance in the global opioid control system illustrates the complexity and potential pitfalls of setting hard international targets—a lesson that is pertinent to the fight against resistance. Although it is crucial to develop strategies to tackle AMR, stringent global targets may not be the answer.

International controls and limits on the supply of opioids have caused major problems. In contrast, domestic-level policies have often been very successful. Several people spoken to during this project highlighted how policies that, on paper, are often very similar to the controls around antimicrobials are much better enforced for opioids. They include requirements for doctor prescription, reporting databases, and stewardship programs that track and encourage moderate use. In Kenya, for example, some observers expressed fear that corruption will lead to some drugs being stolen and sold illicitly from warehouses. This problem has been avoided for opioids, which can be stored only by warehouses that carry a special license. This license is quite lucrative; a breach can lead to its confiscation. Operators are thus heavily incentivized to ensure that the warehouses are not breached.

The more antimicrobials are prescribed, the greater the risk of resistance (provided enough drugs are given out to meet all sick people's needs). However, a relative system, such as ensuring that Access drugs account for more than 60 percent of all antibiotics prescribed, can counterintuitively reward countries that have higher overall antibiotic prescription rates.

The illustrative example presented here is based on data from 19 countries collected by GLASS (WHO 2022a). Egypt and Uganda both use just over 14 defined daily doses (DDDs) of Watch antibiotics per capita per year. This finding suggests that they are behaving similarly. They are not. The average

across all countries is 14 DDD of Access antibiotics per year. Egypt uses 18 DDD and Uganda uses 39—the highest of any country tracked by GLASS. Uganda also uses 5 DDD more of Not-Recommend or not classified antibiotics than Egypt, though it uses 0.4 fewer Reserve drugs (consumption of Reserve drugs is very low in both countries). Although Uganda uses far more Not Recommended antibiotics, the same number of Watch drugs, and far more antibiotics in total, because of its high use of Access drugs, it meets the WHO's target, as 67 percent of its DDDs are Access drugs. By contrast, Egypt falls short because just 55 percent of its consumption is Access

drugs. Perversely, the easiest way for Egypt to achieve the WHO’s target might be to increase its use of Access drugs, despite its use already being very high. Peru uses a third as many Watch and Reserve antibiotics as Egypt and Uganda, but because Uganda uses five times as many Access antibiotics it again scores better on the relative metric. This example—illustrated in figure 4—reveals that although relative targets are important to conserve the efficacy of the most vital drugs, absolute targets should be set within each AWaRe category.

Defining targets for antimicrobial consumption is a task for the High-Level Meeting in 2024 and more generally for national governments working with international organizations. It is challenging because countries all start from a very different basis and there is no consensus on what the long-term consumption goal should be. Data systems for tracking AMR and consumption are inadequate, although they have improved greatly in recent years, thanks to initiatives like the Fleming Fund and GLASS¹² (Leslie and MacDonald 2022; WHO

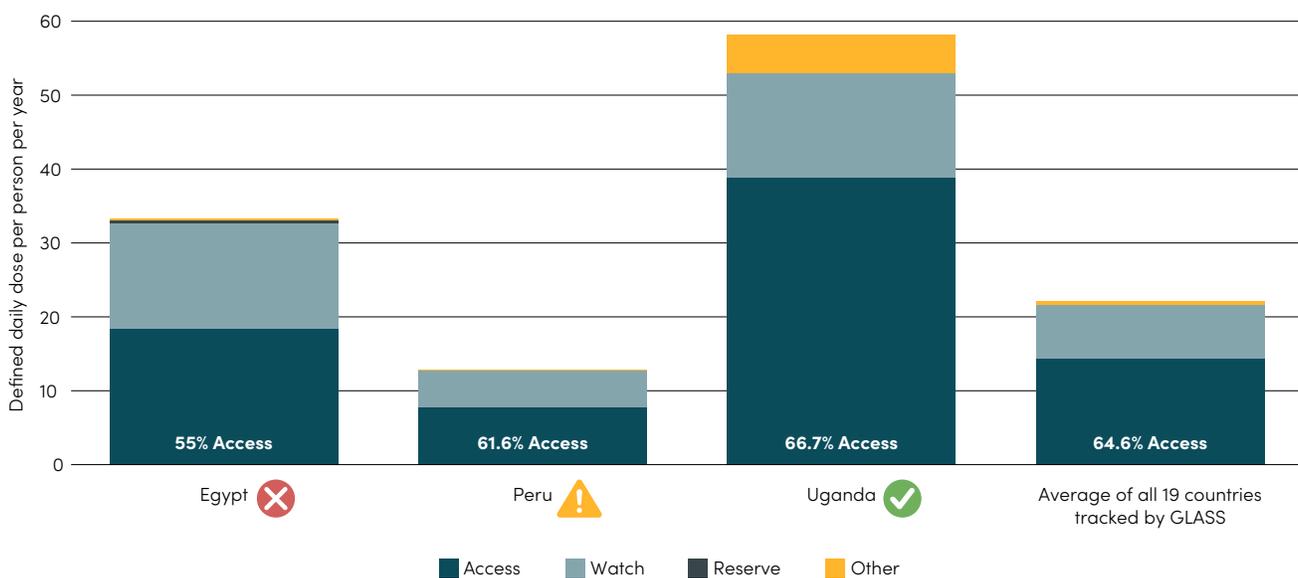
2023b). New models can be developed and leveraged to further inform target setting efforts (box 10).

Current targets are not useful in shaping countries’ antimicrobial usage. Many countries already exceed the target of 60 percent of Access medicines; the average for all GLASS countries is 64.6 percent (figure 4). Targets need to be made more ambitious.

Doing so appears possible. A recent study shows that if treatment guidelines in the AWaRe book were followed correctly, “69 percent of Watch antibiotic use in Burkina Faso and 75 percent of Watch antibiotic use in DR Congo could be replaced by Access antibiotics or no antibiotic use, which implies that the 90 percent Access target is theoretically attainable in both countries” (Ingelbeen et al. 2023), even though there may be people in these countries who would benefit from Watch or Reserve treatments that are not receiving them.

More evidence is likely needed before more ambitious targets are established, and a transition period is likely needed to get

FIGURE 4 Relative use of Access antibiotics



Source: WHO 2022a.

Note: Antibiotics not classified under AWaRe or classified as Not Recommended.

12 The UK government established the Fleming Fund in 2015 (Fleming Fund 2018). One key objective was to help LMICs build surveillance capacity to allow them to generate and use data on antimicrobial consumption in both the human and animal sectors. GLASS was established by the WHO in 2015 to “foster AMR surveillance and inform strategies to contain AMR” (WHO 2022b). Under this system, member states report antimicrobial consumption and resistance rates. GLASS provides a standardized approach to data collection and analysis, supports surveillance capacity building, and promotes a shift from laboratory data to population-wide data.

BOX 10. USING A MODEL TO ASSESS THE NEED FOR ANTIMICROBIALS

To address these limitations, it is crucial to devise a clear, concrete methodology for target-setting, given its political implications and role in assessing national performance. One experience to learn from is the work the One Health Trust did for this working group on developing a model for calculating the maximum volume of antibiotics needed to treat chronic obstructive pulmonary disease (COPD) and pneumonia.* The model estimates the upper bound of antibiotics required in each antibiotic class. Setting

such limits is important because overall use is not a sufficient target for protecting later-line drugs from overuse.

This modelling approach should yield a slight overestimate, in order to increase confidence when identifying inappropriate usage levels. Although this model requires data on local disease burden, it should not be too onerous for each country to use to determine appropriate use targets.

* The model uses the AWaRe treatment guidelines. It assumes that patients who do not respond to the first line of treatment, because of antibiotic resistance or other causes of treatment failure, survive and are prescribed the second, then third, and fourth lines of treatment, if necessary, at which point they are either cured (from either successful treatment or natural resolution of the infection) or do not seek further treatment (possibly because they die). Local rates of treatment failure are used to make assumptions about the percentage of patients moving between treatment lines. Where resistance rates to treatments are high, we assume that a certain portion of patients will start on the next treatment, with more people assumed to skip it, the higher resistance rates are. Analyses are conducted separately for age groups based on WHO guideline dosage recommendations.

there. But this evidence suggests that governments should be more ambitious in the medium term.

Countries' needs differ greatly. Microbes—and by extension resistance—spreads more easily in warmer climates and in densely populated countries (Burnham 2021). These and other natural factors that increase resistance rates should be taken into consideration when setting any targets.

It is also easier to implement stewardship policies in wealthier environments than in settings with fewer resources (figure 5).

Targets need to take into account that LMICs are not able to provide the same level of medical oversight on prescriptions as HICs.

The time needed to implement targets will also vary by country, as some policies can be rolled out much more quickly than others. For example, in some countries antimicrobial use may be high because of low access to sanitation and clean water. In the long term, investments in infrastructure could reduce the need for these drugs. LICs and LMICs should be supported in making these investments, which could greatly reduce AMR

FIGURE 5 Global distribution of medical staff



Source: World Development indices 2023, data from 2018.

Note: There are 3.2 physicians and 11.3 nurses and midwives per 1,000 people in HICs, 2.1 and 3.9 respectively in upper-middle income countries, 0.8 and 1.8 in lower middle-income countries, and 0.4 and 1 in low-income countries. Proportions above are represented by height.

(Pokharel, Raut, and Adhikari 2019). Completing large infrastructure projects takes years, however.

To avoid the problem that has plagued opioid use, targets for antimicrobial use should not limit countries' ability to purchase drugs (see box 9). Countries need to be independently evaluated against targets, however, in order to hold them accountable in their efforts to address resistance. This monitoring is part of a much larger issue of accountability, likely to be discussed as part of the High-Level Meeting in 2024. Evaluations should be carried out by an independent body to ensure that all countries are tracked in the same way according to an international standard and the potential for political pressure is limited. Countries will have to report their consumption data. The WHO launched the GLASS in 2015 for exactly this purpose, but only 27 countries provided national data in 2020

(WHO 2022b). This level of reporting and the frequency of data collection need to increase.

More research is needed to ascertain what longer-term targets should be. If possible, the long-term goal should be to use antimicrobials in a way that keeps resistance levels at a low and sustainable level. Doing so requires understanding what level of antimicrobial use this requires and then determining how to achieve this goal. Research projects such as the Antimicrobial Resistance, Prescribing, and Consumption Data to Inform Country Antibiotic Guidance and Local Action (ADILA) project are working to generate more evidence on how much antimicrobial use is too much (St. George's University of London 2023). This type of information will improve policy. Targets should be reviewed as more information emerges.

Recommendations

This chapter presents six recommendations. The political recommendation outlines why we believe it is both possible and in everyone’s interest to overcome the collective action problems inherent in dealing with AMR through a global agreement. The five operational recommendations suggest ways of implementing such a deal. Figure 6 summarizes these recommendations. Both the political and operational recommendations work best in tandem, but neither relies on the other. The world should not wait for a global agreement to start implementing the operational recommendations.

These recommendations come from an array of sources. Ideas were taken from a review of the literature, discussions with working group members, conversations with a wide array of stakeholders, public discussions, and formal feedback. We

put forward ideas that we believe will greatly improve public health. We do not seek any ownership or monopoly over them.

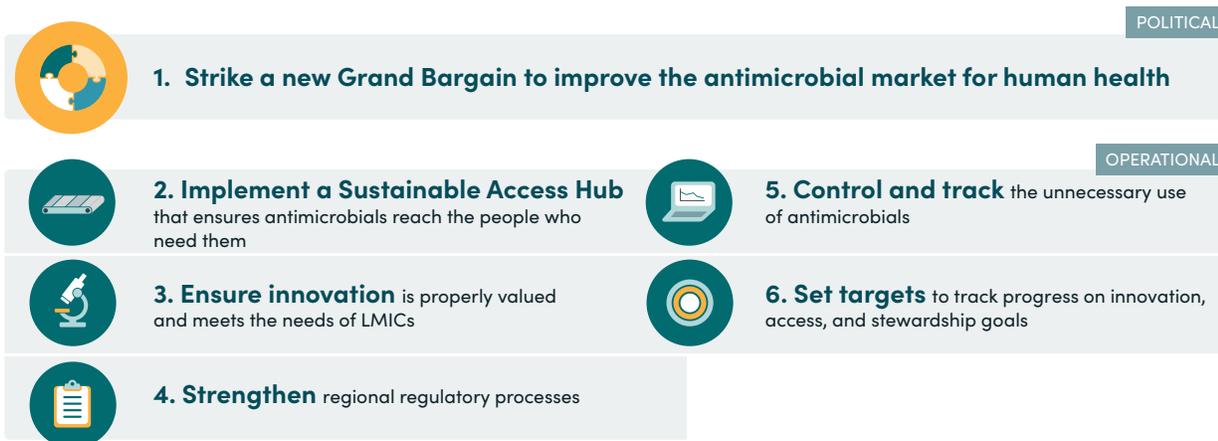
2.1 POLITICAL RECOMMENDATION



Recommendation 1: Establish a new “Grand Bargain” to improve the antimicrobial market for human health

Countries should negotiate and agree on a new political understanding—or Grand Bargain—on antimicrobials at the UN General Assembly High-Level Meeting on AMR in 2024. A Grand Bargain is both achievable and in everyone’s interest.

FIGURE 6 Overview of recommendations from CGD’s working group *A New Grand Bargain to Improve the Antimicrobial Market for Human Health*



International organizations have a key role to play in facilitating this process, supporting the implementation of any agreement. Any agreement should include commitments from the pharmaceutical industry, who should engage constructively in this process.

Many flaws in the current market for antimicrobials need to be tackled in order to mitigate the urgent threat of AMR. Many of these challenges arise from collective action problems. Although the need for action has increased, not enough has been done. Stakeholder interviews conducted as part of our landscape review revealed that different countries have different priorities and objectives, further hindering collaborative action. Most interviewees agree, however, that global action is required.

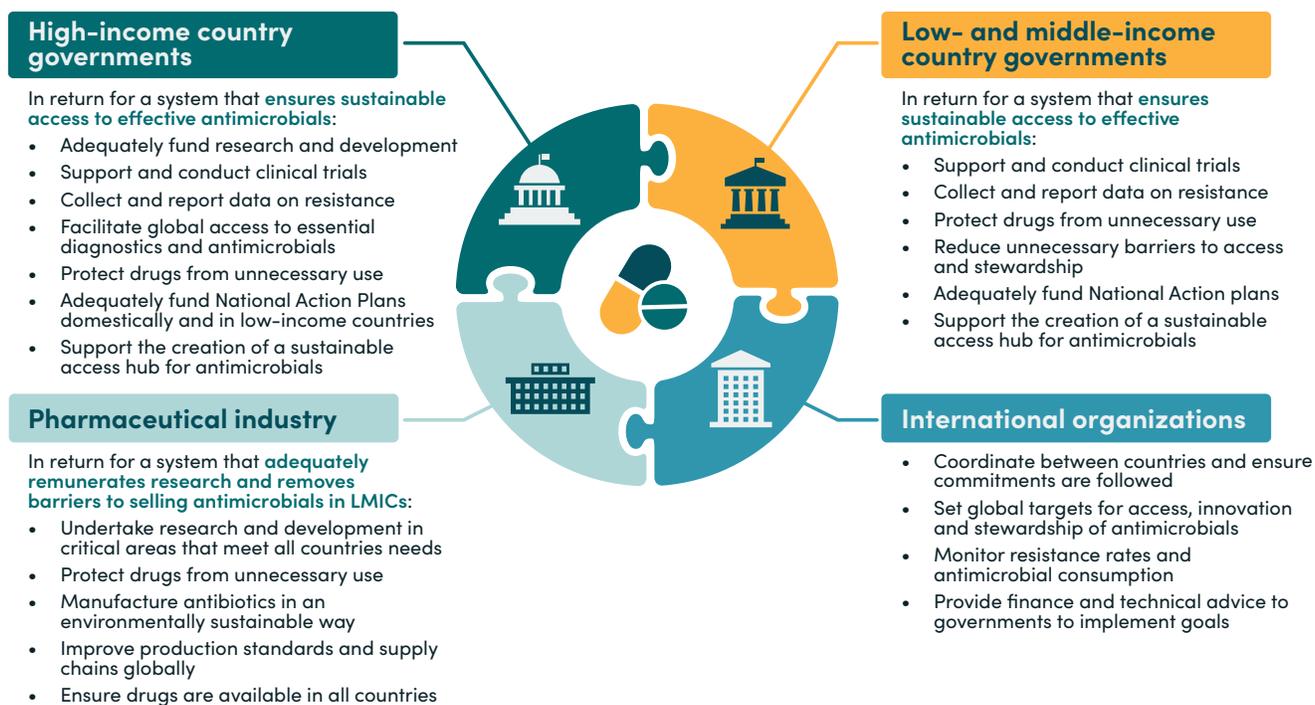
For this reason, we believe there needs to be a new Grand Bargain to Improve the Antimicrobial Market for Human Health,¹³ a mutually beneficial deal designed to meet the priorities of all parties that lays out the responsibilities and rights of each. The agreement would provide a strong set of shared principles

for innovation, access, and stewardship. Based on engagement with key stakeholders spanning industry, government, and international organizations, we believe that a mutually agreeable deal is achievable and workable.

Any bargain requires actions from three important groups of stakeholders: national governments, the pharmaceutical industry, and international organizations (figure 7). Given the interrelatedness of the problems of AMR, action from each of these groups is crucial to ensure the success of the bargain; without contributions from all, the solution will be unsustainable.

The exact nature of the bargain is for national governments to set, but several key goals should be included. First, it could set out standards and obligations that we believe all countries can and should sign on to in order to ensure that the market for antimicrobials functions properly. These standards and obligations should differ for HIC and LMIC governments, based on their capacities and needs. All countries should commit to protecting antimicrobials from unnecessary use

FIGURE 7 Overview of the proposed Grand Bargain to Improve the Antimicrobial Market for Human Health



13 The scope of this working group was human health, but the Grand Bargain should either be combined with commitments on animal health or followed up by a second agreement covering it.

and to collecting and reporting data on resistance. Countries should commit to working to ensure global access to essential diagnostics and antimicrobials, by, for example, reducing unnecessary regulatory barriers, expediting registration processes, and streamlining and harmonizing clinical trial procedures. Access should be further facilitated by the creation of a system that facilitates the distribution of drugs in countries not well served by current systems. We believe that HICs and potentially some MICs should commit to contribute to the R&D efforts of new treatments, in accordance with their ability. This commitment should include funding for early-stage research and development, through both national research funding and product development partnerships like CARB-X and GARDP. R&D should also be funded through the use of purchasing systems that generate sufficient funds but do not encourage unnecessary use of antimicrobials. One way to achieve this would be to delink the profits of antimicrobial sales from the volume of drugs sold. In return for enacting these changes, all countries would gain access to effective antimicrobials and diagnostics.

Second, any bargain should set out important roles for international organizations to coordinate and monitor the system. These organizations would establish frameworks that every country could use to develop responsible use regulations and set national targets for use of different classes of antimicrobials. Monitoring, through regular independent reviews, will be important to ensure that parties are held to account for their progress toward commitments.

Third, the pharmaceutical industry should be called upon to conduct research on new antimicrobials that meet global R&D priorities and ensure that the pipeline of new drugs includes oral treatments that can replace first-line Access treatments as well as formulations and combinations that address the specific needs of neonates, children, and people living in LMICs. Alongside governments, industry should work with the sustainable access hub (Recommendation 2, below) to ensure that drugs are available and affordable worldwide. Manufacturers should also commit to manufacture antimicrobials responsibly, to a high standard, and in a way that limits environmental run-off. They should also remove

incentives for unnecessary antimicrobial prescriptions, by, for example, banning sales bonuses and financial enticements for prescribers. In return for these commitments, national governments must establish a system in which innovation for important new antimicrobials is adequately remunerated, including through the use of tiered remuneration to drive innovation toward most needed products.

National governments, with the support of international organizations, will need to agree to the Grand Bargain, though they will also need buy-in from other key stakeholders, such as the public, medical practitioners, civil society, and industry. During the High-Level Meeting on AMR at the 2024 UN General Assembly, a political declaration will be published. Our hope is that it will reflect the needs of all key stakeholders.

Appendix C provides a suggested text for the Grand Bargain. This text was reviewed by, and incorporates comments from, over 35 organizations including 10 governments, indicating the wide acceptability of such a bargain. Implementation would ensure that effective, affordable antimicrobials are accessible worldwide and that the pharmaceutical industry receives appropriate remuneration.

2.2 OPERATIONAL RECOMMENDATIONS



Recommendation 2: Implement a sustainable access hub for antimicrobials

Governments need to create a sustainable access hub for antimicrobials, as outlined in figure 8. Donor governments should provide the funding to establish this hub. LMIC governments should play a key role in designing it, to ensure that it meets their needs. The WHO should support this work, if possible housing it at an existing institution. This recommendation builds on similar proposals from other experts (Laxminarayan 2022).

Goal and functions of the hub

The goal of the sustainable access hub would be to provide a backstop that ensures reliable access to essential

antimicrobials and diagnostics where the market fails to provide them. It would achieve this goal by handling the following functions:

1. **Procure or support the procurement of antimicrobials and diagnostics.** An essential portfolio of antimicrobials and diagnostics for procurement would be chosen, in consultation with the WHO. It should be sufficient to ensure that eligible countries have access to the drugs required to treat resistant infections. The list, which would be regularly updated, would include Access drugs, in order to prevent improved access to Watch and Reserve antimicrobials from leading to increased consumption of these higher-value drugs when Access drugs are unavailable. The hub would assist countries in determining and aggregating demand and establishing multiyear agreements with manufacturers. Existing procurement processes would be used. The sustainable access hub would sell not just to governments but also to nongovernment entities, such as faith groups and private providers, which are responsible for a significant portion of health procurement in several LMIC.
2. **Reduce market entry barriers.** The hub would simplify registration and distribution procedures, mimicking models like the Stop TB Partnership’s Global Drug Facility and the Pan American Health Organization’s Revolving Fund. This process would be aided by national regulatory authorities expediting regulatory reviews of essential

antimicrobials and participating in collaborative global, regional, and subregional registration procedures underpinned by appropriate reliance mechanisms.

3. **Shape markets.** As a large procurer of antimicrobials, the hub would have the ability to shape the antimicrobial market. To do so, it would need to procure drugs in a way that recognizes the value of sustaining this market rather than always purchasing from the lowest bidder. It should look for five outcomes in its tendering processes:
 - ▶ **Robust manufacturing.** Companies that can demonstrate manufacturing resilience, surge capacity, and the ability to deal with supply shocks could receive greater weight in the tendering system, particularly for drugs for which supply is not considered adequately secure.
 - ▶ **Affordability.** Prices should be affordable, particularly in the poorest parts of the world.
 - ▶ **Environmental standards.** Antimicrobials should be manufactured in a way that does not lead to unnecessary environmental pollution of active pharmaceutical ingredients. The hub should either refuse to purchase from manufacturers that do not meet reasonable manufacturing standards or give greater weight in tendering processes to more environmentally friendly producers.
 - ▶ **Quality assurance.** All antimicrobials should be quality assured.

FIGURE 8 Overarching aim and proposed benefits of a sustainable access hub for antimicrobials



Benefits:

- **Ensure access** access to quality assured products by reducing barriers to entry including facilitating product registration
- **Reduce inappropriate use of antimicrobials** by providing diagnostics, financial and technical assistance, and reducing incentives to oversell
- **Help countries track and report** consumption data to WHO’s GLASS platform
- **Reduce shortages** by shaping markets and forecasting and aggregating demand, tracking suppliers’ capacity, and stockpiling where necessary
- **Reduce prices** of medicines through pooled procurement and multi-year contracts

- ▶ **Market for innovation.** The hub should ensure that there is a market for innovative drugs that meet the needs of LMICs, particularly if they have requirements that are not considered high priorities in HICs.
4. **Track consumption data.** The hub would monitor global antimicrobial consumption and support countries in reporting this information to the Global Antimicrobial Resistance and Use Surveillance System, aiding projections of future demand and assessments of progress.
 5. **Stockpile drugs.** The sustainable access hub could stockpile antimicrobials, in order to manage supply or demand shocks, provide a market where consumption rates are too low, stabilize a market with large supply or demand fluctuations, and overcome routine stockouts. A detailed operational design should be developed to ensure the stockpile's successful implementation and utilization.
 6. **Limit unnecessary use.** The hub would work with countries to improve stewardship practices, including by identifying high usage rates of Watch and Reserve antimicrobials, working with procurers to reduce incentives for overselling, establishing procedures for protecting Watch and Reserve antimicrobials, providing guidance on how to implement surveillance systems and how to incorporate diagnostic technology, and reforming procurement systems to reduce incentives for unnecessary use.
 7. **Provide financial assistance.** Donor governments or international financial organizations could establish grant or concessional loan systems to help resource-constrained countries implement stewardship and surveillance systems. They could provide technical support and loans to national governments to implement health systems on the ground.
 8. **Provide technical support.** The hub could facilitate the adoption of best practices adapted to specific local contexts and provide local technical support to countries that help design and roll out national action plans or improve access and stewardship. It could work with a country that wants support reducing over-the-counter

sales of antibiotics in a way that does not reduce access to treatment or designing and testing prescription policies or pharmacy incentives in a way that reduces unnecessary use without limiting necessary access, or rolling out new diagnostics to strengthen stewardship in hospital settings.

Governance and funding of the hub

A pooled procurement system can be established at the regional or global level or both. Pooling procurement at the regional level could better meet national needs, as it would allow neighboring countries to work together to ensure that supply chains and manufacturing are more localized. If implemented properly, it can reduce the risk of shocks. However, the global nature of trade means that there are advantages to market-shaping and building resilience globally. For some low-volume drugs, regions might be too small to aggregate demand; global aggregation could be needed. The ideal level at which to pool drugs might involve a central hub and regional hubs working together, with the central hub responsible for low-volume drugs that could then be sold to regional hubs (in a manner similar to that in which the Global Drugs Facility (GDF) sells to the revolving fund of the Pan American Health Organization (PAHO); see annex C). In both regional and global options, the hub would ideally be run by an existing organization, such as GARDP, following its SECURE initiative with the WHO; the GDF; the Global Fund to Fight AIDS, Tuberculosis and Malaria; or UNICEF at the global level and/or PAHOs' Revolving Fund or the Gulf Cooperation Council at the regional level. In any hosting institution, it is important that the hub be overseen by a board that represent the interest of recipient countries and donors, if any.

For a global sustainable access hub to reach its full potential, a small secretariat will be needed. These costs should be fixed, predictable, and picked up by donors or middle-income country users. Distribution and storage costs mean that the marginal cost of selling medicines is going to be slightly higher than the cost of purchasing the medicines. This cost could be covered by a subscription fee that users pay to cover purchases or operating costs. The mark-up on the price of drugs would

be less than 10 percent. Alternatively, donors could fund these costs. (Annex C discusses funding options.)

Benefits of the hub

A sustainable access hub would fix many flaws in the antimicrobial market. First, by reducing barriers to entry, including by facilitating product registration, it would decrease the time and cost of filing for registration in many countries.

Second, the hub would ensure the high quality of medicines, thereby reducing resistance-causing manufacturing discharge. It would also ensure that stewardship standards are met. By projecting and aggregating demand, it would ameliorate issues of fragmented, fluctuating demand; reduce the risk of stockouts; strengthen supply chains; and ensure sufficient volumes to encourage innovation. Aggregating demand in a pooled procurement system would also reduce the cost of medicines for governments, which would otherwise need to negotiate for low-volume orders.

Third, creating a hub would serve the interests of both manufacturers and national governments. Manufacturers would earn a return on investment from countries they currently do not reach, and national-level purchasers would gain access to important drugs and diagnostics.

This facility should be available to all LMICs that choose to use it. Many of the problems hindering access to drugs in LMICs also affect smaller HIC markets. The hub should have the flexibility to allow such governments and manufacturers to buy and sell through the hub if they chose to do so. Prices charged to HICs should be higher than prices charged to poorer countries.

Potential risks of the hub

The sustainable access hub must strike a balance between including enough products to meet global needs and limiting the portfolio to ensure that it is implementable, emphasizing the inclusion of Access drugs. Demand for antimicrobials can fluctuate greatly. The hub must decide whether to invest in surge capacity or stockpile medicines, depending on a drug's characteristics. Not all countries can meet stewardship standards; the hub should offer technical and financial support

and work with financial institutions for concessional lending to boost stewardship and surveillance. The model carries financial risk if underutilized by buyers or countries. A comprehensive study is needed to validate and advance the model.



Recommendation 3: Ensure that innovation is properly valued and meets the needs of LMICs

As the development of new antimicrobials is urgently needed, HICs should enact push and pull incentives that ensure sufficient antimicrobial innovation to meet the world's needs. We commend that the WHO help guide innovation by setting global objectives for R&D in the form of target product profiles (TPPs), with greater emphasis on products needed in LMICs, including formulations appropriate for LMIC settings. The WHO should change the methodology by which priority pathogen lists are chosen to ensure prioritization of treatments targeting pathogens that are more prevalent in LMICs.

It is also important to ensure that innovations are remunerated based on their value to society. Toward that end, regional and national health technology assessment (HTA) bodies should update HTA frameworks to better assess antimicrobial value and incorporate the wide societal value that antimicrobials have.

Funding drugs that meet the needs of LMICs

Work by CGD has shown that investments by the US government to secure a supply of new antibiotics would return a 28-fold benefit in the United States and a return of more than 11:1 in every G7 country. HICs should make this investment, both for the good of their citizens and for the good of the world, which would see a 125-fold return on investment (Towse and Silverman Bonnifield 2022). Investments should include investments in drugs that meet the needs of LMICs, which would benefit those not only countries but HICs as well. For this reason, draft legislation for the PASTEUR Act includes extra payments for oral treatments. If incentives of this kind are not sufficient to incentivize the development of drugs needed in LMICs, the funding formula should be tweaked to ensure that all drugs that are needed globally get funded.

Ensuring that target product profiles (TPPs) target the most important needs across all countries

TPPs outline the desired characteristics of new healthcare products. TPPs for antibiotics usually target innovation for treating infections on the Bacterial Priority Pathogen List (BPPL). TPPs also need to recognize that needs in LMICs and HICs differ. LMICs require broader-spectrum treatments rather than antibiotics targeting one bacterial priority pathogen, and they need oral and thermostable drugs. TPPs should therefore place a value on such products, to ensure that innovation meets the needs of the world's poorest people.

Crafting appropriate TPPs also relies on having BPPLs that correctly prioritize the risks from different bacterial pathogens. These lists should consider the health impact and likelihood of losing treatments to resistance, which can be determined using the methodology developed by CGD in collaboration with Boston University (see page 8). Resistance trends at specific sites should be tracked, controlling for sample size and study quality, to determine the progression of resistance. These results should be combined with expert elicitation to enhance estimates of the impact and likelihood of losing an antimicrobial to resistance. The WHO, the US Centers for Disease Control and Prevention, and other agencies that have BPPLs should incorporate this type of analysis when setting their priorities.

In health systems in which HTAs are not used, TPPs can be used to set payment criteria for new drugs. Depending on how well a new drug meets these criteria, countries would commit to pay either a certain price per tablet or a certain subscription price. The advantage of TPPs is that they are forward looking, making it easier for developers to project the financial return from launching a project or undertaking an investment. However, TPPs are not widely used to evaluate treatments, making it difficult to compare value for money across treatment areas and reducing their value in the decision-making processes.

Strengthening national priority-setting processes to recognize the value of antimicrobials

Current HTA systems do not capture the full benefits of new antimicrobials, because of the difficulty of quantifying some of them. Governments could improve HTA systems in two ways. First, countries could undertake detailed analysis of the benefits, as done in the United Kingdom's NICE study (Schurer et al. 2023). Although the goal should be to use epidemiological modelling to estimate the benefit of a new drug, given the weakness in current models, it is likely that these studies will need to rely partly on expert elicitation. An alternative approach would be to rely more heavily on the literature and expert elicitation or to use frameworks such as the MAPS tool (see section 1.2).

These approaches could be combined, as the United Kingdom is doing. Countries could conduct a few detailed studies to better understand the benefits of new antimicrobials before moving to a lighter-touch methodology. Regional entities, such as Africa's Centres for Disease Control and Prevention, could support studies that countries could then adapt by using an approach such as MAPS.

The recommended improvements in surveillance of antibiotic consumption and resistance should lead to better epidemiological understanding of how resistance spreads, making future assessments of the benefits of new antimicrobials easier.



Recommendation 4: Strengthen regional regulatory processes

Governments should work with regional organizations, such as PAHO and Africa's Centres for Disease Control and Prevention, to strengthen regional regulatory processes. Regional approaches to regulating antimicrobials could streamline the approval of clinical trials; reduce the time to issue marketing authorization while guaranteeing consistent standards for safety, efficacy, and quality; and improve post-marketing vigilance and surveillance.

Regional initiatives such as the African Medicines Agency provide a platform for implementing regional regulatory approaches. It recommends the following practices:

- ▶ **Clinical trials.** Clinical trials could undergo a single review by the regional initiative rather than the country-by-country reviews and the multicountry trials for new antimicrobials that are the current norm. Regional initiatives could avoid duplication and delays, building on platforms such as the African Vaccine Regulatory Forum (AVAREF) and the Asian Clinical Research Network (Tirumalaraju 2021).
- ▶ **Marketing authorization.** National regulatory authorities could pool resources and join regional assessments of antimicrobials. Once decisions are made, they could recognize their outcomes, if parliaments establish adequate legal provisions. Alternatively, joint regional or subregional assessments followed by streamlined approval processes at the country level could be used to avoid the need to pass new legislation. Regional regulatory approaches could also provide essential public goods, such as databases for approved active pharmaceutical ingredients and good manufacturing practice inspections.
- ▶ **Vigilance and post-marketing surveillance.** Regional approaches could provide a platform for reporting substandard and falsified antimicrobials, adverse events, and resistance patterns. These regional databases could then be linked to the global initiative hosted by International Coalition of Medicines Regulatory Authorities (ICRMA) or the WHO's global surveillance and monitoring system for substandard and falsified medical products.

Regional regulatory approaches would enhance resource utilization, especially in countries where mature, functional systems do not exist and regulatory capacity is limited. Regional approaches would lead to increased and timely access to antimicrobials and effective regional procurement approaches.



Recommendation 5: Enact systems to track access and control and measure the unnecessary use of antimicrobials

Governments should agree to global protocols that limit unnecessary use of antimicrobials. These protocols should be designed to reflect the fact that stewardship is harder in resource-constrained settings and in many situations with a focus on the medium term. Countries could sign on to these policies at the UN's High-Level Meeting in 2024. Alternatively, the WHO could facilitate the protocols.

Different classes of antimicrobials should be subject to different levels of control, based on their susceptibility to resistance. Countries should design and implement prescription policies for Watch and Reserve antibiotics and create a reporting database for Reserve antibiotics. Based on local factors, such as need and the level of healthcare service provision, countries may opt for different policies for different Watch antibiotics (for example, stricter controls on intravenous drugs). These policies should be underpinned by robust data systems and access to diagnostics. Data collected through these systems should be compared against country-specific consumption targets.

Craft prescription policies

Given the diversity of country contexts and health system capabilities and the continued mortality and morbidity burden of antibiotic-treatable diseases, setting international standards for prescription policy for Access drugs is not appropriate. Countries should identify and implement locally appropriate standards. In some cases, optimal prescription policy may include low-level prescribing for Access antibiotics, including dispensing by pharmacists and community health workers. National surveillance data should be used to regularly update clinical treatment guidelines based on the local resistance profile.

For Watch and Reserve antibiotics, a stricter prescription policy is warranted. Watch antibiotics should be made available

only via a prescription from a physician or nurse practitioner; Reserve antibiotics should be subject to highly restrictive, internationally aligned prescription policy, determined through a collaborative, consultative multistakeholder process. It could include inpatient-only prescribing conditional on documented need and justification.

Develop reporting databases and data systems

An independent evaluator should develop internationally aligned regulatory standards that require physicians to document all prescriptions of Reserve antibiotics to nationally maintained databases, including the rationale for the prescription. Countries should report summary statistics from these databases to the WHO and work toward full (anonymized) data transparency where possible. Requiring documentation of Access drug use would be too onerous for most LMICs.

Countries should invest in robust electronic data systems that enable them to track and monitor the procurement and dispensing of medicines as well as core clinical indicators related to AMR. In low-income settings, these systems can be constructed using open-source, smartphone-based applications. The data needs of those inputting information must be a priority, so that they are incentivized to use any system, for example a system that gives users information on price or supply levels of products might be likely to see more use. Clinical data can be collected from stewardship initiatives. Any inventory reporting systems should also be usable for medicines other than antibiotics.

Develop diagnostic tools

Low-friction, physician-centered diagnostic systems are needed to prevent inappropriate antibiotic use, especially in hospitals. Without quick access to microbiology tests, doctors will continue to overuse broad-spectrum antibiotics. Greater use of diagnostic tests will require different incentive structures for doctors, as well as massive investment in laboratory capacity and reporting systems.

A sustainable access hub should ensure that countries have access to cost-effective diagnostics and help train health

workers to use them, creating a stronger market for these tools that incentivizes more investment. Wealthy governments should supplement these effort with their own investment in diagnostic technologies.

Access

Reporting systems need to be designed with access in mind. The consumption and availability of Access drugs should be monitored, and electronic data systems should be used to track the supply chain of medicines and the volume of prescriptions, to identify blockages or problems. Ideally, problems would be identified early enough to enable short-term responses that prevent shortages. In the longer term, such systems would help identify routine problems. Procurers or the sustainable access hub could use this information to make adaptations to improve the robustness and resilience of the supply chain, help identify areas where Watch or Reserve drugs are being used because of lack of access to Access treatments, and areas where stewardship policies are deterring necessary use of antimicrobials.



Recommendation 6: Set targets to track progress on innovation, access, and stewardship goals

Targets are important to track progress on and commitment to fighting AMR. They can be set to motivate action on innovation, access, and stewardship. Targets should be specific, measurable, achievable, relevant, and timebound and measure milestones on innovation, access, and stewardship. National governments should set global targets for innovation, access, and stewardship at the UN's High-Level Meeting in 2024 or in coordination with the WHO.

Innovation targets

Targets for antimicrobial innovation should be based on TPPs and the BPPL. They should be set by a body with a mandate, such as the WHO or countries at a UN High-Level Meeting. These targets should be clear, timebound, and regularly updated to reflect changing resistance patterns. They should be subdivided into targets for drugs targeting specific priority

pathogens, or designed for specific populations (such as neonates).

Innovation targets can be assessed by using data such as the WHO's analysis of the antibacterial pipeline. They should measure progress toward targets of both approved drugs and candidate drugs in the pipeline. Innovation targets will help assess whether push and pull incentives are working as planned. They can also test whether innovation is likely to meet the needs of all countries and can highlight weaknesses in the pipeline.

Access targets

Measuring access is essential to ensuring that stewardship concerns are not preventing people from accessing the drugs they need, testing whether policies such as a sustainable access hub are working, and identifying shortages. The WHO should facilitate this type of tracking by adapting the Essential Medicines List to provide guidance on which antibiotics are needed in a given setting. Access to medical care should then be tracked, ideally by building or collecting real-time information on supply chains or conducting surveys at points along the supply chain. Efforts should determine how many people need an antimicrobial but do not have access to it and the consequences of this lack of access in terms of both the patients affected and the rise of resistance. This work could build on work by the Global Research on Antimicrobial Resistance (GRAM) Project.

Stewardship targets

Setting targets for appropriate use in different regions would allow countries to demonstrate when they are being good citizens and identify those that are not pulling their weight. The WHO should move away from a relative target, such as requiring 60 percent of antibiotics to be Access antibiotics, instead setting per capita limits by using a defined daily dose (DDD) for each type of drug (see section 1.4). This target system should be aligned with the GLASS reporting system.

Targets could be set using a standard rate for every country, with potential adjustments to reflect factors such as wealth and population density. This approach may be easier to communicate and be seen as more standardized and therefore politically easier. Ideally, such a system would set higher absolute use targets for LMICs, where unnecessary use is more difficult to limit and the need for antibiotics is higher. Alternatively, limits could be set using a simple algorithm accounting for individual countries' needs. These methods would factor in local antibiotic failure rates and high resistance rates, conduct age-specific analysis, and calculate the upper limit of antibiotics per class, which would help protect later-line drugs from overuse.

Measuring multiple targets in tandem

Innovation, access, and stewardship should be measured in tandem to ensure that policies designed to improve stewardship do not undermine access and vice versa and in recognition of the fact that sometimes the easiest long-term solution to problems of access can be innovations that make drugs easier to deliver.

The need for independent evaluation

All categories of targets should be independently evaluated. An independent secretariat within or affiliated with the WHO could be set up and/or charged with this task, leveraging the WHO's resources and expertise while insulating the evaluator from pressure by countries. Such a system could be based on the secretariat for the WHO's Framework Convention on Tobacco Control (FCTC). Ideally, a mechanism like the FCTC could be established. Implementation and targets could be regularly reviewed to ensure that they reflect the latest scientific evidence.

It is also important that this system be about more than just setting targets. Countries should be given guidance, technical assistance, and, in resource-constrained environments, the funds to reduce unnecessary use or support access initiatives.

Acknowledgments

Within CGD, we thank Sara Viglione, Sarah Allen, Stephanie Donahoe, and Emily Schabacker for their excellent communications support. Susie Colville, Sophie Gulliver, Zuzanna Mieloch, Patsy Mills, Maddy Pattison-Sharp, Reetan Patel, Jo Redhead, Irina Stanculeanu, and Kendra White provided outstanding operational support. Peter Baker lent his expertise on health technology assessment, Ranil Dissanayake analyzed the economic problems behind AMR, and Mark Lowcock provided advice on the content of the Grand Bargain. Masood Ahmed and Amanda Glassman provided support and advice throughout the project. Many other CGD colleagues aided this research project over the last 18 months, discussing ideas and supporting the administration of the project.

We are indebted to all of our esteemed working group members, who invested many hours attending meetings, reading drafts, and sharing ideas. This work would not have been possible without them. Many people outside of the working group—whom we affectionately refer to as “friends of the working group”—also put forward ideas that helped shape the direction of this work. Some of those ideas became key recommendations of the final report.

We would like to thank four people in particular who either helped lead research projects related to the working group, organize our event in Geneva in May 2023, or travelled to participate in an in-person working group: Heidi Botero, Jennifer Cohn, Jacob Madden, and Fatema Rafiqi. We are incredibly grateful to all of them. We would also like to thank other friends of the working group, who shared their insights and feedback on key project outputs. Many of their contributions were substantial, and the project is far better for their support.

Those being acknowledged do not necessarily endorse the report’s content or recommendations, and not all of them have had the opportunity to comment on a draft of this paper, but their engagement with the ideas put forward was very valuable. All errors and omissions are those of the authors.

Shibulal A, Kerala Medical Services Corporation

Mohammed Abdul Rahman, Indian School of Business

Andre Luiz de Abreu, Oswaldo Cruz Foundation (Fiocruz)

Mirza Alas Portillo, South Centre

Juliana Aliberti Ortiz, Consultant for Instituto Centroamericano de Administración de Empresas

Najy Alsayed, Menarini

Amer Al-Taie, Pfizer

John Alter, AMR Action Fund

Afreenish Amir, National Institute of Health Pakistan

Aparna Ananthkrishnan, Health Intervention and Technology Assessment Program

James Anderson, International Federation of Pharmaceutical Manufacturers & Associations

Marco Antonio Stephano, University of São Paulo

Anucha Apisarnthanarak, Thammasat University Hospital Thailand

Christine Årdal, Institute of Public Health, Norway

Hala Audi, UNIZIMA

Anna Cecilie Friis Bach, Danish Embassy, Washington, DC

Priyanka Bajaj, PATH

Lucy Barnett, HM Treasury

Emilee Benos, US Department of Health and Human Services

Cornelious Bernard, IBHAR Technologies

Emma Berntman, The FAIRR Initiative

Peter Beyer, Global Antibiotic Research and Development Partnership

Heidi Botero, Independent consultant

Clare Chandler, London School of Hygiene and Tropical Medicine

Claudie Charbonneau, Pfizer Inc.

Jennifer Cohn, Global Antibiotic Research and Development Partnership

Abigail Colson, University of Strathclyde

Carlos Maria Correa, South Centre

Alexandre Costa, UNICEF

Saudamini Dabak, Health Intervention and Technology Assessment Program, Thailand

Snigdha Das, Indian School of Business

Santanu Datta, Bugworks

Sally Davies, Trinity College, University of Cambridge

Damiano de Felice, Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

Sarang Deo, Max Institute of Healthcare Management, Indian School of Business

Rajiv Desai, Indian Pharmaceutical Alliance

Dhanya Dharmapalan, Apollo Hospitals, Navi Mumbai, India

Christiane Dolecek, University of Oxford

Nel Druce, UK Foreign, Commonwealth and Development Office

Amany El-Sharif, Pan African University

Helle Engslund Krarup, International Centre for Antimicrobial Resistance Solutions

Manuel Espinoza, Independent consultant

Sabiha Yusuf Essack, University of KwaZulu-Natal, South Africa

Dian Faradiba, Health Intervention and Technology Assessment Program

Elizabeth Farmer, HM Treasury

Kim Faure, Global Antibiotic Research and Development Partnership

Shaffi Fazaludeen Koya, Boston University

Yann Ferrisse, Global Antibiotic Research and Development Partnership

Maja Fjaestad, Government of Sweden

Greg Frank, Merck & Co Inc., Rahway, NJ, USA

Sébastien Gagnon-Messier, Merck KGaA, Darmstadt, Germany

Ana Cristina Gales, Universidade Federal de São Paulo

Valeria Gigante, World Health Organization, AMR Division

Bilha Githinji, Maisha Meds

Juan José Gómez-Camacho, Foreign Policy Institute, School of Advanced International Studies (SAIS), Johns Hopkins University; former Mexican ambassador to the UN

Sharad Goswami, Pfizer

Malin Grape, Government of Sweden

Madhur Gupta, WHO India

Y.K. Gupta, Global Antibiotic Research and Development Partnership

Will Hall, Wellcome Trust

Petra Hansson, Swedish Embassy, Washington, DC

Abigail Herron, Aviva Investors

Parshuram Hotkar, Indian School of Business

Xun Huang, Infection Control Center, Xiangya Hospital, Central South University, China

Benedikt Huttner, World Health Organization, Access to Medicines and Health Products

Jon Iredell, New South Wales Ministry of Health; University of Sydney

Harish Iyer, Bill & Melinda Gates Foundation

Niclas Jacobson, Government of Sweden

Neeraj Jain, PATH

Vageesh Jain, UK Foreign, Commonwealth and Development Office

Mariatou Tala Jallow, TalaConsult; formerly at the Global Fund

Deepak Jena, Indian School of Business

Andrew Jenner, International Federation of Pharmaceutical Manufacturers & Associations

Tim Jinks, Wellcome Trust

Jyoti Joshi, International Centre for Antimicrobial Resistance Solutions

Elijah Kahn-Woods, Contractor with USAID's Global Health Training, Advisory and Support Contract

Vikrant Khanna, Apollo Hospitals, New Delhi, India

Yuzana Khine Zaw, Sprout Health Solutions

Yui Kohno, Health and Global Policy Institute

Jeremy Konyndyk, Refugees International

Rajiv Kumar, Pahle India Foundation; formerly at Niti Aayog, Government of India

Peter Kvist, Embassy of Sweden in Washington DC

Domenico Larcinese, Pfizer

Joe Larsen, Locus Biosciences

Ramanan Laxmanarian, One Health Trust and Princeton University

Birgitta Lesko, Public Health Agency of Sweden

Maria Lettini, FAIRR

Ruth Lopert, LWC Health

Clare MacIver, UK Department of Health and Social Care

Jacob Madden, Boston University School of Law

Peter Mamacos, US Embassy in Kenya

Daniel Mbuthia, KEMRI Wellcome Trust Research Programme

Mark McClellan, Duke-Margolis Center for Health Policy

Marc Mendelson, Groote Schuur Hospital, University of Cape Town

Anant Mishra, Perelman School of Medicine at the University of Pennsylvania

Atul Mohan Kochhar, National Accreditation Board for Hospitals & Healthcare Providers

Yara Mohsen, Department of Epidemiology, High Institute of Public Health, Alexandria, Egypt

Angela Monahan, Office of Global Affairs, US Department of Health and Human Services

Claudio A. Mora-García, INCAE Business School

Sébastien Morin, Medicines Patent Pool

Alec Morton, National University of Singapore and University of Strathclyde

Viviana Munoz, South Centre

Edna Mutua, KEMRI Wellcome Trust Research Programme

Shridhar Narayanan, Indian Pharmaceutical Alliance

Serina Ng, HM Treasury

Louise Norton-Smith, UK Department of Health and Social Care

Norio Ohmagari, National Center for Global Health and Medicine, Japan

Iruka N. Okeke, University of Ibadan, Nigeria

Jim O'Neill, Former head of AMR review

Obinna Onwujekwe, University of Nigeria

Angus O'Shea, Aranda

Claire Oxlade, UK Department of Health and Social Care

Deepali Patel, AMR Action Fund

Pavrita Paul, Pahle India

Kristine Peers, European Federation of Pharmaceutical Industries and Associations

Patrick Picard, Canadian Embassy, Washington, DC

Elizabeth Pisani, Ternyata

Andrea M. Prado, INCAE Business School

Fatema Rafiqi, Access to Medicine Foundation

Pilar Ramon-Pardo, Pan American Health Organization

John Rex, AMR.Solutions

David Ripin, Clinton Health Access Initiative

Susan Rogers Van Katwyk, Global Strategy Lab

Dan Rosen, Maisha Meds

John-Arne Rottingen, Ministry of Foreign Affairs, Norway; Norwegian Institute of Public Health; Blavatnik School, Oxford University

Joseph Saba, Axios International

Kunal Samanta, Roche

Benn Sartorius, Global Research on Antimicrobial Resistance Project, University of Queensland

Hatim Sati, World Health Organization, AMR Division

Takuko Sawada, Shionogi & Co., Ltd

Sonal Saxena, Maulana Azad Medical College, New Delhi, India

Nusrat Shafiq, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Mike Sharland, St. George's University London, United Kingdom

Sangeeta Sharma, Institute of Human Behaviour & Allied Sciences

Sanjeev Sharma, Apollo Hospitals, New Delhi, India

Yasuhisa Shiozaki, Former Minister of Health, Labour and Welfare; Former Member of House of Representatives, Japan

Sweetie Shreyashi, Indian School of Business

Sanjeev Singh, Amrita Institute of Medical Sciences

Aman Siwach, Clinton Health Access Initiative

Henry Skinner, AMR Action Fund

Emily Smith, HM Treasury

Jae-Hoon Song, Asia-Pacific Foundation for Infectious Diseases

Padmini Srikantiah, Bill & Melinda Gates Foundation

Arjun Srinivasan, US Centers for Disease Control and Prevention

Luka Srot, International Federation of Pharmaceutical Manufacturers & Associations

John Stelling, Brigham and Women's Hospital, Boston

Stéphane Straub, World Bank

Jeffrey L. Sturchio, Aranda

Amit Summan, One Health Trust

Neelam Taneja, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Karin Tegmark Wisell, Public Health Agency of Sweden

Maja Elisabeth Svankjaer Thagaard, Danish Embassy, Washington, DC

Eloise Todd, Pandemic Action Network

Adrian Towse, Office of Health Economics, London

Flavio Toxvaerd, University of Cambridge

Akhona Tshangela, Africa Centres for Disease Control and Prevention

Maarten van der Heijden, World Health Organization

Martijn van Gerven, Access to Medicine Foundation

Marijn Verhoef, Access to Medicine Foundation

Kamini Walia, Indian Council of Medical Research

Hwee Lin Wee, National University of Singapore

Ghada Zoubiane, International Centre for Antimicrobial Resistance Solutions

References

- Access to Medicine Foundation. 2021. *Antimicrobial Resistance Benchmark 2021*. Amsterdam.
- American Addiction Centers Editorial Staff. 2022. "Pseudoephedrine: Side Effects, Safety & Uses of Sudafed." *American Addiction Centers*. <https://americanaddictioncenters.org/over-the-counter-medications/pseudoephedrine> (Accessed July 4, 2023).
- AMR Action Fund. 2023. "AMR Action Fund Announces Investment in BioVersys AG." www.amractionfund.com/blog-2022/amr-action-fund-announces-investment-in-bioversys-ag (Accessed July 10, 2023).
- Anderson, Michael, Dimitra Panteli, and Elias Mossialos. 2023. *How Can the EU Support Sustainable Innovation and Access to Effective Antibiotics? Policy Options for Existing and New Medicines*. <https://eurohealthobservatory.who.int/publications/i/how-can-the-eu-support-sustainable-innovation-and-access-to-effective-antibiotics-policy-options-for-existing-and-new-medicines>.
- Årdal, Christine et al. 2018. *DRIVE-AB Revitalizing the Antibiotic Pipeline - Stimulating Innovation While Driving Sustainable Use and Global Access*. <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>.
- Belachew, Sewunet Admasu, Lisa Hall, and Linda A Selvey. 2021. "Non-Prescription Dispensing of Antibiotic Agents among Community Drug Retail Outlets in Sub-Saharan African Countries: A Systematic Review and Meta-Analysis." *Antimicrobial resistance and infection control* 10(1): 13.
- Bianco, Aida et al. 2018. "Antibiotic Prescriptions to Adults with Acute Respiratory Tract Infections by Italian General Practitioners." *Infection and drug resistance* 11: 2199–2205.
- Boluarte, Till, and Ulrik Schulze. 2022. Boston Consulting Group *The Case for a Subscription Model to Tackle Antimicrobial Resistance Another Pandemic on the Horizon*.
- Burke-Shyne, Naomi et al. 2017. "How Drug Control Policy and Practice Undermine Access to Controlled Medicines." *Health and human rights* 19(1): 237–52.
- Burnham, Jason P. 2021. "Climate Change and Antibiotic Resistance: A Deadly Combination." *Therapeutic Advances in Infectious Disease* 8: 2049936121991374. <https://doi.org/10.1177/2049936121991374>.
- Cama, J et al. 2021. "To Push or To Pull? In a Post-COVID World, Supporting and Incentivizing Antimicrobial Drug Development Must Become a Governmental Priority." *ACS Infectious Diseases* 7(8): 2029–42. <https://pubs.acs.org/doi/10.1021/acsinfecdis.0c00681>.
- CARB-X. 2023. *Working Together to Address the Global Threat of Antimicrobial Resistance*. <https://carb-x.org/carb-x-news/2021-22-annual-report/>.
- CDC. 2021. "Prescription Drug Monitoring Programs (PDMPs)." www.cdc.gov/drugoverdose/pdmp/index.html (Accessed July 4, 2023).
- Centers for Disease Control and Prevention. 2022. "Measuring Outpatient Antibiotic Prescribing." <https://www.cdc.gov/antibiotic-use/data/outpatient-prescribing/index.html>.
- Chigome, Audrey K, Maliehi Matlala, Brian Godman, and Johanna C Meyer. 2019. "Availability and Use of Therapeutic Interchange Policies in Managing Antimicrobial Shortages among South African Public Sector Hospitals; Findings and Implications." *Antibiotics* (Basel, Switzerland) 9(1).
- Cohen, Robert et al. 2023. "The Shortage of Amoxicillin: An Escalating Public Health Crisis in Pediatrics Faced by Several Western Countries." *The Journal of Pediatrics* 257. <https://doi.org/10.1016/j.jpeds.2023.01.001>.
- Colson, Abigail R et al. 2021. "Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem?" *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research* 24(12): 1828–34.
- Daulaire, Nils et al. 2015. "Universal Access to Effective Antibiotics Is Essential for Tackling Antibiotic Resistance." *Journal of Law, Medicine & Ethics* 43(S3): 17–21. www.cambridge.org/core/product/identifier/S1073110500019276/type/journal_article.
- Davies, Madlan, Rahul Meesaraganda, and Ben Stockton. 2019. "Drug Company Reps Give Quack Doctors Fridges and Televisions to Sell Antibiotics." *The Bureau of Investigative Journalism*. www.thebureauinvestigates.com/stories/2019-08-19/drug-company-reps-give-quack-doctors-fridges-and-televisions-to-sell-antibiotics.
- Davies, Sally Claire, Jonathan Grant, and Mike Catchpole. 2013. *The Drugs Don't Work: A Global Threat*. London: Viking. [www.ncbi.nlm.nih.gov/nlmcatalog?cmd=PureSearch&term=101640226\[nlmid\]](http://www.ncbi.nlm.nih.gov/nlmcatalog?cmd=PureSearch&term=101640226[nlmid]).
- Eban, Katherine. 2019. *Bottle of Lies: The Inside Story of the Generic Drug Boom*. New York, New York: Ecco Press.
- European Commission, and European Health and Digital Executive Agency. 2023. *Study on Bringing AMR Medical Countermeasures to the Market – Final Report*. Publications Office of the European Union.
- Fazaludeen Koya, Shaffi et al. "Forthcoming: Injectable Antibiotic Use in India: Public-Private Share in Volume and Cost."
- Fleming Fund. 2018. "About the Fleming Fund." www.flemingfund.org/about-us/ (Accessed August 24, 2023).
- G20 Leaders. 2022. "G20 Bali Leaders' Declaration." www.whitehouse.gov/briefing-room/statements-releases/2022/11/16/g20-bali-leaders-declaration/ (Accessed July 31, 2023).
- G7 Health ministers. 2022. G7 Health Ministers' Communiqué. Berlin. www.g7germany.de/resource/blob/974430/2042058/5651daa321517b089cdccfaffd1e37a1/2022-05-20-g7-health-ministers-communique-data.pdf?download=1.
- G7 Health Ministers. 2023. "G7 Nagasaki Health Ministers' Communiqué." www.mhlw.go.jp/content/10500000/001096403.pdf (Accessed July 10, 2023).
- Global Antibiotic Research & Development Partnership. 2022. "Shionogi, GARDP and CHAI Announce Landmark License and Collaboration Agreements to Treat Bacterial Infections by Expanding Access to Cefiderocol in 135 Countries." <https://gardp.org/shionogi-gardp-and-chai-announce-landmark-license-and-collaboration-agreements-to-treat-bacterial-infections-by-expanding-access-to-cefiderocol-in-135-countries/> (Accessed July 31, 2023).
- GlobalData Healthcare. 2023. "ECCMID 2023: Updating the Global Bacterial Priority Pathogens List." *Clinical Trials Arena*. www.clinicaltrialsarena.com/comment/eccmid-2023-global-bacterial-priority-pathogens-bppl/ (Accessed July 10, 2023).
- Hall, William, Anthony McDonnell, and Jim O'Neill. 2018. *Superbugs: An Arms Race against Bacteria*. www.hup.harvard.edu/catalog.php?isbn=9780674975989.

- Hellamand, Moska, Martijn van Gerven, and Fatema Rafiqi. 2022. *Lack of Access to Medicine Is a Major Driver of Drug Resistance. How Can Pharma Take Action?* Amsterdam. https://accessmedicinefoundation.org/medialibrary/62c2f0dcca565_atmf_appropriate_access_to_antimicrobials_2022-1666595390.pdf.
- Hotkar, Parshuram et al. 2023. *Overcoming Barriers to Improve Antimicrobial Access, Innovation, and Stewardship in India.* www.cgdev.org/sites/default/files/overcoming-barriers-improve-antimicrobial-access-innovation-and-stewardship-india.pdf.
- Ikuta, Kevin S et al. 2022. "Global Mortality Associated with 33 Bacterial Pathogens in 2019: A Systematic Analysis for the Global Burden of Disease Study 2019." *The Lancet* 400(10369): 2221–48. [https://doi.org/10.1016/S0140-6736\(22\)02185-7](https://doi.org/10.1016/S0140-6736(22)02185-7).
- Ingelbeen, Brecht et al. 2023. "Setting a Realistic AWaRe Target for Primary Care Antibiotic Use in LMICs." *The Lancet. Infectious diseases* 23(2): 152–53.
- Innovative Medicines Initiative. "ENABLE: European Gram-Negative Antibacterial Engine." www.imi.europa.eu/projects-results/project-factsheets/enable.
- . "ND4BB." www.imi.europa.eu/projects-results/project-factsheets/nd4bb (Accessed July 10, 2023b).
- Institute for Health Metrics and Evaluation (IHME). 2023. "GBD Results." <https://vizhub.healthdata.org/gbd-results/> (Accessed August 21, 2023).
- Institute for Health Metrics and Evaluation (IHME), and University of Oxford. 2023. "Measuring Infectious Causes and Resistance Outcomes for Burden Estimation (MICROBE)." <https://vizhub.healthdata.org/microbe/> (Accessed August 21, 2023).
- International Narcotics Control Board. 2023. "Mandate and Functions." <https://www.incb.org/incb/en/about/mandate-functions.html> (Accessed August 23, 2023).
- Islam, M Mofizul, and Ian S McRae. 2014. "An Inevitable Wave of Prescription Drug Monitoring Programs in the Context of Prescription Opioids: Pros, Cons and Tensions." *BMC pharmacology & toxicology* 15: 46.
- Islam, Md Ariful et al. 2022. "Pattern of Antibiotic Dispensing at Pharmacies According to the WHO Access, Watch, Reserve (AWaRe) Classification in Bangladesh." *Antibiotics (Basel, Switzerland)* 11(2).
- Jørgensen, Lars Christian et al. 2013. "Antibiotic Prescribing in Patients with Acute Rhinosinusitis Is Not in Agreement with European Recommendations." *Scandinavian Journal of Primary Health Care* 31(2): 101–5. <https://doi.org/10.3109/02813432.2013.788270>.
- Källberg, Cecilia et al. 2018. "Introduction and Geographic Availability of New Antibiotics Approved between 1999 and 2014" ed. Joel Lexchin. *PLOS ONE* 13(10): e0205166. <https://dx.plos.org/10.1371/journal.pone.0205166>.
- Kelesidis, Theodoros, and Matthew E Falagas. 2015. "Substandard/Counterfeit Antimicrobial Drugs." *Clinical microbiology reviews* 28(2): 443–64.
- Kickbusch, Ilona et al. 2021. "The Lancet and Financial Times Commission on Governing Health Futures 2030: Growing up in a Digital World." *Lancet (London, England)* 398(10312): 1727–76.
- Klemperer, Katherine, Fatema Rafiqi, and Anthony McDonnell. *Forthcoming: The Broken Wheel of Access for Antimicrobials: Barriers to Rolling out Antimicrobials in Low- and Middle-Income Countries.*
- Knaul, Felicia Marie, William E Rosa, Héctor Arreola-Ornelas, and Renu Sara Nargund. 2022. "Closing the Global Pain Divide: Balancing Access and Excess." *The Lancet Public Health* 7(4): e295–96. [https://doi.org/10.1016/S2468-2667\(22\)00063-9](https://doi.org/10.1016/S2468-2667(22)00063-9).
- Kostyanev, T et al. 2016. "The Innovative Medicines Initiative's New Drugs for Bad Bugs Programme: European Public-Private Partnerships for the Development of New Strategies to Tackle Antibiotic Resistance." *Journal of Antimicrobial Chemotherapy* 71(2): 290–95. <https://doi.org/10.1093/jac/dkv339>.
- Laxminarayan, Ramanan. 2022. "Greater Access to Antibiotics Is Essential for Curbing Drug Resistance." *Financial Times.* www.ft.com/content/4a1c4f4f-f062-4bdf-b2e8-d9c1030ea1a0.
- Leonard, Colm et al. 2023. "Can the UK 'Netflix' Payment Model Boost the Antibacterial Pipeline?" *Applied health economics and health policy* 21(3): 365–72.
- Leslie, Toby, and Mott MacDonald. 2022. "How the Fleming Fund Has Worked to Build Surveillance Capacity in LMICs across Human and Animal Health Sectors." *The Fleming Fund.* www.flemingfund.org/publications/how-the-fleming-fund-has-worked-to-build-surveillance-capacity-in-lmics-across-human-and-animal-health-sectors/ (Accessed August 22, 2023).
- Li, Jinxi et al. 2023. "Worldwide Dispensing of Non-Prescription Antibiotics in Community Pharmacies and Associated Factors: A Mixed-Methods Systematic Review." *The Lancet Infectious Diseases.* [https://doi.org/10.1016/S1473-3099\(23\)00130-5](https://doi.org/10.1016/S1473-3099(23)00130-5).
- Lowe, Richard, and Dominic Montagu. 2009. "Legislation, Regulation, and Consolidation in the Retail Pharmacy Sector in Low-Income Countries." *Southern Medical Review* 2.
- Lu, Fangwen. 2014. "Insurance Coverage and Agency Problems in Doctor Prescriptions: Evidence from a Field Experiment in China." *Journal of Development Economics* 106: 156–67. www.sciencedirect.com/science/article/pii/S0304387813001272.
- Luepke, Katherine H et al. 2017. "Past, Present, and Future of Antibacterial Economics: Increasing Bacterial Resistance, Limited Antibiotic Pipeline, and Societal Implications." *Pharmacotherapy* 37(1): 71–84.
- Madden, Jacob, and Kevin Outterson. 2023. "Trends in the Global Antibiotics Market." *Nature reviews. Drug discovery* 22(3): 174.
- Mancini, Donato Paolo, and Hannah Kuchler. 2022. "Surge in Infections Leads to Global Shortage of Antibiotics." *Financial Times.* www.ft.com/content/fe24d669-7a6b-4df2-adc6-654265b66e7a.
- McDonnell, Anthony et al. 2021. *A Path to Resiliency: Mitigating the Impacts of COVID-19 on Essential Medicines Supply Chains.* Washington DC; USA. www.cgdev.org/sites/default/files/Mitigating-impact-covid-essential-medicine-supply-chain_0.pdf.
- . *Forthcoming: Workhorse Antibiotics Are in Jeopardy: Resistance Trajectories and the Need for an R&D Response.*
- McDonnell, Anthony, and Katherine Klemperer. 2022. "Drug-Resistant Infections Are One of the World's Biggest Killers, Especially for Children in Poorer Countries. We Need to Act Now." *Center for Global Development* blog: 1–8.
- McDonnell, Anthony, Katherine Klemperer, Morgan Pincombe, and Javier Guzman. 2022. *Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation: A Landscape Review of Current and Potential Market Structures for Antimicrobials.* www.cgdev.org/publication/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review.
- Miller, Rosalind, and Catherine Goodman. 2016. "Performance of Retail Pharmacies in Low- and Middle-Income Asian Settings: A Systematic Review." *Health policy and planning* 31(7): 940–53.
- Ministry of Health and Family Welfare. 2023. "National Health Accounts Estimates for India (2019–20) Released." *Press Information Bureau Delhi.* <https://pib.gov.in/PressReleaseFramePage.aspx?PRID=1919582> (Accessed July 10, 2023).
- Morgan, Christopher E et al. 2023. "Streptothricin F Is a Bactericidal Antibiotic Effective against Highly Drug-Resistant Gram-Negative Bacteria

- That Interacts with the 30S Subunit of the 70S Ribosome." *PLOS Biology* 21(5): 1–26. <https://doi.org/10.1371/journal.pbio.3002091>.
- Murray, Christopher JL et al. 2022. "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis." *The Lancet* 399(10325): 629–55. <https://linkinghub.elsevier.com/retrieve/pii/S0140673621027240>.
- National Institute for Health and Care Excellence. 2022. "Cefiderocol for Treating Severe Drug-Resistant Gram-Negative Bacterial Infections." www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol (Accessed August 15, 2023).
- NHS. 2023. "'Hospital Only' Red List." <https://westsexccg.nhs.uk/your-health/medicines-optimisation-and-pharmacy/hospital-only-red-list> (Accessed July 4, 2023).
- Nickerson, Jason W et al. 2017. "Access to Controlled Medicines for Anesthesia and Surgical Care in Low-Income Countries: A Narrative Review of International Drug Control Systems and Policies." *Canadian journal of anaesthesia = Journal canadien d'anesthésie* 64(3): 296–307.
- Niewiadomska, Anna Maria et al. 2019. "Population-Level Mathematical Modeling of Antimicrobial Resistance: A Systematic Review." *BMC medicine* 17(1): 81.
- Outerson, Kevin. 2021a. "BU AMR Model with Dashboard." <https://open.bu.edu/handle/2144/42568>.
- . 2021b. "Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines." *Health Affairs* 40(11): 1758–65. www.healthaffairs.org/doi/10.1377/hlthaff.2021.00688.
- "Pharmacist-Only Medicines." 2013. www.medsafe.govt.nz/consumers/pharmonly.asp.
- Pincombe, Morgan, Anthony McDonnell, and Javier Guzman. 2023. *Leveraging Brazilian Leadership and Procurement Arrangements in the Fight Against Antimicrobial Resistance*. www.cgdev.org/publication/leveraging-brazilian-leadership-and-procurement-arrangements-fight-against.
- Pisani, Elizabeth, and Anthony McDonnell. "Forthcoming: Antibiotic Needs and Use in Low Income Countries: What Do We Know?"
- Pokharel, Sunil, Shristi Raut, and Bipin Adhikari. 2019. "Tackling Antimicrobial Resistance in Low-Income and Middle-Income Countries." *BMJ Global Health* 4(6). <https://gh.bmj.com/content/4/6/e002104>.
- Public Health England. 2018. "Research Reveals Levels of Inappropriate Prescriptions in England." www.gov.uk/government/news/research-reveals-levels-of-inappropriate-prescriptions-in-england (Accessed July 10, 2023).
- Pulcini, Céline et al. 2012. "Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia." *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 54(2): 268–74.
- Raghavendran, Vimala, and Matthew Christian. 2022. "Supply Chain Vulnerabilities Exist for Antimicrobial Medicines: USP Medicine Supply Map Analysis." *US Pharmacopeia*. <https://qualitymatters.usp.org/supply-chain-vulnerabilities-for-antimicrobial-medicines>.
- ReAct. "Few Antibiotics under Development." www.reactgroup.org/toolbox/understand/how-did-we-end-up-here/few-antibiotics-under-development/ (Accessed July 6, 2023).
- Review on Antimicrobial Resistance. 2016. *Tackling Drug-Resistance Infections Globally: Final Report and Recommendations*.
- Rex, John H et al. 2019. "Designing Development Programs for Non-Traditional Antibacterial Agents." *Nature Communications* 10(1): 3416. www.nature.com/articles/s41467-019-11303-9.
- Robertson, Sherryl G, Naomi T Hehonah, Rose D Mayaune, and Beverley D Glass. 2021. "Prevalence of Substandard Amoxicillin Oral Dosage Forms in the National Capital District of Papua New Guinea." *The American journal of tropical medicine and hygiene* 105(1): 238–44.
- Roser, Max, and Hannah Ritchie. 2019. "Cancer." *Our World in Data*. <https://ourworldindata.org/cancer> (Accessed August 24, 2023).
- Rothery, Claire et al. 2018. *Framework for Value Assessment of New Antimicrobials*. www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf.
- Saleem, Zikria et al. 2020. "Sale of WHO AWaRe Groups Antibiotics without a Prescription in Pakistan: A Simulated Client Study." *Journal of pharmaceutical policy and practice* 13: 26.
- Schäfermann, Simon et al. 2020. "Availability, Prices and Affordability of Selected Antibiotics and Medicines against Non-Communicable Diseases in Western Cameroon and Northeast DR Congo." *PLOS ONE* 15(1): e0227515. <https://doi.org/10.1371/journal.pone.0227515>.
- Schurer, Marieke et al. 2023. "Recent Advances in Addressing the Market Failure of New Antimicrobials: Learnings from NICE's Subscription-Style Payment Model." *Frontiers in medical technology* 5: 1010247.
- Shionogi. 2019. "FETROJA® (Cefiderocol) Approved by the FDA for Treatment of Complicated Urinary Tract Infections (CUTI) in Adult Patients with Limited or No Alternative Treatment Options." www.shionogi.com/us/en/news/2019/11/fetroja-cefiderocol-approved-by-the-fda-for-treatment-of-complicated-urinary-tract-infections-cuti-in-adult-patients-with-limited-or-no-alternative-treatment-options.html (Accessed July 31, 2023).
- Shionogi & Co LTD, and GARDP Foundation. 2022. *License and Technology Transfer Agreement*. <https://gardp.org/wp-content/uploads/2022/06/License-and-Technology-Transfer-Agreement-1.pdf>.
- Silverman Bonnifield, Rachel, and Katherine Klemperer. 2023. *The Not-So-Invisible Hand of "Stewardship," Within and Beyond Antibiotics: Implications of Non-Monetary Pharmaceutical Controls for Access to Medicines*. Washington DC, USA. www.cgdev.org/publication/not-so-invisible-hand-stewardship-within-and-beyond-antibiotics-implications-non.
- Silverman Bonnifield, Rachel, and Adrian Towse. 2022a. "Estimating Canada's Return on Investment from an Ambitious Program to Incentivize New Antibiotics."
- . 2022b. "Estimating Japan's Return on Investment from an Ambitious Program to Incentivize New Antibiotics."
- . 2022c. "Estimating the European Union's Return on Investment from an Ambitious Program to Incentivize New Antibiotics."
- . 2022d. "Estimating the UK's Return on Investment from an Ambitious Program to Incentivize New Antibiotics."
- Silverman, Rachel, Janeen Madan Keller, Amanda Glassman, and Kalipso Chalkidou. 2019. *Tackling the Triple Transition in Global Health Procurement*. Washington DC, USA. www.cgdev.org/sites/default/files/better-health-procurement-tackling-triple-transition.pdf.
- St George's University of London. 2023. "Antimicrobial Resistance, Prescribing, and Consumption Data to Inform Country Antibiotic Guidance and Local Action." <https://cnpi-amr.org/research/adila/> (Accessed July 31, 2023).
- Stop TB Partnership. 2022. *The Global Drug Facility (GDF)*. <https://omnibook.com/view/9512cb3e-0cfc-44fb-a8fd-fa3d3d03fa6a/539fd4.xcml#panel-z-6a61d28b534f614f>.
- . 2023. "GDF's Results." www.stoptb.org/mission/gdfs-results (Accessed August 22, 2023).

- Sulis, Georgia et al. 2020. "Antibiotic Overuse in the Primary Health Care Setting: A Secondary Data Analysis of Standardised Patient Studies from India, China and Kenya." *BMJ Global Health* 5(9): e003393. <http://gh.bmj.com/content/5/9/e003393.abstract>.
- Taber, Jennifer M, Bryan Leyva, and Alexander Persoskie. 2015. "Why Do People Avoid Medical Care? A Qualitative Study Using National Data." *Journal of general internal medicine* 30(3): 290–97.
- Thakur, Dinesh Singh, and Prashant Reddy T. 2022. *The Truth Pill: The Myth of Drug Regulation in India*. Simon & Schuster India. <https://thetruthpill.in/>.
- Tirumalaraju, Divya. 2021. "Asian Clinical Research Network Launches to Fight Drug-Resistant Infections." *Clinical Trials Arena*. www.clinicaltrialsarena.com/news/asian-clinical-research-network/.
- Towse, Adrian, and Rachel Silverman Bonnifield. 2022. *Center for Global Development Policy Papers An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment*. www.cgdev.org.
- United States National Library of Medicine. "ClinicalTrials.gov." <https://clinicaltrials.gov/> (Accessed August 21, 2023).
- Weldon, Isaac et al. 2022. "A Pandemic Instrument Can Start Turning Collective Problems into Collective Solutions by Governing the Common-Pool Resource of Antimicrobial Effectiveness." *The Journal of law, medicine & ethics: a journal of the American Society of Law, Medicine & Ethics* 50(S2): 17–25.
- Whitman, M S, and A R Tunkel. 1992. "Azithromycin and Clarithromycin: Overview and Comparison with Erythromycin." *Infection control and hospital epidemiology* 13(6): 357–68.
- WHO. 2019. "Ten Threats to Global Health in 2019." www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019 (Accessed September 7, 2021).
- . 2020. "Lack of New Antibiotics Threatens Global Efforts to Contain Drug-Resistant Infections." www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections (Accessed July 10, 2023).
- . 2021. "2021 AWaRe Classification." : Exce. <https://apps.who.int/iris/bitstream/handle/10665/327957/WHO-EMP-IAU-2019.11-eng.xlsx?ua=1>.
- . 2022a. "Glass Dashboard - Global AMC Data." https://worldhealthorg.shinyapps.io/glass-dashboard/_w_b63a5d7d/#!/amc (Accessed July 10, 2023).
- . 2022b. *Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022*. Geneva. <https://reliefweb.int/attachments/4aefb77-6ab9-45e0-8953-ed33d20f2c4b/9789240062702-eng.pdf>.
- . 2022c. "Global Database for Tracking Antimicrobial Resistance (AMR) Country Self- Assessment Survey (TrACSS)." <https://amrcountryprogress.org/#/visualization-view> (Accessed August 22, 2023).
- . 2023a. "Analysis of the Antibacterial Pipeline." www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/antimicrobial-resistance/analysis-of-the-antibacterial-pipeline (Accessed August 22, 2023).
- . 2023b. "Global Antimicrobial Resistance and Use Surveillance System (GLASS)." www.who.int/initiatives/glass (Accessed August 22, 2023).
- . 2023c. "Health Technology Assessment." www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/assessment (Accessed August 22, 2023).
- . 2023d. "New WHO Report Highlights Progress, but Also Remaining Gaps, in Ensuring a Robust Pipeline of Antibiotic Treatments to Combat Antimicrobial Resistance (AMR)." [www.who.int/news/item/15-05-2023-new-who-report-highlights-progress-but-also-remaining-gaps-in-ensuring-a-robust-pipeline-of-antibiotic-treatments-to-combat-antimicrobial-resistance-\(amr\)](http://www.who.int/news/item/15-05-2023-new-who-report-highlights-progress-but-also-remaining-gaps-in-ensuring-a-robust-pipeline-of-antibiotic-treatments-to-combat-antimicrobial-resistance-(amr)).
- . 2023e. "Supporting Countries with National Action Plan Implementation." www.who.int/activities/supporting-countries-with-national-action-plan-implementation (Accessed July 31, 2023).
- Williams, Phoebe Cm et al. 2022. "Antibiotics Needed to Treat Multidrug-Resistant Infections in Neonates." *Bulletin of the World Health Organization* 100(12): 797–807.
- Woods, Beth et al. 2022. *Final Report for the Technology Evaluation of Cefiderocol for Treating Severe Aerobic Gram-Negative Bacterial Infections*. Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU). <https://drive.google.com/file/d/19sVkhHwwMbyHIQTiISAE3A1sSH12X7PE/view>.
- World Health Assembly (WHA). 2019. *Seventy-Second World Health Assembly Agenda Item 11.8: Antimicrobial Resistance*. https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R5-en.pdf.
- World Health Organization. 2018. *WHO Essential Medicines and Health Products: Annual Report 2017: Towards Access 2030*. World Health Organization. <https://apps.who.int/iris/handle/10665/272972>.
- . 2021. *World Health Organization Model List of Essential Medicines: 22nd List (2021)*. World Health Organization. <https://apps.who.int/iris/handle/10665/345533>.
- . 2022a. *World Health Organization 2021 Antibacterial Agents in Clinical and Preclinical Development: An Overview and Analysis*. www.who.int/publications/i/item/9789240021303.
- . 2022b. *The WHO AWaRe (Access, Watch, Reserve) Antibiotic Book*. Geneva. www.who.int/publications/i/item/9789240062382.
- World Health Organization Global Health Expenditure database. 2023. "Out-of-Pocket Expenditure (% of Current Health Expenditure)." World Bank Group. <https://data.worldbank.org/indicator/SH.XPD.OOPC.CH.ZS> (Accessed August 22, 2023).
- Yadav, Prashant. "Forthcoming: Medicine Stockpiles and AMR: A Review of Conceptual Benefits and Operational Feasibility."
- Yadav, Prashant and Anthony McDonnell. "Forthcoming: Incentivizing Antibiotic Stewardship in out-of-Pocket Markets: The Role of Distributors and Channel Aggregators."
- Zanichelli, Veronica et al. 2023. "The WHO AWaRe (Access, Watch, Reserve) Antibiotic Book and Prevention of Antimicrobial Resistance." *Bulletin of the World Health Organization* 101(4): 290–96.

Annex A. Research Projects Undertaken as Part of the Working Group

The working group commissioned or undertook research projects aimed at understanding how best to adapt AMR policies to various contexts and fix problems related to innovation, access, and stewardship of antimicrobials. A theoretical piece examined the broader market failures that explain the lackluster response to AMR.

The Local Context

- ▶ The working group conducted three country case studies (on Brazil, India, and Kenya) led by the INCAE Business School, KEMRI-Wellcome, and the Indian School of Business, respectively.
- ▶ In Kenya, it worked with the pharmaceutical aggregator Maisha Meds to understand consumption patterns for antimicrobials.
- ▶ In India, it worked with Shaffi Fazaludeen Koya (Boston University School of Public Health) to understand the consumption of injectable antibiotics.
- ▶ Prashant Yadav (CGD) explored the possibility of delinking antibiotic sales from the return on investment for sellers when drugs are purchased over the counter.
- ▶ The working group worked with Elizabeth Pisani (Ternyata Ltd) to conduct stakeholder interviews to understand the needs of LICs.
- ▶ The working group worked with the Global Research and Development Partnership (GARDP) to design a toolkit for assessing which antimicrobial platforms work best in which countries.

Innovation

- ▶ Rachel Silverman Bonnifield (CGD) worked with Adrian Towse (Office of Health Economics), to understand the return on investment to G7 countries from investing in new antimicrobials.
- ▶ CGD collaborated Kevin Otterson and Jacob Madden from Boston University to assess the risk of not replacing the work-horse antimicrobials that LMICs are particularly reliant on.
- ▶ Manuel Espinoza (Pontificia Universidad Católica de Chile) researched how best to value new antimicrobials in LMICs.

Access

- ▶ CGD worked with the Access to Medicine Foundation to track the rollout of new antimicrobials and understand why treatments are rolled out so much more slowly (if at all) in LMICs.
- ▶ Heidi Botero (independent consultant) led a project aimed at understanding how the Global Drugs Facility was set up and how it overcame problems in TB similar to those in AMR.

Stewardship

- ▶ The working group commissioned the One Health Trust to design a methodology for tracking and comparing antimicrobial consumption across countries and to consider how to set targets.
- ▶ Rachel Silverman Bonnifield (CGD) and Katherine Klemperer (CGD) reviewed the tools used in all areas of medicine to protect drugs from unnecessary use and how to balance them against the need to ensure access to new drugs.

Annex B. Policy Recommendations Included in the Case Studies of India and Brazil

To combat AMR in India, we propose modifying procurement systems to improve access to important Watch and Reserve antimicrobials that treat critical priority pathogens on the Indian Priority Pathogen List while also ensuring appropriate stewardship practices (Hotkar et al. 2023). We also propose creating an innovation ecosystem that supports antimicrobial R&D.

The National and State Action Plans should be modified to explicitly outline the guidelines for procurement of these antimicrobials. These drugs should be added to state drug procurement lists, and states should coordinate with one another to reduce duplicative efforts and benefit from economies of scale. Alternate channels such as private aggregators should be considered for procuring low-volume antimicrobials. These policies to improve access need to be enacted alongside policies to ensure stewardship, such as encouraging hospitals to follow stewardship practices and improving the monitoring of hospitals. Diagnostic facilities should be improved and surveillance of Watch and Reserve antimicrobials enhanced to prevent resistance. There is also a need to develop a target product profile specific to the Indian context, alongside procedural changes to enhance innovation such as expedited approvals.

In Brazil, a version of an existing model—the Product Development Partnerships (PDP) model—could be leveraged to expand access to critical antimicrobials, stimulate local manufacturing, and protect against overuse and inappropriate use (Pincombe, McDonnell, and Guzman 2023). The model—in use since 2009 for many antiretrovirals, anticancer, and immunosuppressant drugs—could be applied to key high-cost antibiotics or ones available from a single supplier. The model entails transferring technology from a pharmaceutical company to a Brazilian public laboratory that would gradually increase production of a given health product over the course of 10 years. The Ministry of Health would then purchase the products and sell them through Brazil's universal health coverage scheme. As of December 2022, there was a PDP for only one antimicrobial, making this model a largely untapped opportunity.

We propose a modified version of the PDP model—the annual-fee PDP—that would delink profit from sales volume in order to prevent excess sales of health products. The annual-fee PDP would charge a fixed annual price independent of the number of units purchased. Brazilian health stakeholders are already familiar with the traditional PDP infrastructure, which could facilitate implementation of the annual-fee PDP. Products produced through annual-fee PDPs could be procured at the national, regional, or global level.

Annex C. Illustrative Example of the Text of a Grand Bargain

Preamble

- 1.1 Primary health care systems play a crucial role in preventing and diagnosing illness, providing access to antimicrobials, and reducing unnecessary and inappropriate use. Proper hygiene procedures, sanitation systems, access to clean water, and high vaccination rates are critical to reducing the need for antimicrobials. We recognize our collective responsibility to tackle antimicrobial resistance (AMR) and the need for wealthier countries to support low-income countries (LICs) in improving these systems and services.
- 1.2 We applaud the work by the World Health Organization (WHO) to classify antimicrobials into the AWaRe categories of Access (common, first-line treatments); Watch (limited use because of risk of resistance); and Reserve (last resort, used to treat severe infections). We believe that it is particularly crucial to protect Reserve antimicrobials from unnecessary and inappropriate use. This categorization, together with national lists based on consideration of national risk, accessibility, and needs, plays an important role in guiding appropriate antimicrobial use.
- 1.3 It is essential that Access and Watch antibiotics be available to all who need them. We recognize that lack of access to these drugs can facilitate resistance by failing to stop the spread of infections or by encouraging people to use Watch and Reserve antibiotics when they are available but Access treatments are not. We recognize that protecting Access and Watch antimicrobials from unnecessary and inappropriate use is important but that standards for stewardship need to be less stringent than for Reserve antimicrobials, to ensure greater access to these drugs.
- 1.4 We recognize the important priority-setting work done by the WHO in developing the priority bacterial pathogen list and the need to develop new antimicrobials that can treat infections identified on this list. We welcome the efforts of international initiatives such as CARB-X and GARDP. The research and development (R&D) pipeline must include drugs that address the priorities of LMICs, such as ensuring oral and thermostable treatments. We also acknowledge that current economic incentives are not sufficient to generate the private investment needed to develop the new antimicrobials that the world needs.
- 1.5 Many new antimicrobials classified as Reserve by the WHO have been made available only in a small number of countries. We recognize the important work of the quadripartite agencies—the Food and Agriculture Organization (FAO) of the United Nations, the UN Environment Programme (UNEP), the WHO, and the World Organisation for Animal Health (WOAH)—in simplifying regulation, through, for example, the WHO prequalification program and the collaborative procedure for accelerated registration but note the need for improvement. These drugs have not been adapted, where relevant, to address the particular needs of vulnerable populations, especially children and babies, and the companies that have developed them have often struggled to succeed commercially. The business case for ensuring availability in LMICs is particularly challenging.
- 1.6 Rapid diagnostics can reduce the unnecessary use of antimicrobials, enable health providers to get people the treatments they need in a timelier fashion, and improve the market for new antimicrobials. R&D and the delivery of diagnostics are underfunded. Work is required to improve the economic model for diagnostics.

- 1.7 Information on the prevalence and burden of both antimicrobial-sensitive and antimicrobial-resistant micro-organisms has improved, in part because of the work of the Global Research on Antimicrobial Resistance project and the WHO's Global Antimicrobial Resistance Use Surveillance System (GLASS). These estimates should improve the understanding of which priority pathogens to focus innovation on and which interventions work best for combatting resistance.
- 1.8 The current procurement hubs for antimicrobials fail to stimulate sufficient R&D for new antimicrobials, promote affordable and equitable access to new and existing products, or ensure stewardship of new products. There is a need to optimize the way antimicrobials are purchased to ensure their availability and appropriate use while promoting innovation and address the rising rates of antimicrobial resistance (AMR).
- 1.9 In much of the world, antimicrobials have very high rates of substandard and counterfeit medicines, and environmental pollution from the manufacturing of antimicrobials can cause great damage.
- 1.10 The problems of AMR can be solved only by an aligned and organized response that provides reciprocal rights and ensures accountability. There is a need for coordination by all stakeholders— governments, international organizations, the pharmaceutical industry, civil society, health care providers, and patients—to support implementation of this declaration and oversee and report on progress toward the commitments on a regular basis. The sections that follow lay out those rights and responsibilities for all countries and stakeholders.
- 1.11 For the purpose of this document, we define stewardship as reducing antimicrobial consumption in instances where use provides very little or no medical benefit or alternative treatments would generate less resistance without compromising patient care. We define access as increasing the number of essential antimicrobials available to people who need them. We define innovation as the creation of new treatments or products that improve patient outcomes.

International Collaboration and Coordination:

- 2.1 We call for the establishment of an antimicrobial procurement hub, or hubs, to enable antimicrobials to reach all countries that need them. This procurement hub should work as a backstop where the market fails to ensure access to essential antimicrobials and diagnostics. Functions should include product registration, procurement, and distribution; market-shaping; reduction of unnecessary use; the tracking of consumption data; technical assistance; and financial assistance. The hub have the capacity to fund policy research and demonstration projects to help countries implement these commitments. It should be run by an existing international organization or organizations, operating either globally or regionally.
- 2.2 We call upon the WHO to develop a framework for responsible use regulations for Reserve and, where appropriate, Watch antimicrobials. Such a framework would ensure that governments can provide timely access and effective management, distribution, and tracking of these antimicrobials in accordance with each country's national action plan. The framework should establish procedures for limiting distribution of these antimicrobials to specific authorized facilities or prescribers and provide guidance to log and document prescriptions of Reserve antimicrobials, including the rationale for their use.
- 2.3 We call for the creation of a framework for setting national targets or guidelines for Reserve and, where appropriate, Watch antimicrobial use by 2026. This framework should take advantage of the improved availability of data on resistance rates and use data collected from industry as well as national governments. The framework should reflect the fact that the need for antimicrobials will likely be higher in poorer, hotter, and more densely populated countries as well as in countries with higher levels of resistance. It should include a mechanism by which antimicrobial commitments can be regularly updated

and independently verified, akin to the WHO's Framework Convention on Tobacco Control or the Intergovernmental Panel on Climate Change.

- 2.4 We call on international financing institutions to increase concessional lending for countries to improve their stewardship and surveillance systems.
- 2.5 We call for biannual independent reviews to track progress toward commitments included in appropriate international agreements.
- 2.6 We call for funders to always include specific contractual commitments on global stewardship and access, including ensuring access to LMICs through timely registration, affordable pricing, and/or voluntary licensing.
- 2.7 We call for the WHO to continue its work expanding the prequalification system to cover more essential antimicrobials and better incentivize their use.

National Obligations

- 3.1 We commit to implementing antimicrobial resistance national action plans that protect antimicrobials from unnecessary use and ensure access to these drugs.
- 3.2 We commit to enacting and enforcing responsible use regulations, including mechanisms to log and document prescriptions of Reserve and, where appropriate, Watch antimicrobials, including the rationale for their use, in a sustainable access hub. We commit to creating national targets and using the agreed framework for the use of Reserve and, where appropriate, Watch antimicrobials. To achieve this goal, we commit to tracking Reserve and, where appropriate, Watch antimicrobial use in all countries and sharing the information with the Global Antimicrobial Resistance and Use Surveillance System (GLASS).
- 3.3 We commit to expediting regulatory reviews of essential antimicrobials and participating in collaborative global, regional, and subregional registration procedures underpinned by appropriate reliance mechanisms while ensuring efficacy, safety, and quality. We commit to using platforms such as the International Coalition of Medicines Regulatory Authorities (ICMRA) to exchange information on quality-assured, substandard, and falsified antimicrobials in our territories, especially on products to be exported. We commit to explore methods to harmonize clinical trials and to expedite, align, and simplify regulatory reviews for children and neonates to reduce the lag between approvals for adults and younger patients.
- 3.4 We commit to strengthening national, regional, and global surveillance systems of both resistance pathogens and antimicrobial consumption through improved data management, private sector engagement, implementation of data-driven practices, and the reporting of data to GLASS.
- 3.5 We commit to ensuring that a strong combination of push and pull incentives will deploy and attract sufficient funds to deliver necessary innovation. We commit to establishing a system in which countries support R&D in accordance with their ability. Under such a system, wealthier countries would put policies in place that generate incentives for innovative R&D, and all countries would collect resistance data and conduct and support clinical trials of potential new treatments. R&D funding should also be tied to commitments on ensuring access to new drugs.
- 3.6 We commit to ensuring that essential antimicrobials are purchased in a manner that does not encourage unnecessary use, including by delinking the profits of antimicrobial sales from the volume of drugs sold. Price would be set based on the value of a drug, as determined by a health technology assessment or a target product profile. We also recognize that the ideal

payment system will vary by country and that more evidence is needed on which systems could work best in LMICs. We call for demonstration projects in these countries (as stated in commitment 2.0).

3.7 We commit to procuring antimicrobials in a way that takes account of a broader set of criteria than price, including by rewarding supply chain resilience, quality assurance of medicines, and manufacturing that limits runoff of raw materials, including active pharmaceutical ingredients.

3.8 We commit to establishing transparency platforms for the disclosure of all financial and nonfinancial incentives for the use of antimicrobials.

Role of the Pharmaceutical Industry

We recognize our responsibility as national governments, to establish a system in which innovation for important new antimicrobials is properly remunerated, including by establishing tiers of rewards to drive innovation toward the products that are most needed. We recognize the need for a procurement hub that reduces the challenges associated with registering and distributing antimicrobials across the world. We understand that in order to improve resilience, quality, and environmental standards in manufacturing, governments must pay more when purchasing some generic drugs. In return for overcoming these challenges, we call on industry to make the following commitments:

4.1 We call on industry to commit to bring products to market that meet global R&D priorities. We call on pharmaceutical companies to consider the needs of all countries and populations in the antimicrobial research agenda from the start of the development chain, including by ensuring that the pipeline generates oral treatments that could replace first-line Access treatments, should they be lost to resistance, as well as adapted formulations and combinations that address the specific needs of children and neonates and people living in LMICs.

4.2 We call on the pharmaceutical industry to do its part to ensure the availability and affordability of essential antimicrobials in all parts of the world, by either improving their registration and distribution systems or working closely with the procurement hub to ensure swift rollout of essential antimicrobials.

4.3 We call on the pharmaceutical industry to work with regulators on a clinical trial system that generates the evidence needed both for those setting pull incentives and prescribers, including better information on safety and efficacy compared with other antimicrobials and resistant phenotype and genotypes.

4.4 We call on the pharmaceutical industry, GLASS, and other surveillance initiatives to share data on antimicrobial consumption, disease burden, and resistance rates.

4.5 We call on manufacturers to work with national governments to create workable regulations to remove incentives for unnecessary antimicrobial prescriptions, including banning sales bonuses and financial enticements for clinicians and medical care workers.

4.6 We call on all manufacturers to manufacture antimicrobials in a responsible way and to work with governments to establish workable regulations that ensure that all medicines are produced to internationally agreed upon high standards, that counterfeits do not enter the drug supply chain, and that products are manufactured in a way that limits environmental runoff to safe and sustainable levels.



CENTER
FOR
GLOBAL
DEVELOPMENT

Center for Global Development

2055 L Street NW
Floor 5
Washington DC
20036

CGD Europe

1 Abbey Gardens
Great College Street
London
SW1P 3SE

WWW.CGDEV.ORG

