# Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation

## A LANDSCAPE REVIEW OF CURRENT AND POTENTIAL MARKET STRUCTURES FOR ANTIMICROBIALS

Anthony McDonnell, Katherine Klemperer, Morgan Pincombe, and Javier Guzman

## Abstract

This working paper aims to synthesise existing research and thinking on how antimicrobials are procured and ways to improve the current purchasing system. It examines interventions designed to improve innovation, access, and stewardship of antimicrobials and seeks to lay the foundation for a new CGD working group, A New Grand Bargain for Antimicrobial Procurement: Improving Purchasing Systems to Enhance Access, Stewardship, and Innovation for Antimicrobials in Low- and Middle-Income Countries (LMICs). We conducted a systematic review of academic and grey literature and identified 141 papers. We also interviewed 28 stakeholders with a broad range of expertise in this field. Key findings include:

- The literature is overly focused on high-income countries (HICs). Whilst 51 percent of papers mention an LMIC (72/141), fewer than 10 percent exclusively focus on LMICs (14/141). Also, just 12.5 percent of papers with listed authors (16/128) have any authors based in an LMIC. LMIC- and HIC-based groups have very different priorities, as evidenced in both the interviews and the literature. Those in the former group focus more on access to drugs, while the latter are more concerned about innovation. Both groups highlighted stewardship as a priority.

- There is broad agreement that a new purchasing system is needed for antimicrobials in LMICs. Although the literature lacks consensus about the best way to reform purchasing systems, interview findings suggest a more recent coalescence around subscription models in HICs. In these models, purchasers pay annually for a drug, regardless of how many units are needed. The National Health System in the United Kingdom is currently piloting such a system with two drugs, and the US Congress is considering its own version with the PASTEUR Act. There is less clarity on the optimal system for LMICs.

- There is insufficient research on how to implement policies and—with the exception of the GAIN Act, a 2012 piece of US legislation that grants an additional five years of exclusivity for qualifying antimicrobials—a dearth of research evaluating previously implemented initiatives.

# Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation: A Landscape Review of Current and Potential Market Structures for Antimicrobials

**Anthony McDonnell, Katherine Klemperer, Morgan Pincombe, and Javier Guzman**
*Center for Global Development*

Anthony McDonnell, 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." CGD Working Paper 619. Washington, DC: Center for Global Development. https://www.cgdev.org/publication/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review

# Contents

## List of Figures

## List of Tables

# Abbreviations

| | |
|---|---|
| AMC | Advanced Market Commitment |
| AMR | Antimicrobial Resistance |
| BARDA | US Biomedical Advanced Research and Development Authority |
| BEAM | Biotech Companies from Europe Innovating in Anti-Microbial Resistance Research |
| 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 |
| DCM | Diagnosis Confirmation Model |
| DISARM | Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms |
| DRG | Diagnosis-Related Group |
| DRIVE-AB | Driving Reinvestment in Research and Development and Responsible Antibiotic Use |
| EDCTP | European & Developing Countries Clinical Trials Partnership |
| EMA | European Medicines Agency |
| FAO | Food and Agriculture Organization of the United Nations |
| FDA | US Food and Drug Administration |
| GAIN | Generating Antibiotic Incentives Now |
| GARDP | Global Antibiotic Research and Development Partnership |
| IACG | Interagency Coordination Group on Antimicrobial Resistance |
| IMI | Innovative Medicines Initiative |
| IP | Intellectual Property |
| JPIAMR | Joint Programming Initiative on Antimicrobial Resistance |
| HIC | High-Income Country |
| HTA | Health Technology Assessment |
| LMICs | Low- and Middle-Income Countries |
| LPAD | Limited Population Pathway for Antibacterial and Antifungal Drugs |
| MER | Market Entry Reward |
| NAP | National Action Plan |
| ND4BB | New Drugs for Bad Bugs |
| NHS | National Health Service |

| NTAP | New Technology Add-on Payment |
| OIE | World Organisation for Animal Health |
| OMA | Options Market for Antibiotics |
| PASTEUR | Pioneering Antimicrobial Subscriptions to End Up surging Resistance |
| PAVE | Priority Antimicrobial Value and Entry |
| PCAST | US President's Council of Advisors on Science and Technology |
| RCT | Randomised Controlled Trial |
| R&D | Research and Development |
| SMEs | Small and Medium Enterprises |
| TATFAR | Transatlantic Taskforce on Antimicrobial Resistance |
| TEV | Transferable Exclusivity Voucher |
| TPP | Target Product Profile |
| WASH | Water, Sanitation, and Hygiene |
| WHO | World Health Organization |

# Executive summary

## Introduction

Antibiotic resistance directly causes an estimated 1.27 million deaths per year. Another 3.68 million people per year contract a resistant infection, as calculated by a recent report in *The Lancet* (Murray et al. 2022). This burden falls heaviest on the world's poor, with a child born in Africa being 58 times more likely to die from resistance in the first five years of life than one born in a high-income country (HIC). Despite this disproportionate burden, the majority of literature identified in previous studies of antimicrobial resistance (AMR) and economic models for the antimicrobials market focus on HICs. This is likely in part because the largest markets by financial value are in HICs. Existing literature also indicates a lack of consensus on the procurement incentives best suited to overcome AMR. However, this gap has not been explored systematically. To examine different ways to purchase antimicrobials in low- and middle-income countries (LMICs), the Center for Global Development (CGD) is launching a working group, *A Grand Bargain for Antimicrobial Procurement: Improving Purchasing Systems to Enhance Access, Stewardship, and Innovation for Antimicrobials in Low- and Middle-Income Countries*. This working paper seeks to lay the foundation for the working group by synthesising existing research and current thinking on how antimicrobials are procured and ways to improve the system. Working group discussions and additional research will further explore tailored solutions for different LMICs, given the socioeconomic and political diversity among these countries.

## Methodology

Literature was identified through a systematic search of peer-reviewed journals using seven online databases. Articles were included if they discussed alterations to procurement systems—in any setting, including both LMICs and HICs—designed to incentivise antibiotic research and development (R&D), increase access, or support stewardship. Grey literature was identified by searching the references of key review articles and searching the archives of key organisations and advocacy groups. Twenty-eight experts were also interviewed using a standard set of questions.

## Shortcomings of current antimicrobial purchasing systems

The literature analysed and interviews conducted revealed three fundamental flaws in current procurement arrangements for antimicrobials: providing insufficient and inequitable access to antimicrobials, incentivising overuse and inappropriate use, and failing to adequately fund R&D for new drugs. Current purchasing systems fail to ensure availability and affordability of antimicrobials, especially in LMICs, where small market sizes often deter manufacturers from registering and selling their products due to low profit projections and unjustified barriers to entry including burdensome and inefficient registration processes. Concern about access to antimicrobials was greatest among interviewees based in LMICs or whose work focuses on LMICs. Fundamental market

failures in current procurement models also undermine stewardship, motivating overmarketing and overuse by coupling profit with volume of antimicrobial sales. A broad range of experts emphasised the need for greater stewardship embedded in new purchasing models. Pharmaceutical representatives' greater interest in stewardship than access issues was particularly notable, demonstrating their focus on protecting the supply of antimicrobials and concern that expanded access could speed up exhaustion of the drugs. Finally, the small market for new antimicrobials creates insufficient incentives for R&D, leading to a dry pipeline for new antimicrobials, which are especially needed to replace drugs when resistance crops up. The pharmaceutical industry and other HIC-focused experts voiced this concern most prominently. To incentivise innovation, experts generally agreed on the need to expand the use of "pull" mechanisms—those that encourage R&D through promises of future profit. The literature review focuses on proposed and implemented interventions to incentivise innovation in the antimicrobials market.

Numerous new purchasing systems have been theorised and piloted to address these weaknesses in the antimicrobial pipeline, but the market for antimicrobials remains largely unchanged. Global declarations and national action plans (NAPs) serve as commendable first steps to advancing access, promoting stewardship, and incentivising innovation, but many countries lack the political will to go beyond words by fully funding these initiatives and implementing changes. For example, in fiscal year 2019–2020, only 19.9 percent of countries reported that their NAPs had funding sources identified (WHO, FAO, and OIE 2021). Moreover, NAPs often lack detail on how to promote R&D for AMR. Experts from LMICs and HICs alike cited lack of awareness of the issue and collective action issues as key barriers to driving action. Along with the lack of political will to implement solutions, experts disagree on the most effective and appropriate purchasing systems in each setting.

## Overview of recently implemented interventions

Both the academic and grey literature provide many economic solutions for AMR. A preliminary step for all interventions, addressed by the WHO through their priority pathogen list and subsequent set of target product profiles (TPPs), is to form consensus on what pathogens should be targeted, ensuring that the drugs developed consider the needs of smaller markets in the Global South, which tend to be less profitable.

This section summarises the main interventions put forward in the literature and analyses them along the axes of increasing innovation, reducing unnecessary use, and improving access (see Figure E.1).

**FIGURE E.1. A successful procurement system needs to provide access, stewardship, and innovation**



ACCESS
without stewardship, speeds resistance and undermines innovation

STEWARDSHIP
constrains access and undermines innovation

INNOVATION
unjust without access, wasteful without stewardship

*Hoffman & Outterson 2015*
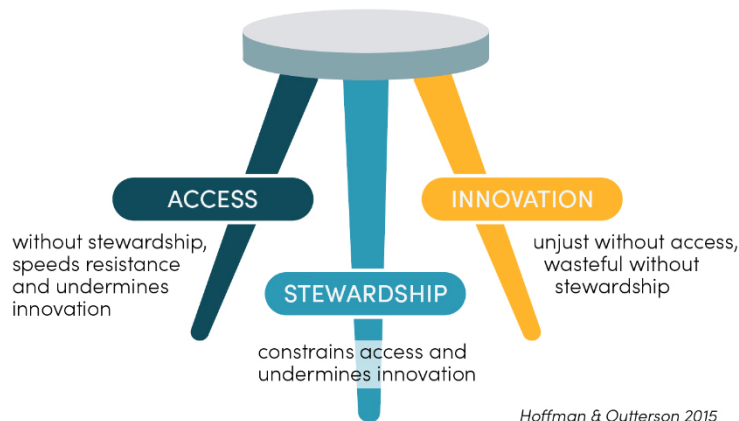
Over the past decade, many countries have adapted their procurement systems[1] or created new funding mechanisms to develop and purchase antimicrobials:

- Grants are the most widely used intervention to increase innovation in antimicrobial development. This funding to bring new products through the early stages of R&D is particularly important for small and medium enterprises. Some funders of innovation currently build in explicit provisions for access and stewardship, but this is not universal.

- The Global Antibiotic Research and Development Partnership (GARDP) similarly supports the drug development process but extends beyond providing grants by partnering with companies to support the development of affordable new treatments that address global public health needs, and by repurposing older antibiotics that are no longer profitable.

- Clinical trial and drug approval reforms—such as fast-tracking and accepting data from noninferiority trials—have been implemented to make the drug development process more efficient, thereby stimulating R&D. While these changes can support increased innovation in and access to antimicrobials, modifying the clinical trial and drug approval process does not address stewardship concerns.

- Increasing reimbursement per dose offers another way to incentivise innovation through increased revenues, since manufacturers are typically paid per pill sold. However, this intervention is backed by only small-scale evidence, and its financial impact is unclear. Further, increased reimbursement does not directly address access issues and may worsen stewardship by providing an incentive for companies to overmarket their products.

- The 2012 GAIN (Generating Antibiotic Incentives Now) Act in the United States grants an additional five years of exclusivity for qualifying antibiotics, protecting them from generic entry and thus allowing an additional five years of sales revenues. Although GAIN does not

---

1 For the purpose of the screening, *procurement system* was defined broadly and included funding support aimed at drugs in development and policies that had a large influence on sales, reimbursement, and revenues, such as some stewardship policies.

address stewardship or access concerns—and indeed potentially worsens each of these by incentivising overuse of drugs and delaying the entry of affordable generics—further use of similar strategies is frequently proposed in the literature.

- Restrictive prescribing is intended to directly improve the stewardship of drugs by increasing the regulations for dispensing and prescribing. These measures may limit consumption of certain antibiotics, but they may also increase the use of other antibiotics as alternatives. In some instances, this shift in usage could be beneficial by shifting consumption toward antibiotics that show lower resistance potential. The problem arises when restrictions on first-line drugs lead to increased usage of more important drugs that have higher resistance potentials or for which multi-drug-resistant organisms have already evolved.

- Finally, financial incentives have been shown to alter prescribing behaviour, thereby helping to improve stewardship. However, like restrictive prescribing, this intervention may undermine access to key drugs, and it fails to directly incentivise innovation and thus may not be workable, particularly in LMICs.

## Ideas that have not been implemented

Beyond the interventions that have been implemented, many more have been proposed and piloted:

- Market entry rewards (MERs) are the most commonly proposed intervention to drive antimicrobial innovation. This pull incentive is likely to be beneficial because it would provide a known return for developers (i.e., reduce their risk), enable targeting of the incentive to areas of high unmet need, and ensure global access to and appropriate use of resulting new drugs. While MERs provide a good balance of stewardship, access, and innovation, there is significant debate over what form such rewards would take.

- Subscription models—a subset of MERs—incentivise R&D by providing regular payments to manufacturers. Pilots in the United Kingdom and Sweden have generated small-scale evidence for this model, although the latter was criticised by many interviewees for not being large enough to spur innovation. A subscription model would be implemented at scale in the United States through the proposed PASTEUR (Pioneering Antimicrobial Subscriptions to End Up surging Resistance) Act.

- Transferable exclusivity vouchers would address the limitations of the GAIN Act, granting drug developers the ability to either lengthen the patent life of another drug it markets or sell the voucher to another drug developer. This model would be simple to implement, though it could hinder access by delaying the transition of a different drug to generics.

- The options market for antibiotics builds from the MER approach and would allow payers to purchase the right to buy a set number of units at a discounted price, which would directly aid in access and provide steady funding to support innovation but has only limited ability to promote stewardship.

- The diagnosis confirmation model reimburses the use of novel antimicrobials at a higher price only when the diagnosis is confirmed with a diagnostic test or by physician judgment—thereby promoting stewardship and potentially stimulating innovation by paying for the value of antibiotics when justified. However, this model relies on diagnostic capabilities and data systems that are comparatively weaker in LMICs, potentially limiting access to needed antimicrobials.

Successful implementation of any of these models requires updating strategies for drug pricing and forming consensus on what pathogens should be prioritised. To this end, health technology assessments (HTAs) should be used to consider the societal benefits of each drug.

The literature on procuring antimicrobials is primarily focused on HICs. Many papers (51 percent; 72/141) do mention LMICs, but often just in passing. Fewer than 10 percent of papers (14/141) exclusively focus on LMICs. Just 12.5 percent of the papers with listed authors in this study (16/128) had an author based in an LMIC. No papers with an LMIC-based author discussed increasing the price of antibiotics. These papers were also less likely to focus on tax incentives but more likely to discuss diagnostic confirmation of infections models and financial incentives for prescribers. In recent years, there have been relatively fewer papers discussing MERS and market exclusivity extensions, and far more papers discussing subscription models.

## Limitations

Due to limitations in the literature, this paper did not usually distinguish between first-, second-, and third-line treatments, or different LMICs—despite the diversity among countries to which this term applies. The literature is predominantly focused on HICs, with fewer than 10 percent of papers (14/141) focused exclusively on LMICs. This bias in the literature likely impacted the interventions discussed in this paper. Where the literature or interviewees raised concerns about specific interventions not working in LMICs, we have shared these. One-quarter of the interviewees for this study currently live in LMICs; several more were from an LMIC but lived and worked in an HIC at the time of the interview. A higher response rate from those based in HICs and a greater likelihood that interviewees would suggest HIC-based researchers led to a lower portion of interviewees being based in LMICs than originally intended. The research focus on procurement systems meant that a greater number of papers focused on innovation than on access or stewardship.

## Discussion

Political problems, not technical issues, are the primary issues contributing to AMR and undermining the implementation of solutions. Numerous new purchasing systems have been theorized and piloted to address these weaknesses in the antimicrobial pipeline, but the market for antimicrobials remains largely unchanged. Without clear, actionable strategies to translate commitment into action, many of these declarations simply pay lip service to the cause. NAPs must

be funded, operationalized, and evaluated to successfully mitigate AMR through known solutions. Arrangements and incentives for antimicrobial procurement must be a key part of these national policies. While there has been progress in advancing "push" incentives to stimulate innovation in antimicrobial R&D, further work is needed, since neither push nor pull incentives alone will be sufficient to drive the required levels of innovation (Outterson 2021). Future research should focus on methods for driving awareness and action to address AMR; effective implementation of these systems; and evaluation of these interventions along the axes of access, stewardship, and innovation. While innovation is the primary concern for HICs, LMICs focus on access or stewardship. This imbalance leads to a response to resistance that is disproportionately focused on the needs of HICs, neglecting analysis and recommendations for the appropriate policies and effective implementation to address AMR in resource-constrained settings. Going forward, more research is needed to understand the best-fit solutions for LMICs.

Overcoming the AMR crisis requires global coordination, and LMICs and HICs must define their distinct—yet complementary—rights and responsibilities. Such complementary action will ensure there is sufficient funding for innovation and access to critical products while protecting the value of these products by reducing unnecessary use. Going forward, CGD's working group will examine different ways to purchase antimicrobials in LMICs in order to identify actionable policies for improving access to and stewardship of key products and to increase funding for research into new ones. Our current procurement system for antimicrobials results in unintended consequences: we need to buy smarter. Governments, civil society, industry, health providers, and patients need to strike a new grand bargain to govern the rights and responsibilities to develop, protect, and ensure access to these vital medicines.

## 1. Introduction

The arrival of the antimicrobial era in the 1940s greatly improved global health, driving a large decrease in deaths caused by infectious disease. In part due to antimicrobials, infectious diseases killed 22 times fewer people in the United States in 1999 than they did in 1900 (Armstrong, Conn, and Pinner 1999). However, as bacteria and other microbes evolve to counter the drugs we use to treat infections, existing antimicrobials are increasingly failing (Hall et al. 2018). Antimicrobial resistance (AMR) directly causes an estimated 1.27 million deaths per year. Another 3.68 million people contract a resistant infection each year, as calculated by a recent report in *The Lancet* (Murray et al. 2022). People in low- and middle-income countries (LMICs) are 1.5 times more likely to die from AMR. The people dying in poorer parts of the world also tend to be much younger and thus lose more of their lives to AMR. *The Lancet* report's findings suggest 99.65 percent of deaths due to AMR in children under five happen in LMICs, with a child in Africa being 58 times more likely to die from AMR than one in a high-income country (HIC) (McDonnell and Klemperer 2022). It is thought that, if this problem is left unchecked, the burden of disease will rise further and could reach 10 million deaths per year (Review on Antimicrobial Resistance 2014).

The majority of literature identified in previous studies of economic models for the antimicrobials market—such as the papers included in the 2014 review by Renwick et al.—focuses on HICs. Existing literature also indicates a possible lack of consensus on the procurement incentives best suited to overcome AMR. When less wealthy countries are mentioned, they are often criticised for their weaker regulatory controls or "contribution" to the problem of resistance, with even less research on how to tackle the unique challenges of resistance in resource-constrained settings. However, this gap has not been explored systematically. To examine different ways to purchase antimicrobials in LMICs, the Center for Global Development (CGD) is launching a working group titled *A Grand Bargain for Antimicrobial Procurement: Improving Purchasing Systems to Enhance Access, Stewardship, and Innovation for Antimicrobials in Low- and Middle-Income Countries*. This group will identify actionable policies to improve access to and stewardship of key products, and to increase funding for research into new ones. Working group discussions and additional research will further explore suitable procurement incentives for various contexts, given the socioeconomic and political diversity among LMICs.

This working paper seeks to lay the foundation for the working group by synthesising existing research on the procurement of antimicrobials. This report—and the broader research project—seeks to analyse the various purchasing systems theorized, piloted, and implemented and their impact on access, innovation, and stewardship. The report extrapolates lessons from HICs, among other methods, to lay the groundwork for the working group, which will envision ways to improve the procurement of antimicrobials in LMICs. The definition of *procurement* used for this analysis was kept intentionally broad and includes grants, which provide support for late-stage research and are often linked to price, access, and stewardship. A combination of interviews with key stakeholders and a review of both grey and academic literature were used to identify the problems with the current economic model for antimicrobials that need to be fixed, solutions that have been implemented successfully, and proposals on how to improve the economic model for AMR. This analysis is guided by the three pillars of access, stewardship, and innovation.

Section 2 outlines the methodology for this paper. Section 3 explores problems identified with the current system. Section 4 looks at the solutions that have been implemented. Section 5 explores proposals not yet implemented. Section 6 considers limitations of this study, and Section 7 discusses policy implications from the findings.

## 2. Methodology

This analysis is based on a combination of literature reviews and interviews. Literature was identified through a systematic search of peer-reviewed journals complemented with a grey literature search (see Appendix 1 for the full strategy). In January 2022, an electronic search was performed of seven databases: PubMed, Web of Science, Cochrane Library, Scopus, Business Source Complete, EconLit, and the Cumulative Index to Nursing and Allied Health Literature. In each database, two separate

searches were run: a broader search, filtered by publication year of 2014 or later, and a narrower search (including LMIC terms) for all years. This strategy was chosen in order not to overlap with the results yielded by the 2014 Renwick, Brogan, and Mossialos review. Search results were initially screened by applying ineligibility criteria to titles and abstracts. Articles were excluded if they did not focus directly on human health; were not in English; or focused on surveillance, characterisation of antimicrobials or resistant microbes, or non-financial stewardship interventions. The second screening stage involved assessing full texts against eligibility criteria: articles were included if they discussed alterations to procurement systems[2] (in any setting, including both LMICs and HICs) designed to incentivise antibiotic research and development (R&D), increase access, or support stewardship. During screening, literature was included, excluded, or—if there was any ambiguity about whether the criteria were met—sent to a three-person review group to assess eligibility. Grey literature was identified by searching the references of key review articles and searching the archives of key organisations and advocacy groups (see Appendix 2 for the list of organisations).

We interviewed 28 people working to address AMR, including experts from a diverse range of industries: 4 healthcare professionals, 4 from donor organisations, 6 policymakers, 6 from the pharmaceutical industry, and 8 from academia. These interviewees were identified based on findings from the literature review and the researcher team's contacts, and interviewees were asked for suggestions of other people to speak to, in a process known as snowball sampling. Of the 28 interviewees, 7 were based in LMICs and an additional 9 were categorised as development-focused; these were people working in development organisations or international organisations with an LMIC remit or academics with a substantial focus on LMICs. Twelve were based in HICs and were not focused on development; however, this group included individuals from organisations like the Wellcome Trust and CARB-X, whose focus extends beyond HICs. A breakdown of interviewees by industry type and status of development focus can be found in Table 1.

### TABLE 1. Breakdown of interviewees by industry and development focus status

|  | LMIC–based | Nondevelopment–focused, HIC | Development–focused, HIC | Total |
|---|---|---|---|---|
| **Academia** | 3 | 4 | 1 | 8 |
| **Funder** | 0 | 2 | 2 | 4 |
| **Healthcare** | 3 | 1 | 0 | 4 |
| **Pharmaceutical** | 0 | 4 | 1 | 5 |
| **Policymaker** | 1 | 1 | 5 | 7 |
| **Total** | 7 | 12 | 9 | 28 |

We used a standard set of questions to guide these discussions (as outlined in Appendix 3), which was shared with interviewees in advance, asking experts for their views on priority issues contributing

2    For the purpose of the screening, *procurement system* was defined broadly and included funding support aimed at drugs in development and policies that had a large influence on sales, reimbursement, and revenues, which included some stewardship policies.

to AMR, the current purchasing system for antimicrobials, possible alternative purchasing systems, and barriers to building consensus to implement solutions. Interviews were conducted between January and March 2022. Individuals were identified based on our prior knowledge of stakeholders in this space, prominent names in the literature, and additional recommendations from those interviewed.

# 3. Shortcomings of current antimicrobial purchasing systems

## Priorities in tackling resistance

The interviews revealed wide consensus that there is a problem with the way antibiotics are procured, making the need for a new purchasing system clear. Current procurement arrangements have three fundamental flaws: providing insufficient and inequitable access to antimicrobials, incentivising overuse and inappropriate use, and failing to adequately fund R&D for new drugs. The relative importance of each of these shortcomings varies depending on the country in question. Experts from both LMICs and HICs also acknowledged that "there is no one-size-fits-all approach to procurement," emphasizing the need for tailored solutions.

The first question interviewees were asked was, "What are the two or three biggest policy problems contributing to AMR?" Respondents were counted as identifying access, innovation, or stewardship as a key issue if they highlighted that area in answer to this question, or if a later answer emphasised it as an important contributor to the problem. Figure 1 outlines the distribution of these results.

**FIGURE 1. Number of interviewees who identified access, innovation, and/or stewardship as key contributors to AMR**



Access
2

None
4

Total
28

2    4
6

Innovation    Stewardship
4
2    4
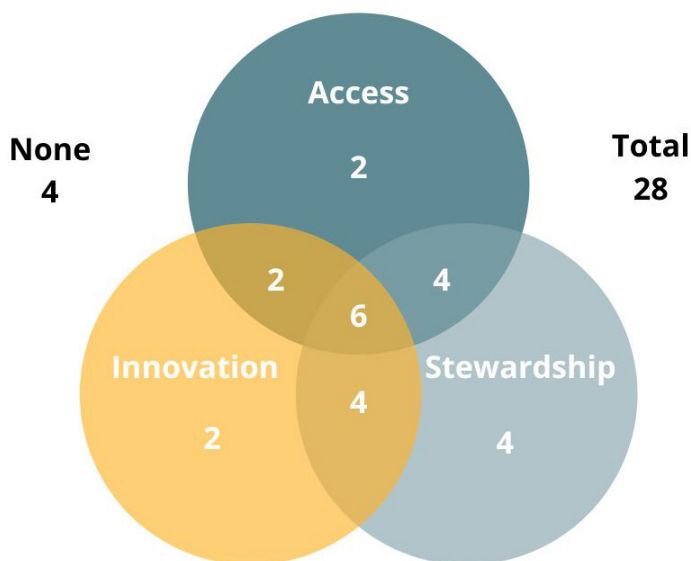
There was no consensus among interviewees on the main problem; instead, interviewees' responses and prioritisation correlated with their background. Those based in an LMIC or working in the development field but residing in a HIC more frequently prioritised access and less commonly mentioned the lack of innovation as a problem. Only 5 of the 17 LMIC-based or -focused individuals highlighted innovation as a key issue. Instead, these respondents often said things like "lack of access to second-line drugs drives the burden of deaths, rather than lack of access to new, innovative drugs"; "not convinced of the urgent need to get new antibiotics, but it would be useful to have some in the locker for the future"; "I am worried that implementing pull incentives would just distract people from WASH [water, sanitation, and hygiene] work—which would be better value for money in LMICs." Table 2 breaks down the priorities of the major problems in AMR based on respondents' residency and whether their work has a development lens.

**TABLE 2. Interviewees' views on the major driver(s) of AMR, broken down by geography and/or development focus**

| | Access as a Major Policy Problem | Stewardship as a Major Policy Problem | Innovation as a Major Policy Problem |
|---|---|---|---|
| **LMIC-based (*n* = 7)** | 4 (50%) | 5 (63%) | 3 (38%) |
| **Development-focused, HIC-based (*n* = 9)** | 6 (67%) | 4 (44%) | 2 (22%) |
| **Nondevelopment-focused, HIC-based (*n* = 12)** | 4 (33%) | 9 (75%) | 9 (75%) |

Access issues were most highlighted by people working in development. Many of these respondents stated that current purchasing systems do not ensure access to antimicrobials, leading to voids and stockouts, and facilitating the spread of resistance. In markets with weak regulatory capacity and a large presence of falsified antimicrobials, access to quality assured medicines is far from guaranteed. Barriers such as small market sizes and unstable demand limit the production and stable supply of existing antibiotics. Fear of resistance and inappropriate use also "give pharmaceutical companies pause when deciding whether to register products in new countries." Regulatory hurdles were also seen as delaying access to quality-assured products, especially in LMICs. This reflection echoes the Access to Medicine Foundation's *Antimicrobial Resistance Benchmark 2021*, which found only six on-patent antibacterial and antifungal medicines and vaccines had been filed for registration in 10 or more of the 102 LMICs considered (Access to Medicine Foundation 2021). Small market sizes often deter manufacturers from registering and selling their products in LMICs due to low profit projections. Instead, manufacturers were seen by these respondents to often focus their efforts on large HIC markets, where they get the most payoff.

In contrast, most nondevelopment-focused, HIC-based respondents identified innovation as a critical policy problem, as outlined in Table 2. This ratio held true among the HIC-based pharmaceutical representatives interviewed as well, with three-quarters highlighting innovation as a key problem. Thus, this difference does not seem to be driven by the different makeup

of our interviewees. These nondevelopment-focused, HIC-based respondents were also more likely to highlight stewardship as a concern and were the least likely to focus on access—the biggest barrier identified by LMIC residents. Fundamental market failures in current procurement models, leading to inappropriate overuse of antimicrobials, were highlighted by eight interviewees. These interviewees highlighted that current purchasing systems couple profit with volume of antimicrobial sales, incentivising manufacturers to sell as many units as possible. Notably, pharmaceutical representatives were more focused on stewardship than access issues, demonstrating their focus on protecting the supply of antimicrobials and concern that expanded access could speed up exhaustion of the drugs.

This difference in perspectives was also stated directly in some interviews. One LMIC resident told us, "There's a divergence of interests between the Global North and South. The Global North is interested in new antibiotic production, R&D, stewardship, and surveillance. This is being done to identify threats to the Global North—not to help the Global South. The Global South is more interested in infection burden and reducing infectious disease." These distinct interests suggest the need for a grand bargain, which would establish different expectations for LMICs and HICs in order to deliver on each stakeholder's separate, yet complementary, objectives.

This difference in priority is particularly important because there is often a direct trade-off between policies that improve access to antibiotics and those that ensure stewardship. Many of the LMIC residents and development-focused, HIC-based individuals stressed this point, saying that in areas with low state capacity or a shortage of doctors, rules that require a prescription for antibiotic dispensing would lead to a large increase in fatalities. Thus, policy solutions need to balance trade-offs between access and stewardship. For example, one respondent stated, "Although maternal and child health has some of the highest burden of infection and AMR, this should not be the first target for reducing unnecessary use since antibiotics are key to mitigating high mortality rates among these demographics." This respondent further emphasised the tension between decreasing use to conserve antimicrobials and ensuring access to life-saving drugs, highlighting that rapid access to the appropriate course of antimicrobials is critical to survival among young children, since infections can quickly become fatal.

Attitudes from HICs often differed again, with one nondevelopment-focused respondent telling us that "the vast majority of the high prevalence [of resistance] is in LMICs—with the exception of China—so it's an overuse issue . . . Some countries don't even require prescriptions." Balancing these competing goals and perspectives is the goal of CGD's new working group, *A Grand Bargain for Antimicrobial Procurement.*

## A new model for purchasing antimicrobials

The second question posed to interviewees was, "Do we need a new system for purchasing antibiotics?" Out of the 28 respondents, 20 said yes; 3 expressed doubts that a new system was needed, citing

political and financial challenges; 1 said that change was only needed in LMICs with small markets; and 4 did not feel they had sufficient knowledge to answer. Those who advocated a new system called attention to various considerations in line with their distinct priorities, outlined above. Respondents cited a lack of investment in R&D due to limited returns, incentives to oversell antibiotics, and systems that often fail to get antibiotics to those who need them, particularly in LMICs.

When asked to describe what the ideal system would look like, about half of respondents advocating a new purchasing system thought that there needed to be separate purchasing systems for LMICs compared with HICs. They suggested models for antibiotic purchasing including pooled procurement mechanisms and donor funding. They highlighted how global procurement mechanisms have advanced access to key medical products in other disease areas. For example, Gavi, the Vaccine Alliance supplies vaccines to LMICs, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria procures medicines for HIV, tuberculosis, and malaria. Some highlighted the importance of strengthening the global architecture and having a more focused and coordinated procurement, including through existing mechanisms like UNICEF and initiatives like SECURE, to facilitate access, stewardship, and innovation for antimicrobials. Respondents also advocated antibiotic purchasing systems that vary based on population size. Indeed, three respondents thought that it was important to distinguish between large markets in LMICs and small countries that often struggle with regulatory or supply chain issues. Two respondents underlined the need for countries' contributions to global purchasing systems to vary by income level. One such person told us that the "ideal system would be for nations to pay, according to GDP, into a pot that acts as a pull incentive." This interviewee went on to suggest that this could mean subsidies for the poorest countries so that antimicrobials were "nearly free," to be funded by much higher fees from wealthier countries. These perspectives suggest there is a wide recognition that any future procurement system should consider the needs of countries with greater resource constraints.

Of the 20 respondents who wanted a new system, 15 favoured an approach that delinks profit from sales volume.[3] Delinking revenues and profits from sales volumes was generally seen as the best way to manage the competing demands of raising revenue, ensuring access, and removing the pressure to overprescribe.

There was no consensus among respondents on which drugs to include in such a scheme. Most respondents who expressed an opinion believed any scheme should include new drugs. However, opinions varied on whether there needed to be a new system for other drugs. Some respondents worried that changing policies for the generic market might raise prices or reduce access. These respondents felt that while some regulation might be needed—to improve medicine quality or reduce unnecessary use—no fundamental change is needed in the way these drugs are purchased. However,

........................................

3   Note that the word *delinkage* has previously been defined to mean delinking the cost of investment in R&D from the price and volume of drug sales. However, we define *delinkage* to mean delinking profit from sales volume—this is how *delinkage* is most commonly used in the literature. Note also that the concept of delinking profit from sales volume is occasionally referred to *decoupling.*

several respondents who advocated a new procurement system thought a new system is needed for older treatments. These experts called for purchasing systems to increase production of existing treatments that face low commercial viability—despite high effectiveness—due to limited demand, in addition to older antibiotics that "may be on a shelf somewhere" and can be repurposed to address multi-drug-resistant infections. Some experts highlighted the failure of current purchasing systems to provide stable access to first- and second-line drugs, let alone new ones, in LMICs, where most purchasing is program- or disease-specific. Two respondents suggested that a wider solution to AMR might be to place a small tax on generic antibiotics to secure the supply chain or maintain capacity to surge up production of newer drugs. Some experts said there may be promising older drugs that no longer have intellectual property protection, thereby failing to incentivise the clinical trials needed to bring these drugs to market. An interviewee suggested that a system to incentivise the screening of old libraries and conduct relevant clinical trials would have significant societal value, but this is not well incentivised under the current system.

Seventeen interviewees cited the need for international coordination on solutions to address AMR. However, nobody suggested a single system for purchasing drugs across the world. Rather, interviewees called for widespread agreement on the goals for such a system and coordination among countries, including between LMICs and HICs. Ultimately health, economic, and political systems vary greatly between countries, and the right solution will need to be tailored to each specific country.

## Political problems

Sixteen interviewees from LMICs and HICs alike cited lack of awareness of the issue and collective action issues as a key barrier to driving action, leading to "a lack of dedicated financing for AMR." The collective action problem undermining effective and equitable procurement leads to a "race to the bottom," where individual countries are incentivised to pay the minimum price for new drugs. These low prices imperil both the quality and security of the supply chain. Given the "leadership void," AMR may be the "perfect issue for LMICs to step up" and take the lead in facilitating global collaboration and advancing the implementation of alternative purchasing systems for antimicrobials. LMICs "should have a mandate for saying what changes are needed" because they have a disproportionate burden of AMR and distinct priorities.

Many interviewees drew parallels between the issues of AMR and climate change, pointing out wider trends in the inability to deal with long-term threats. Four people made this analogy, pointing out that climate change is also "slow moving, not an acute problem." Because of this lack of political will, an interviewee stated that "far less is spent on AMR than other health issues." This underinvestment in AMR is backed up in the statistics on global health expenditure: Of the more than $274 billion[4]

......................................

4    This was calculated using pharmaceutical research expenditure from Statista in 2018 and global funding for government and philanthropic R&D from 2009 as measured by Røttingen et al. 2013.

invested in health R&D in 2018, only 1.8 billion (0.65 percent) was allocated for products and technologies to address AMR (Statista 2022; Global AMR R&D Hub 2022). This, in turn, leads to far less research in this space. Of the 413,591 medical studies currently being tracked by ClinicalTrials.gov, just 2,689—also 0.65 percent—are for antimicrobials, antibacterials, or antibiotics (US National Library of Medicine 2022).

Different approaches were put forward to drive action, with some respondents suggesting greater public awareness to raise the public profile of AMR. In line with this, one former senior government official told us that "politicians only respond to things people are concerned about." Several of the respondents who had worked in government went on to advocate the "need to do far more to bring policymakers from finance and health together." These respondents felt that finance departments are usually key to mobilising extra resources. There was also a belief that COVID had highlighted the economic costs of a pandemic and could therefore make arguments about the economic benefits of tackling AMR more compelling. However, the pandemic has also reduced most governments' spending, making its effect on the funding for AMR a double-edged sword. Other respondents highlighted that the recent Global Research on Antimicrobial Resistance (GRAMS) study estimating the global burden of AMR (Murray et al. 2022) could play an important role by highlighting the severity of this problem to policymakers.

Despite the political difficulties, all but one of the respondents who discussed collective action issues thought policy was moving in the right direction. "We actually have come quite a long way in making action." This change is mostly due to the implementation of grants and other funding that lower the costs of R&D, changes around the use of antimicrobials in agriculture in some countries, and measures to promote stewardship. There was a sense that progress toward larger changes in the structure of the antimicrobials market has been far slower than efforts to "protect the early-stage pipeline," especially due to the efforts of CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) and the AMR Action Fund, and to support new products in achieving regulatory approval. These reflections align with our findings from the literature review, which suggest that larger structural changes are more difficult to implement. Many respondents cited hope that the Global Antibiotic Research and Development Partnership (GARDP), through its SECURE initiative, could come to play a major role in ensuring that access, innovation, and stewardship reach people in poorer parts of the world. Others highlighted the progress made through the subscription models piloted by the United Kingdom and Sweden and outlined their hope that the US PASTEUR (Pioneering Antimicrobial Subscriptions to End Up surging Resistance) Act would create greater funds for innovation.

# 4. Overview of recently implemented interventions

Both the academic and the grey literature provide many solutions for antimicrobial resistance, as summarised in Table 3. Over the past decade, many countries have adapted their systems or created new funding mechanisms for antimicrobials. This section summarises the main interventions put forward in the literature and analyses them along the axes of increasing innovation, reducing unnecessary use, and improving access (see Figure 2). Section 5 then looks at ideas put forward in the literature that have not yet been Implemented.

**FIGURE 2. A successful procurement system needs to provide access, stewardship, and innovation**



*Hoffman & Outterson 2015*
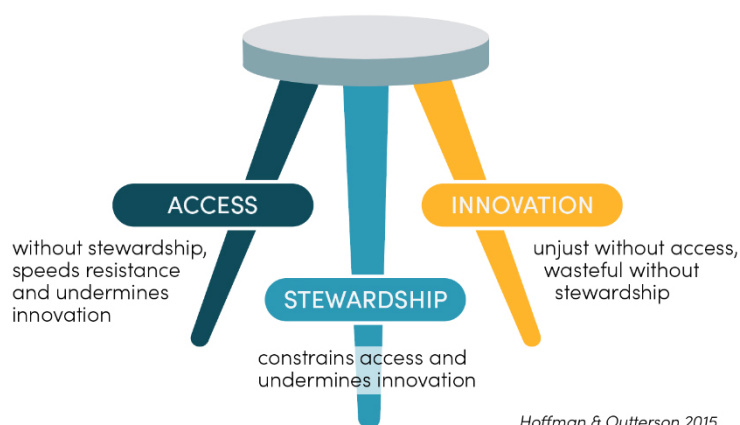
For all interventions discussed, a preliminary step is to form a consensus on what pathogens should be targeted. When making these decisions, it is important to ensure we are not just developing drugs for the Global North markets but also considering the needs of smaller (less profitable) markets in the Global South. According to some literature, the current pipeline is clustered around a few pathogens of interest to developers—with this interest most likely dependent on the countries where developers operate and where pathogens occur (Baraldi et al. 2018). However, experts we consulted stated that this is no longer a concern, as the pipeline is adequately focused on pathogens on the CDC and WHO target product profile (TPP) lists. Moreover, the 2022 GRAMs report shows that the WHO priority pathogen list is well targeted, including all six of the leading pathogens that contribute to the burden of AMR. However, the exclusion of MDR tuberculosis from the WHO list has proven controversial (Burki 2017), and the rating of methicillin-resistant *S. aureus* (the pathogen responsible for most direct deaths in 2019) as *high* rather than *critical* priority is notable. ReAct has called for future iterations of TPPs to be developed collaboratively with patients, doctors, and nurses in different settings (Aagaard, Malpani, and Zorzet 2021).

Incentives around antimicrobial innovation can be broadly broken down into two types. "Push" incentives are those that lower the cost of R&D, such as through funding or changes in regulation. "Pull" incentives are those that aim to improve revenue for products after they have been created (Cama et al. 2021)

**TABLE 3. Key features of interventions in the literature**

| Intervention | | | Number of Papers Referenced In | Key Characteristics | Implemented? |
|---|---|---|---|---|---|
| Market Entry Reward (MER) | Overview | | Number of papers (NP): 76, percentage of papers with at least one LMIC-based author (LA): 7.4% | *A commonly proposed class of incentive whereby the drug developer receives a payment after regulatory approval of a drug meeting predefined criteria. Payment may be linked to attached sustainable use obligations or provisos about access. This would incentivise innovation, as well as stewardship and access, if correctly designed. The developer will earn additional revenues from sales of the antibiotic in the ordinary course (i.e., this is a partially delinked pull incentive).* | – |
| | Subscription model | Overview | NP: 39, LA: 5.6% | An alternative version of MER whereby developers receive regular payments post market regulation in return for access to their product, as required. These payments are generally in lieu of market sales in the country, meaning that subscription models can be fully delinked. | – |
| | | PASTEUR Act | NP: 15, LA: 7.1% | Proposed US legislation that would create a mechanism for developers to enter subscription contracts (worth US$750 million to US$3 billion), provided they commit to maintaining drug availability and supporting stewardship. Under this arrangement, the US government will have pre-purchased these antibiotics for a decade, with no additional payments dependent on the volume used. | N |
| | | National Health Service (NHS) pilot, England | NP: 30, LA: 3.7% | A fully delinked subscription scheme giving the NHS access to two antimicrobials (one novel and one existing). Contract price is set according to the value of the antimicrobial, with a cap of £10 million per annum. No additional payments will be made based on sales volumes. | Y (in pilot form) |
| | | Swedish minimum revenue guarantee | NP: 18, LA: 0% | A partially delinked subscription scheme* to ensure access to patented antimicrobials that might otherwise not be available in Sweden due to insufficiently large sales volumes. Developers are guaranteed a minimum annual revenue; if this is exceeded, they receive a bonus. | Y |
| | Priority Antimicrobial Value and Entry (PAVE) Award | | NP: 6, LA: 0% | A hybrid model proposed by Daniel et al. (2017). Developers would receive a substantial initial payment upon market entry followed by smaller payments, in accordance with sustainable use, availability, and data collection provisos. This would incentivise innovation while also ensuring access and stewardship. | N |
| Extended Exclusivity | | | NP: 50, LA: 6.5% | A form of intervention designed to incentivise innovation. Drug developers would receive extended exclusivity for the novel antimicrobial. However, this does not ensure access or stewardship. | Y (2012 US, Generating Antibiotic Incentives Now, or GAIN, Act) |

| Intervention | | Number of Papers Referenced In | Key Characteristics | Implemented? |
|---|---|---|---|---|
| Transferable Exclusivity | | NP: 37, LA: 6.1% | The developer of a novel antimicrobial would receive an exclusivity-extending voucher they could apply to another drug or sell. Award of this voucher could be reliant on submission of access plans. However, this approach may cause higher costs in other areas of healthcare and does not ensure stewardship. | N |
| Advanced Market Commitment (Options market) | | NP: 16, LA: 8.3% | A proposed model whereby investors purchase the right to buy a set number of antibiotics at a discounted price if/when the antibiotic makes it to market (Brogan and Mossialos 2016). This incentivises innovation and secures access, but the impact on stewardship is less clear. | N |
| Diagnosis Confirmation Model (DCM) | | NP: 6, LA: 16.7% | A proposed model using a dual pricing structure: a premium price is charged only if the antibiotic is confirmed as clinically necessary (Lum et al. 2018). This encourages treatment de-escalation when appropriate and thus is beneficial for stewardship. However, requirements for diagnostics and data limit the feasibility of using this model in lower-resource settings. | N |
| Pay or play | | NP: 14, LA: 7.7% | A tax, designed to incentivise innovation, imposed on any large pharmaceutical company not developing antimicrobials (AMR Review). The fees could go towards funding an MER. However, this approach does not consider access or stewardship concerns. | N |
| Tax incentives | | NP: 33, LA: 3.4% | These are usually a form of push incentive for innovation (although, depending on the stage of the drug development process at which they are implemented, they can be pull incentives). They can take the form of credits or cuts. However, tax incentives do not ensure access or stewardship. | Y |
| *Higher reimbursement* | *Overview* | NP: 37, LA: 0% | *A volume-based approach to increase drug developer profit by increasing the reimbursement per pill—that is, through ensuring higher prices more reflective of the drugs' true value to society. However, volume-based approaches may disincentivise appropriate stewardship.* | – |
| | Diagnosis-Related Group (DRG) carve-out | NP: 27, LA: 0% | Hospitals are paid via DRGs; thus, ensuring higher prices for antimicrobials requires that these drugs be reimbursed separately from the DRG payment. This approach has already been adopted in France, Germany, and the United States via the New Technology Add-On Payment (NTAP). Further US legislation (the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms, or DISARM, Act) has also been proposed to allow for broader add-on Medicare payments. | Y (France/Germany/NTAP in US) N (DISARM) |

| Intervention | | Number of Papers Referenced In | Key Characteristics | Implemented? |
|---|---|---|---|---|
| Grants | | NP: 87, LA: 9% | A form of push incentive designed to incentivise innovation. Developers are given money to assist with preclinical and clinical development of antimicrobials. Grants could be tied to access or stewardship provisions. Grants are especially important for small and medium enterprises, which may not otherwise have sufficient funds. | Y (CARB-X, AMR Action Fund, Joint Programming Initiative on Antimicrobial Resistance [JPIAMR], New Drugs for Bad Bugs [ND4BB], etc.) |
| Restrictive prescribing | | NP: 22, LA: 40% | A class of policies designed to support stewardship by preventing excess use. Examples include banning over-the-counter sales of antibiotics without prescriptions, limiting who is qualified to prescribe, and limiting where later-line drugs can be prescribed. However, there is a very fine balance between excess and access. | Y |
| Regulation of trials/drug approval | *Overview* | NP: 68, LA: 9.4% | *A suite of policies designed to incentivise innovation through making the trials/approvals process faster and cheaper for developers. Examples include accelerated reimbursement review and use of noninferiority trials.* | – |
| | 21st Century Cures Act | NP: 12, LA: 0% | A 2016 US law that included the limited-population antibacterial drug pathway. This provides a new mechanism for the US Food and Drug Administration review of new antibiotics designed for use in patients with unmet medical needs, allowing approval based on preclinical data and small preliminary studies. | Y |
| Financial strategies targeting prescribers | | NP: 12, LA: 16.7% | A class of policies designed to support stewardship. Examples include separating prescribing from dispensing (and thus from sales profits), pay-for-performance schemes, and financial penalties for overprescribing. | Y |
| Long-term supply continuity model | | NP: 4, LA: 25% | A delinked payment model that would ensure a predictable supply of important generic antimicrobials (Aagaard, Malpani, and Zorzet 2021). It is similar to an MER in that a government pays a delinked reward in return for supply of an antimicrobial; it could thus be used as a test implementation of a delinked model. | N |

*Some interviewees contested categorising the Swedish minimum revenue guarantee as "subscription"—see Subscription subsection.

## Grants

The most widespread intervention to increase innovation in antimicrobial development is the use of grants as a push incentive. Grants are used in many countries, provided by many different bodies, and targeted at different stages of development. Targeting each stage of development is vital to ensure a robust chain of links. For example, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) finances basic and preclinical research and had invested US$80 million as of 2018 (IACG 2018). CARB-X, a nonprofit, was launched in 2016 to provide around US$825 million over 16 years for projects in the preclinical and early clinical phases. It focuses on pathogens of critical or high priority on the WHO priority pathogen list (IACG 2018). To date, it has backed 92 projects (60 of which are active), including 19 new classes of antibiotics, 8 vaccines, and 12 diagnostic products (Boluarte and Schulze 2022). To be eligible for funding, grantees must commit to sell, promote, and distribute antibiotics responsibly and to strive for equitable availability—there can be no geographic restrictions (Savic and Årdal 2018). These requirements follow the patents until expiration, and the standards, including contractual language, have been published for others to use (CARB-X 2021). While CARB-X funds up to 90 percent of the costs in preclinical development and 80 percent of Phase I costs, grantees must also secure private-sector financing. Europe's largest public–private partnership, New Drugs for Bad Bugs (ND4BB), funded to the tune of US$860 million by the Innovative Medicines Initiative, invests across the full R&D chain, although with a focus on clinical-trial and similar expenses (Eichberg 2015; IACG 2018).

The AMR Action Fund, a global coalition including the pharmaceutical industry, philanthropic funders, and multilateral development banks, focuses on late-stage clinical development. The fund expects to invest more than US$1 billion in 15–20 projects by small biotech companies (Boluarte and Schulze 2022) focusing on directly acting antibacterial compounds targeting priority pathogens (according to the WHO and CDC threat lists). It has recently made two investments in novel antimicrobials. The hope is that this will bring three or four new antibacterial agents to clinical practice by 2030 (BEAM Alliance 2020). However, the BEAM (Biotech Companies from Europe Innovating in Anti-Microbial Resistance Research) Alliance believes that a diversified armamentarium of products will be needed to tackle the threat of AMR and thus calls for widened eligibility criteria to ensure that a broader scope of products is funded (BEAM Alliance 2020). Grants such as these should buy time to allow governments to enact broader pull incentives and models that can support long-term pipeline sustainability (Brennan, Williams, and Hsu 2022). Indeed, grants have been found to be very important for small and medium enterprises (SMEs) (Dutescu and Hillier 2021)—more so than are pull incentives such as MERs (Ciabuschi et al. 2020). However, not all funders currently build in explicit provisions for access and stewardship. Moreover, one interviewee advocated for making environmentally sustainable antibiotic production a condition of grants. If grants are to be used as the main part of incentives, it will be important to include such provisions in the future.

## Partnership building: GARDP

GARDP is an organisation that similarly aims to support the drug development process, but it differs from the above-mentioned initiatives by focusing on late-stage development (clinical phase III and post-approval) and partnering with companies rather than providing grants. It is designed to develop affordable new treatments that address global public health needs, including needs ignored by other developers due to risk and/or cost (Lomazzi et al. 2019). For example, GARDP has partnered with Entasis Therapeutics to launch phase III trials of zoliflodacin and with the Clinton Health Access Initiative (CHAI) and Shionogi & Co., Ltd to accelerate access to cefiderocol (GARDP 2019; 2021).

GARDP can enter at any point along the drug development pipeline—and thus is also applicable to repurposing older antibiotics that are not profitable because they are not patentable (Årdal, Lacotte, and Ploy 2021). GARDP works with industry, research organisations, academia, governments, and nonprofits, targeting clear product profiles and explicitly building sustainable access into its R&D strategies. Thus, GARDP aims to ensure access while avoiding excess. By considering the three pillars of innovation, access, and stewardship, this model should ensure sustainable progress in tackling AMR.

## Clinical trial and drug approval reform

Another approach to increase the speed and number of drugs coming to market is to reform clinical trial and drug approval systems. For example, the US 21st Century Cures Act of 2016 included the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway), which provides a new mechanism for FDA review of new antibiotics designed for use in patients with unmet medical needs (Pew Charitable Trusts 2021). This change allows approval of a drug based on preclinical data and small preliminary studies (Savic and Årdal 2018). However, as of November 2021 only two drugs have been approved through this pathway.[5] Drugs falling under provisions of the Generating Antibiotic Incentives Now (GAIN) Act (see below) are eligible for fast-track and priority review (Pew Charitable Trusts 2013); given the broad GAIN specifications, this covers the vast majority of antimicrobials in the pipeline. Similarly, legislation in Germany allows for accelerated reimbursement review of specific antimicrobials (Gotham et al. 2021).

Clinical trials can be supported through partnerships such as the public–public European & Developing Countries Clinical Trials Partnership (EDCTP) between Europe and sub-Saharan Africa, and through infectious diseases–specific clinical trial networks (McDonnell et al. 2016). One paper called for a Networked Institute Model to conduct all trial stages up to market authorisation (Glover et al. 2021). Requirements for antibiotic clinical trials can also be altered—for example, many regulators moved to accepting data from noninferiority randomised controlled trials (RCTs) many

---

5   The first drug approved under the LPAD pathway, in September 2018, was Arikayce—for the treatment of lung disease caused by *Mycobacterium avium* complex (MAC) in a limited population of patients who do not respond to conventional treatment. In August 2019, pretomanid tablets were approved in combination with bedaquiline and linezolid for treatment of a specific type of drug-resistant TB (FDA, 2020).

years ago. These trials compare new drugs with existing therapies in patients with non-resistant disease and look for an unacceptable loss in efficacy, rather than an improvement (Lanini et al. 2019). The rationale behind this is that even if drugs do not currently provide a clinical benefit compared with existing treatments, in the long run they may be valuable as existing treatments become less effective due to resistance. Additionally, such trials are much easier to run as they do not require recruiting patients with rare drug-resistant pathogens. However, some authors argue that noninferiority trials are ethically problematic since they effectively lower the bar (Hey and Kesselheim 2017), and there is concern about compromising drug safety in favour of shortcuts (So and Shah 2014). A majority of European countries interviewed by Årdal, Lacotte, and Ploy (2021) "want to see superiority trials" instead. Moreover, Lanini et al. (2019) point out that "the proportion of noninferiority RCTs that successfully claim noninferiority is so high that it suggests a bias in design, analysis, or interpretation." They therefore call for use of adaptive RCTs, whereby study parameters can be modified (mid-trial) according to interim data analyses. However, interviewees expressed concern that such adaptive trial designs pose a problem for some LMIC regulators as many lack either the legal framework or the experience to accept this data—and, as a result, may delay access to these drugs. For example, one interviewee explained how new tuberculosis drugs were approved by the FDA and the European Medicines Agency (EMA) based on phase IIb data—but this raised difficulties in countries with strict requirements for phase III trials. Harmonisation among health regulatory agencies could overcome this issue (and is complementary to fast-track systems). Authorisation of drugs that decolonise carriers of resistant bacteria poses a particular issue, since these drugs only provide indirect benefits (helping patients other than the one treated). Therefore, when considering only the patient treated, they perform poorly on comparisons of side effects versus clinical benefit, and thus are less likely to be authorised. However, they are potentially highly cost-effective when considering indirect benefits to populations vulnerable to outbreaks (Toth, Samore, and Nelson 2021).

Overall, changes to clinical trials and approvals have made the drug development process more efficient for companies, thus stimulating drug development (Bax and Green 2015). Such changes can also aid in ensuring access to needed drugs. However, it has been argued that much more dramatic changes are needed to truly promote drug development—reducing the time to market by as much as 80 percent (Sertkaya, Jessup, and Wong 2017). While these initiatives don't explicitly address stewardship concerns, these are considered if market authorization is granted only for specific indications or under condition of diagnostic testing.

## Increased reimbursement

Under a traditional payment system, drug producers receive a fee per pill or dose sold. Increasing revenue (and thus the incentive for innovation) requires increasing price, or volume sold, or both. France, Germany, and the United States have all enacted legislation to increase reimbursement per dose, providing exceptions in cost-containment mechanisms to allow higher prices for certain

antibacterials (Gotham et al. 2021). In countries using diagnosis-related groups (DRGs) for hospital billing, such measures require a DRG carve-out—that is, charging antibiotics separately from the DRG.[6] In the United States, the New Technology Add-On Payment (NTAP), enacted in 2001, serves such a purpose, allowing for an additional payment for the use of a new antibacterial when a traditional DRG would provide insufficient reimbursement. However, one interviewee told us that NTAP is "widely viewed as a total failure" since it has limited positive impact on sales. Further changes were made in fiscal year 2020 when the Centers for Medicare & Medicaid Services changed the inpatient prospective payment system, increasing the NTAP from 50 to 75 percent of the cost not reimbursed by a DRG when a qualifying antimicrobial is used. Additionally, the eligibility criteria to demonstrate substantial clinical improvement over existing treatments were waived (Schneider, Harrison, and McClellan 2020). The severity classification for 18 types of resistant infections was also changed to allow for greater DRG reimbursement. These changes seem to have improved the impact of NTAP: while only three antibiotics qualified under NTAP between 2001 and 2020 (Schneider 2020), six new antibiotics qualified for fiscal year 2021 (McCaughan 2020).

In France, antibiotics are exempt from turnover liable to clawbacks[7] and are guaranteed a price no lower than the lowest across four reference countries. Manufacturers can also request a price increase for medicines at risk of shortages. In Germany, qualifying antibiotics receive an exemption from internal price reference groups (Gotham et al. 2021). However, critics claim that these alterations to reimbursement mechanisms will have only a minor impact since they act as exceptions to broader rules, rather than a norm, and differ between markets (thus increasing the translational costs for companies, which will have to consider opportunities in each market individually; this may be especially difficult for SMEs) (Gotham et al. 2021). Accordingly, the financial impact is unclear—the fragmentation of markets and schemes makes it hard to assess the overall impact of such schemes (Gotham et al. 2021). Moreover, these approaches might not consider access issues and may worsen stewardship issues by providing an incentive for companies to overmarket their products.

## Extended exclusivity: the GAIN act

The revenue that companies receive per pill sold dramatically decreases after their product goes off patent and generic manufacturers step in. Therefore, one way to potentially generate greater reimbursement for companies is to extend their product exclusivity. This is the motivation behind the 2012 GAIN Act in the United States, which granted an additional five years of exclusivity for

....................................................

6   DRGs are a form of hospital financing whereby the hospital is reimbursed a set price according to the diagnosis of the patient—as compared with a fee-for-service system, whereby hospitals are reimbursed for every procedure/ medication provided. DRGs thus encourage efficiency of healthcare provision. While this is beneficial in most situations, such a system disincentivises hospitals from using expensive, novel antimicrobials (even when clinically necessary), as the higher costs of this medicine will be not reimbursed. A DRG carve-out allows hospitals to be separately reimbursed for these antimicrobials, thereby preventing the provider from shouldering the high costs.

7   In France, pharmaceutical companies must contribute to the social security budget if their year-over-year turnover increases above a set level. This is known as a clawback scheme (Gotham et al. 2021).

any antibiotic designated as a "qualified infectious disease product," defined as "an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections." This extension is in addition to any existing exclusivity period (e.g., through the Orphan Drug Act of 1983). As of 2017, this was the only non-push incentive that had been implemented (Årdal, Røttingen, et al. 2017). However, there is debate over GAIN's impact. While some authors believe it could have helped stimulate antifungal drug development (Perfect 2017) and could be used as a model for policy change in China (Tang et al. 2016), others believe that it will have limited economic impact—for example because sales during this period have little net present value, as they occur decades after the initial research was done (PCAST 2014). Indeed, the US President's Council of Advisors on Science and Technology (PCAST) stated that GAIN has "no significant impact on pharmaceutical companies and only modest impact on small biotechnology firms." Moreover, some authors believe that GAIN does not properly target incentives and so does not actually ensure innovative R&D (Outterson and McDonnell 2016; So and Shah 2014). Furthermore, GAIN does not address stewardship or access concerns—and indeed potentially worsens each of these by incentivising overuse of drugs and delaying the entry of affordable generics. Despite these concerns, further use of similar strategies is frequently proposed in the literature (see next section).

## Restrictive prescribing

While the above-mentioned strategies primarily target innovation, several purchasing approaches have been used to improve the stewardship of drugs. For example, many countries use restrictive prescribing—restricting which drugs can be dispensed without prescriptions and/or who is able to write such prescriptions. Many countries have banned over-the-counter sales of antibiotics without a prescription. For example, in 2010, Brazil enforced the requirement of medical prescriptions for antibiotic sales in private pharmacies, leading to a drop in oral antibiotic usage (Kliemann et al. 2016). A review of such policies found a reduction in antibiotic consumption in four out of five instances (and no effect in the fifth) (Lim et al. 2020). However, imposing restrictions on some antibiotics may have the effect of "squeezing the balloon"—increasing use of other antibiotics as alternatives. In some instances, this shift in usage could be beneficial: indeed, the WHO advocates shifting antibiotic consumption patterns so that at least 60 percent of total usage is of antibiotics in the "access" category of its AWaRe classification, which indicates lower resistance potential (WHO 2021). The problem arises when restrictions on first-line drugs lead to increased usage of more important drugs, which are on the "watch" or "reserve" lists, encompassing, respectively, drugs with higher resistance potentials and drugs for which multi-drug-resistant organisms have already evolved. For example, a policy in China that included imposing limits on the percentage of patients treated with antibiotics, limiting the number of antibiotics in use, and limiting the use of IV antibiotics in primary care was effective at reducing total antibiotic consumption but increased the percentage contribution of third- and fourth-generation cephalosporins (Wang et al. 2020). Other restrictive prescribing initiatives include Australia's reduction of default prescription repeats available and its 2020 change of advice from completing antibiotic packets to following prescriber guidelines

(Glasziou et al. 2022). However, a concern with all restrictive policies is that they may inhibit access to needed antibiotics. The balance between stewardship (i.e., preventing excess) and access is very delicate. Indeed, there is "no single sustainable model in LMICs that increases access while preventing excess" (Zhang et al. 2022). Thus, it is important to have context-adjusted programmes that consider the local access needs when designing stewardship measures.

## Financial incentives for prescribers

Purchasing behaviours can also be changed through financial strategies that target prescribers. For example, in multiple settings, separating drug prescribing from dispensing (thus removing the financial incentive for prescribers to overprescribe) reduced both prescriptions and antibiotic use (Lim et al. 2020). Restriction on the reimbursement achieved from antibiotic prescription also had the same impact. Yoshikawa et al. (2021) found that financial penalties were more effective than capitation or pay-for-performance schemes in changing prescriber behaviour—though improvements in appropriate prescribing were only in the short term. Thus, such incentives for prescribers can be effectively deployed to promote stewardship activities. If incentives are correctly designed only to minimise inappropriate prescribing, then there should not be any impact on access. However, in the absence of other interventions, such incentives could decrease incentives for innovation. Moreover, one working group member expressed concern that such incentives may not be sustainable for LMICs—thus, further research may be required to determine the contexts in which such incentives may be applicable.

## Tax incentives

Tax incentives can take many forms, according to different objectives. Tax credits or tax cuts can be used as push, or sometimes pull, incentives to drive innovation, depending on the time in the development process when they are implemented (Larsen 2016). However, tax credits have limited impact on SMEs because they do not help cash flow, and the public often has an unfavourable opinion of giving tax breaks to pharmaceutical companies (Baraldi et al. 2016). Moreover, they do not directly target access or stewardship. An alternative form of tax incentive is a hypothecated, Pigouvian tax on use (Hollis and Maybarduk 2015; Giubilini 2019). This would be charged to the users of antibiotics, thus motivating good stewardship, and the revenue could be used to drive innovation. However, these taxes would have to be designed very carefully to avoid unintended consequences, particularly on access (Harring and Krockow 2021).

# 5. Ideas that have not been implemented

In addition to the interventions already implemented, the literature includes many further proposed models. The majority of these are forms of pull incentives. This section outlines the literature on the perceived strengths and weakness of these proposed interventions with respect to the three pillars

of access, innovation, and stewardship. It is important to consider these in concert because of the potentially deleterious trade-offs between them—for example, interventions to improve stewardship may have negative consequences for access, and vice versa. Indeed, Årdal et al. (2016) stated that "access, conservation, and innovation are beneficial when achieved independently, but much more effective and sustainable if implemented in concert within and across countries." Despite this, a 2017 paper by Simpkin et al. found that "antibiotic sustainability and patient access requirements are poorly integrated into the array of incentive mechanisms" (Simpkin et al. 2017). Given the differing priorities people have in relation to access, stewardship, and innovation, as highlighted in section 3, considering all these different aspects will likely assist with consensus building and thus with achieving change.

## Market entry reward

The most commonly proposed intervention to drive antimicrobial innovation is a pull incentive in the form of a market entry reward (MER). This could be a lump-sum reward, as proposed by the AMR Review (Review on Antimicrobial Resistance 2016), or a reward in the form of regular payments (see next subsection on subscription models). This reward could be contingent on sustainable use and access provisions (Årdal, Baraldi, et al. 2017; Monnier et al. 2019; Theuretzbacher, Årdal, and Harbarth 2017). For example, in order to receive delinked payments, companies might have to agree to restrict sales to humans only, not promote their drug, perform environmental waste monitoring, label the drug for specific uses, and/or transparently report sales (Theuretzbacher, Årdal, and Harbarth 2017). Researchers at Duke propose a specific model they call the Priority Antimicrobial Value and Entry (PAVE) Award, which would grant developers a significant reward upon market entry followed by smaller subsequent payments contingent on sustainable use, availability, and continued data collection (Daniel et al. 2017).

Many papers agree that such a reward would be beneficial because it would provide a known return for developers (i.e., reduce their risk), enable targeting of the incentive to areas of high unmet need, and ensure global access and appropriate use of resulting new drugs (Årdal, Røttingen, et al. 2017; PCAST 2014). However, there is significant debate over what form such a reward would take—in particular, whether it would be partially or fully delinked from sales volume. In a partially delinked system, a healthcare system would pay an annual fee for access to a certain volume of the drug, but any dose beyond that would be paid per use: the developer would receive some reimbursement for each pill sold beyond a certain point (BEAM Alliance 2019). In a fully delinked system, the developer's return on investment is entirely independent of the volume of drug sold (Outterson 2014). In a fully delinked system, there is no incentive for developers to overmarket their products, so the system scores high in terms of stewardship. ReAct is therefore very supportive of a fully delinked approach, believing that a full change is needed since old methods have not worked (Aagaard et al. 2021). Indeed, they advise to "avoid partial delinkage" since it has "potentially negative consequences with respect to priority setting, stewardship, access, and developing appropriate formulations for

neglected populations" (Aagaard, Malpani, and Zorzet 2021, 43). However, most literature favours a partially delinked approach (the Transatlantic Taskforce on Antimicrobial Resistance, or TATFAR, and the BEAM Alliance) (Årdal, Johnsen, and Johansen 2018; Bhatti et al. 2018; Towse et al. 2017). Dutescu and Hillier (2021) found five papers advocating a partially delinked system, two proposing full delinkage, and seven whose position was unclear.

One reason that a partially delinked model is preferred is that the shift to a partially delinked system would be less disruptive than a shift to a fully delinked approach: a partially delinked system can work within existing reimbursement mechanisms (Årdal, Røttingen, et al. 2017) and has been successfully used before in different contexts by the US Biomedical Advanced Research and Development Authority, or BARDA (PCAST 2014). Årdal, Johnsen, and Johansen (2018) expressed a belief that the added benefit of a fully delinked system for only a few drugs would not exceed the costs of setting it up. For example, in the Norwegian context it would require legal changes. On the other hand, Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) has pointed out that testing a long-term supply continuity model can also test the feasibility of implementing a delinked MER—and this could be done immediately while waiting for a novel antibiotic to be approved (Årdal, Findlay, et al. 2018). Moreover, Årdal, Johnsen, and Johansen (2018) argued that the unit price of zero in a fully delinked model could in fact lead to overuse, thereby countering stewardship goals. Additionally, fully delinked systems are less popular than partially delinked ones because they place all the risk on the payer—and, as argued by Bhatti et al. (2018), for the government to assume all the risk in a fully delinked model is not an optimal use of public resources. Also, if the payer misjudges future resistance patterns or innovation needs, then the system would result in funding innovation that is misaligned with needs (BEAM Alliance 2019; Bhatti et al. 2018). In contrast, the market dynamics at play in a partially delinked model would encourage innovation through differentiation (Bhatti et al. 2018).

All of the literature we found discussing whether to focus on a fully or partially delinked model predates the NHS's pilot of a fully delinked model and the US legislation written with the same aim (both classed as subscription rather than MERs). Interviewees suggested that this pilot and draft legislation have addressed many of the concerns about a fully delinked model. In particular, these two schemes appear to have allayed the fear that governments would not be willing to fund incentives large enough to pay for antimicrobial innovation.

One paper suggested that the lower sums required for partial delinkage may make the system more sustainable (Årdal, Røttingen, et al. 2017). In contrast, one interviewee pointed out that the overall cost of a partially delinked system is likely similar to that of a fully delinked system, since the initial reward is topped up by revenue from sales via normal channels. Moreover, even in a partially delinked model there are questions around how such an MER would be funded. For example, a designed fund or tax (such as a pay-or-play tax) may be required to ensure its sustainability (Årdal, Røttingen, et al. 2017; Daniel et al. 2018).

This high cost may be one reason why MERs have struggled to achieve political backing, despite having been proposed for many years (OECD et al. 2017). Indeed, Clift (2019) stated that the "problem with the [AMR] Review's recommendations on market entry rewards is that they have not been taken forward politically, at the level of the G20 or G7, in any meaningful sense." Moreover, the required shift in payment system may be a daunting undertaking. For example, the literature implies there is debate about the best way to implement an MER—in particular, around the issue of intellectual property (IP) rights. This has been historically contentious, and thus a clear plan is needed at the point of implementation (OECD et al. 2017). However, both the PASTEUR Act and the NHS England pilot have avoided this issue by leaving IP largely untouched. No interviewee raised IP as a concern, and the interviewees we spoke to about IP suggested that this debate is no longer relevant.

MERs are undoubtedly very effective at increasing the net present value (NPV) of a drug at all stages of R&D (Ciabuschi et al. 2020; Outterson 2021). While they may therefore be the best solution for stimulating innovation from Big Pharma, an MER alone does not provide any support to a company in the earlier stages of development. Thus, for SMEs, grants are likely more important (Ciabuschi et al. 2020). When implementing an MER, care must be taken to ensure that SMEs are sufficiently incentivised to continue innovating—such as by complementing an MER with a push incentive. Overall, MERs provide a good balance of stewardship, access, and innovation—indeed, they scored best on a modified version of Renwick's framework that assessed whether the incentive improved NPV; promoted participation from both SMEs and large pharmaceutical companies; promoted cooperation, access, stewardship, and innovation; involved delinkage; and had been successfully implemented before (Dutescu and Hillier 2021).

## Subscription model

Subscription models are a subset of MERs, whereby the developer receives regular payments after regulatory approval in return for providing access to the drug. The amounts of these payments can be varied according to value of the drug. For example, Rex and Outterson (2016) proposed a model whereby a single global buyer pays a base amount for every qualifying drug. This amount can be increased according to the novelty of drug mechanism, unmet need addressed, reduction in healthcare costs, targeting of priority pathogens, and post-approval expansions of usage.

As with MERs as a whole, subscription models can be either partially or fully delinked. They have the benefit of effectively incentivising innovation while also providing guarantees to enable access after approval (BEAM Alliance 2022). While their effectiveness has yet to be demonstrated, the National Health Service of England (NHS England) has recently launched a pilot subscription scheme to demonstrate the potential benefits of such an approach. Two drugs have been selected; the contract will reimburse drug makers according to the value of the drug, with a cap set at £10 million per annum (National Institute for Health and Care Excellence NHS England 2020). This is a fully delinked subscription scheme.

Sweden is also piloting a subscription scheme—but has chosen to adopt a partially delinked model. Some respondents have questioned whether this is really a subscription scheme and whether the funding is large enough to generate innovation. This scheme aims to ensure access to products under patent protection for which current demand is insufficient to incentivise the proprietor to sell in Sweden. The Public Health Agency of Sweden will set a minimum guaranteed annual revenue; if this is exceeded through unexpectedly high sales, the developer will be paid a bonus equal to 10 percent of the guaranteed annual revenue (Gotham et al. 2021; Public Health Agency of Sweden 2020). Legislation has also been proposed in the United States to implement such a model. The PASTEUR Act would create a mechanism for developers to enter subscription contracts guaranteeing revenue of between US$750 million and US$3 billion for critical antibiotics, provided they commit to maintaining availability and supporting stewardship endeavours (Duke-Margolis Center for Health Policy 2020). While there is widespread support for use of such subscription models in HICs, ReAct has expressed concern that such models "may not be relevant or applicable in LMICs" due to a lack of health technology assessment (HTA) agencies, insufficient resources to pay large subscription fees, and low interest from companies to market new antibiotics in LMICs (Aagaard et al. 2021, 43). Two interviewees mentioned the need for more research on how to make these interventions relevant to LMICs.

## Transferable exclusivity vouchers

Transferable exclusivity vouchers (TEVs) have been proposed to address the limitations of other incentive structures. TEVs would be awarded to drug developers after regulatory approval of a high-value drug to lengthen the patent life of another drug the same developer markets (Dutescu and Hillier 2021). Alternatively, the voucher could be sold to another drug developer. The level of reward could be tailored to the value of the new drug by changing the length of exclusivity provided by the voucher (Outterson and McDonnell 2016), such as by using a tiered system (Boyer, Kroetsch, and Ridley 2022). There is broad agreement in the literature that this would be a powerful way to stimulate innovation (Årdal, Lacotte, and Ploy 2020; Årdal, Røttingen, et al. 2017; Boyer et al. 2022). Indeed, the BEAM Alliance described a TEV as the best tool to reward the development of new therapies, since it is fast and simple to implement, provides a predictable return on investment for companies, and comes at an acceptable cost (BEAM Alliance 2022). One expert interviewed for this report stated that the European Commission is considering implementing transferable vouchers since it would be simpler to implement than other models, despite raising costs for individual member states. The European Federation of Pharmaceutical Industries and Associations also pushed for this model (EFPIA 2022), and the idea has support in the United States since it doesn't require annual appropriations from Congress and can be sold as a "zero-budget" item (Outterson and McDonnell 2016).

However, critics have pointed out several downsides to this approach—in particular, in terms of access. By delaying the transition (of a different drug) to generics, a TEV would effectively subsidize

one area of healthcare at the expense of another, burdening patients in this other area with higher costs (Årdal, Røttingen, et al. 2017; PCAST 2014). This may be especially harmful for patients in LMICs, with higher prices inhibiting access to the patented drugs. TEVs also do not guarantee predictable access to the new drug (Årdal, Lacotte, and Ploy 2020), although Duke-Margolis Center for Health Policy proposed that developers could be required to submit an access plan before being awarded a voucher (Boyer et al. 2022). Similarly, TEVs do not guarantee appropriate use of a drug (Årdal, Røttingen, et al. 2017). Although we were told by an interviewee that TEVs could be designed to overcome stewardship issues, we have not seen any evidence of this impact. Moreover, critics argue that this system is inefficient and the cost too great (Årdal, Lacotte, and Ploy 2020; Årdal, Røttingen, et al. 2017; Outterson and McDonnell 2016; PCAST 2014). While guardrails to cap the financial impact on the insurer could be used in some contexts, this would not be possible in a multipayer European scenario (Årdal, Lacotte, and Ploy 2020). Another suggested amendment is to auction the vouchers and use the profit for an antibiotic innovation fund (Outterson and McDonnell 2016). In the US context, researchers at Duke University have suggested that such a program be administered by the FDA, which already has experience administering priority review vouchers (Boyer et al. 2022). However, even with such adjustments, such an incentive scheme is likely to over-incentivise developers and may not sufficiently address access and stewardship issues.

## Advanced market commitment (options market for antibiotics)

Building from an MER approach is the idea for a hybrid options market for antibiotics (OMA), modelled on the principle of financial call options (Brogan and Mossialos 2016). Under this system, early in the drug development process, the payer can purchase the right (an "option") to buy a set number of units of the drug at a discounted price (the "strike price") if it makes it to market. Since the purchaser is guaranteed a pre-agreed number of doses, this approach should support access. However, if options prices are set too high, then LMICs may struggle to get access to the drug (Årdal, Røttingen, et al. 2017). The option and strike prices could be based on the value of the drug developed (in terms of clinical need, efficacy, and innovativeness). Thus, this approach should support innovation—although the total revenue generated may be significantly less than that generated by other incentives (Brogan and Mossialos 2016).

The OMA differs from a traditional MER in that investment can come at any stage of the R&D process (rather than just at regulatory approval). Thus, the government shoulders greater risk because the product may or may not reach market (Årdal, Røttingen, et al. 2017). However, this approach also allows investors to moderate their risk level by adjusting the time of their investment. Early investment would bring greater risks but a lower option price. Early investment could also help move toward a delinked system, since the strike price would be very low, meaning that even high sales volumes of new products would generate relatively small revenues. However, full delinkage is probably untenable, as the option price would need to be extremely high (Brogan and Mossialos 2016). Overall, the model as a whole has only limited ability to promote stewardship. For instance, firms

may overmarket their products to make up for the loss in revenue from the discounts given to options holders (Brogan and Mossialos 2016).

## Diagnosis confirmation model

Another volume-based remuneration system proposed in several papers is the diagnosis confirmation model (DCM). This approach uses a dual pricing structure, whereby novel antimicrobials are reimbursed at a higher price (reflective of their value) only when a patient's diagnosis is confirmed with a diagnostic test or by physician judgment (Lum et al. 2018). This model therefore encourages both the use of diagnostics and the de-escalation of therapy if a patient does not have a multi-drug-resistant infection (i.e., when a novel antibiotic is not necessary, and a cheaper generic medication can be used). Thus, this model performs moderately well on the stewardship criterion and may have beneficial implications for patient outcomes (Årdal, Røttingen, et al. 2017). By paying for the value of antibiotics when justified, this model should stimulate innovation of a greater diversity of broad- and narrow-spectrum antibiotics (DRIVE-AB 2016). However, only a few SMEs have expressed belief that the DCM would significantly stimulate innovation (Årdal, Findlay, et al. 2018). Moreover, implementation of a DCM is reliant on diagnostic capacity, physician decision-making capability, and good data systems—and thus may be harder for LMICs to implement, where these capabilities are comparably weaker than in HIC settings. Moreover, a DCM has no conditions to ensure access. For these reasons, the DRIVE-AB project chose not to select this model, stating that the MER seemed better aligned with the initiative's overall goals (Årdal, Findlay, et al. 2018). Although DRIVE-AB prioritised MERs, DCMs may still warrant renewed consideration.

## Long-term supply continuity model

The long-term supply continuity model was proposed by ReAct as a way to ensure a predictable supply of important generic antimicrobials (Aagaard, Malpani, and Zorzet 2021). Like an MER, this model relies on government payments of a delinked reward in return for supply of an antimicrobial. It could thus be used to test the feasibility of implementing a delinked model. While this system is a relatively new idea and thus is not frequently mentioned in the literature, it nonetheless garnered support, with one interviewee calling it "a worthy idea." The model serves an aim like that of the SECURE initiative, developed by GARDP and the WHO: to expand access to essential antibiotics (WHO 2022).

## Pay or play

"Pay or play" is a tax-based incentive proposed by the Review on Antimicrobial Resistance (AMR Review). This incentive would levy a tax on any large pharmaceutical company not developing antimicrobials, with the aim of incentivising pharmaceutical companies to maintain or start antimicrobial research programs. Additionally, the revenue raised could go towards funding innovation, for example through an MER. However, most pharmaceutical federations are strongly

opposed to this approach (ABPI, EFPIA, and IFPMA 2016). Moreover, the BEAM (Biotech Companies from Europe Innovating in Anti-Microbial Resistance Research) Alliance expressed concern that surcharges may be shifted onto consumers or health systems through higher prices from penalised companies (BEAM Alliance, 2019). Careful implementation would be required to ensure that companies are not incentivised to game the system through half-hearted investments (Årdal, Lacotte, and Ploy 2020). The proposal also does not address the issues of access and stewardship. Due to these concerns, pay or play appears to have fallen out of favour recently and is no longer frequently mentioned in the literature.

## Drug valuation systems

All of the above options require setting a price that is reflective of each drug's true value to society. Determining this value requires updating strategies for drug pricing. It is also important to ensure that developers are not able to game any interventions by overinflating the worth of their product or providing false information to investors. Setting appropriate drug prices can be especially hard when drugs are approved under noninferiority trials that do not explicitly demonstrate the additional value of the drug.

It will be important to update HTAs in order to better consider societal benefits, as current systems do not capture the value that antibiotics offer beyond the individual patient treated (Neri et al. 2019). Indeed, a report from the Boston Consulting Group cited HTAs as one of the four main barriers to implementing a subscription model (Boluarte and Schulze 2022), although Bhatti et al. (2018) recognised that updating HTA systems is an immediate, concrete action authorities can take while broader changes are explored. To ensure that HTAs better reflect antimicrobial value, Outterson and Rex (2020) and Schneider, Harrison, and McClellan (2020) proposed use of the STEDI system: considering the *spectrum* value (since narrow-spectrum antimicrobials are preferred due to their decreased adverse impacts on the gut microbiome), the *transmission* value (in avoiding infection spread), the *enablement* value (in enabling procedures with otherwise too great an infection risk), the *diversity* value (since a greater diversity of antimicrobial mechanisms limits the emergence of resistance), and the *insurance* value (against future threats) of antimicrobials. Similarly, Årdal, Johnsen, and Johansen (2018) proposed broadening HTA criteria to include (1) the value of an antimicrobial in controlling a specific drug-resistant target, (2) the value of having a stable drug supply, and (3) the value of preparedness against future threats. The BEAM Alliance welcomed the European Commission's 2017 commitment to "develop new or improved methodological HTA approaches" (BEAM Alliance 2017)—but in 2021 called for "common, tailored HTA valuation" across member states (BEAM Alliance 2021). While some countries have made some alterations to HTAs for antibiotics, such as the new HTA system used in the NHS England pilot scheme, further changes are required (Neri et al. 2019).

An alternate to using updated HTA systems is to use a TPP-based system to value drugs—this is the approach taken in the proposed PASTEUR scheme. Since this system is prospective rather than retrospective, it may be better at reducing commercial risk (unless HTAs are extremely predictable even when drugs are in early development). However, it increases the risk of funding drugs that end up not having large societal value—although the payments from the PASTEUR Act will likely be adapted based on real world evidence, during the subscription period.

In our interviews, all those who said they had reviewed the criteria for the US PASTEUR Act or the UK's pilot scheme suggested that they thought both these systems would appropriately assess the value of new antibiotics. However, one person did raise concerns about a potential overemphasis on novel classes when new within-class antibiotics can have large therapeutic value.

## Trends in the literature

The majority of papers captured by this literature review were focused only on HICs—despite including an additional search specifically targeting LMIC-focused studies. Just over half the papers (51.1 percent; 72/141) include any reference to "LMICs" or a specific LMIC country. However, most of these references were just in passing, with the paper primarily focused on policy in HICs. Only 14 papers—fewer than 10 percent—are focused exclusively on LMICs. Moreover, of the 128 papers with named authors, just 16 (12.5 percent) had any authors based in an LMIC. Papers with LMIC-based authors were more likely to discuss restrictive prescribing, financial incentives for prescribers, and diagnostic confirmation models. They were less likely to discuss tax incentives or increasing reimbursement for antibiotics. Indeed, of the 37 (26.2 percent) papers discussing the role for increased reimbursement, not one had an LMIC-based author. With the exception of GAIN, discussions of policies tested in HICs, such as the Swedish and United Kingdom pilots, are also less discussed by LMIC-based authors.

As discussed in the methodology section, papers that included, either in their title or abstract, the phrase "low- and middle-income countries"—or the name of any country defined as such by the World Bank—were included in our search terms regardless of the year of publication. Other papers were included only if they were published in the last eight years (see appendix 3 for more details). Only one paper published before 2014 (2013) met the screening criteria. There is a noticeable shift in how often some interventions are discussed over time. MERs are one of the most discussed interventions in 2016, 2017, and 2018 but appear less frequently in more recent papers. In contrast, subscription models are discussed in only 7 papers before 2019 but have been mentioned in 32 papers since then. The number of papers on extending market exclusivity has also declined. Papers discussing a single policy, such as the GAIN Act, get more attention closer to the implementation of the policy. The frequency of papers discussing most other interventions appears to stay stable over time. A table outlining these results can be found in appendix 4.

# 6. Limitations

The interviews were semi-structured. All were based on a standard set of questions that was shared with interviewees in advance. Although these questions were used as a starting point in all interviews, the interviewers did ask unscripted follow-up questions, which varied based on responses, as well as additional questions tailored to respondents' particular expertise. This approach allowed greater flexibility and helped to clarify responses and explore nuances. However, it may also have introduced additional biases on the part of the research team.

The literature is predominantly focused on HICs, with almost half the papers making no reference to either LMICs or naming a country classed as an LMIC. In contrast, fewer than 10 percent of papers (14/141) focus exclusively on this group. This bias in the literature likely impacted the interventions discussed in this paper. Where the literature or interviewees raised concerns about specific interventions not working in LMICs, we have shared these. However, the large gaps in the literature mean that there will likely be some interventions identified by the literature review that will not be applicable in LMICs—but we did not find evidence to suggest not using them.

A quarter of the interviewees for this study currently live in LMICs; several more were from an LMIC but lived and worked in an HIC at the time of the interview. As previously outlined, the vast majority of authors in the literature were based in HICs, biasing our selection sample. A higher response rate from those based in HICs and a greater likelihood that interviewees would suggest HIC-based researchers led to a lower portion of interviewees being based in LMICs than the research team had intended.

The literature review was focused on how procurement system choices impact innovation, access, and stewardship. Therefore, procurement terms formed the basis of our search strategy, which biased our search toward papers focused on innovation. When linked to specific drugs, grants were included in the search, since grant funding is often linked to later procurement, setting conditions for price or sale. The literature on procurement systems appears to focus more on innovation than access and stewardship, leading this paper to focus more heavily on this goal. The specific search terms used to capture discussions on procurement (outlined in Appendix 1) might have further biased the paper in that direction.

The literature review did not distinguish between first-, second-, and third-line treatments. This decision was based in part on the fact that this distinction is not made in most of the existing literature. Additionally, this review focused more on new treatments, which are not typically first- or second-line.

We looked at all AMR literature related to LMICs in general. In practice, the needs of countries will vary significantly depending on wealth (which varies greatly even among LMICs) and population size as well as geographic, political, and cultural considerations. One goal of CGD's working group is

to understand how these factors impact the needs of countries with respect to purchasing systems for antimicrobials.

# 7. Discussion

One of the main takeaways from the interviews is that economic issues (and the political difficulties in fixing them), not scientific issues, are the primary issues contributing to AMR and undermining the implementation of solutions. AMR is a slow-burning, long-term problem, and many respondents expressed a belief that our political and economic systems are not sufficient to meet these challenges. While a significant amount of research has been undertaken on the technical specifics of a new purchasing system in HICs, greater research—and evidence—must be generated to determine the best-fit models in each setting and to facilitate implementation, as well as to determine what approaches would work best in LMICs. Numerous new purchasing systems have been theorized and piloted to address these weaknesses in the antimicrobial pipeline, but the market for antimicrobials remains largely unchanged. Although global declarations and national action plans (NAPs) serve as commendable first steps to advancing access, promoting stewardship, and incentivising innovation, many countries lack the political will to go beyond words by fully funding these initiatives and implementing changes. For example, in fiscal year 2019–2020, only 19.9 percent of countries reported that their NAPs had funding sources identified (WHO, FAO, and OIE 2021). Moreover, NAPs often lack detail on how to promote R&D for AMR. Without clear, actionable strategies to translate commitment into action, many of these declarations simply pay lip service to the cause. NAPs must be funded, operationalized, and evaluated to successfully mitigate AMR through known solutions. Arrangements and incentives for antimicrobial procurement must be a key part of these national policies. While there has been progress in advancing push incentives to stimulate innovation in antimicrobial R&D, further work is needed, since neither push nor pull incentives alone will be sufficient to drive the required levels of innovation (Outterson 2021). Moreover, incentives implemented to date to incentivise innovation tend to not focus enough on adequate provisions for access and/or stewardship. Therefore, further work is needed to implement solutions that address all three of these crucial components.

Based on gaps identified through this analysis, additional research is needed to focus on effective implementation of a new purchasing system and to raise awareness of the severity of this issue among policymakers and the general public. Further research focusing on the specific point of implementation is needed—since Sertkaya, Jessup, and Wong (2017) found that at this timepoint, incentives may under-incentivise early-stage developers (i.e., do not achieve the desired outcome) and over-incentivise late-stage developers (i.e., achieve the desired outcome but at a cost that is higher than needed). Thus, transitional policies may be needed (such as the smaller transition subscriptions included in the PASTEUR Act (Bennet et al. 2021)). Where policies have been implemented, there was a dearth of research evaluating them—most likely because these interventions have been implemented too recently to be properly assessed, especially since the time

frames for drug innovation are long. However, the impact of any policy on access and stewardship ought to be much quicker to spot. An exception to the above is the US GAIN Act, which, as highlighted in Table 3, has been widely discussed and evaluated in the literature.

The literature found in this review was more focused on innovation than on access or stewardship. Our search strategy emphasised procurement and payment mechanisms, in line with the lens through which researchers usually view antimicrobial innovation. The overlap between procurement, stewardship, and access is relatively narrow, since solutions to promote stewardship and increase access are often broader than interventions related to purchasing systems. Thus, our search strategy included more innovation terms and so might also have biased the results in this direction.

There was also a large divide in the outlook of respondents based in HICs compared with those in LMICs. The former group is much more interested in innovation to overcome resistant pathogens and measures to restrict unnecessary use. In contrast, those based in or focused on LMICs are much more concerned about access to antibiotics and infection control measures that would reduce unnecessary use (but are beyond the scope of this project). This imbalance leads to a research agenda disproportionately focused on the needs of HICs, neglecting analysis and recommendations for the appropriate policies and effective implementation to address AMR in resource-constrained settings. The disproportionate production of research in HICs likely also underpinned the identification of more papers focused on innovation (the primary concern for HIC-focused individuals) than access or stewardship (the primary concerns for LMIC-focused individuals) in this review. Going forward, more research is needed to understand the best-fit solutions for LMICs.

AMR is a global problem that requires international coordination. Different countries will have different priorities and roles in overcoming this crisis and must, therefore, define distinct rights and responsibilities in the global response. Such complementary action will ensure there is sufficient funding for innovation and access to critical products while protecting the value of these products by reducing unnecessary use.

This paper serves as the first output for CGD's working group on antimicrobial resistance, *A Grand Bargain for Antimicrobial Procurement: Improving Purchasing Systems to Enhance Access, Stewardship, and Innovation for Antimicrobials in Low- and Middle-Income Countries*. The research outlined here was undertaken in part to frame this working group. In future work, the working group will examine different ways to purchase antimicrobials in LMICs in order to identify actionable policies to improve access to and stewardship of key products as well as increase funding for research into new ones. Ultimately, governments, civil society, industry, health providers, and patients need to strike a new grand bargain to govern the rights and responsibilities to develop, protect, and ensure access to these vital medicines.

# Bibliography

## Papers from systematic review—cited

Aagaard, Helle, Rohit Malpani, and Anna Zorzet. 2021. *Ensuring Sustainable Access to Effective Antibiotics for Everyone—Everywhere*. Stockholm: ReAct Europe.

ABPI (Association of the British Pharmaceutical Industry), EFPIA (European Federation of Pharmaceutical Industries and Associations), and IFPMA (International Federation of Pharmaceutical Manufacturers & Associations). 2016. *ABPI, EFPIA and IFPMA Issue Joint Statement on AMR*. Geneva: IFPMA.

Access to Medicine Foundation. 2021. *Antimicrobial Resistance Benchmark 2021*. Amsterdam.

Årdal, Christine, Enrico Baraldi, Francesco Ciabuschi, Kevin Outterson, John H. Rex, Laura J. V. Piddock, and David Findlay. 2017. "To the G20: Incentivising Antibacterial Research and Development." *Lancet Infectious Diseases* 17(8):799–801.

Årdal, Christine, David Findlay, Miloje Savic, Yehuda Carmeli, Inge Gyssens, Ramanan Laxminarayan, Kevin Outterson, and John H. Rex. 2018. *Revitalizing the Antibiotic Pipeline—Stimulating Innovation While Driving Sustainable Use and Global Access*. Geneva: DRIVE-AB.

Årdal, Christine, Jostein Johnsen, and Karianne Johansen. 2018. "Designing a Delinked Incentive for Critical Antibiotics: Lessons from Norway." *Journal of Law, Medicine & Ethics* 46(S1):43–49.

Årdal, Christine, Yohann Lacotte, and Marie-Cécile Ploy. 2020. "Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe." *Clinical Infectious Diseases* 71(8):1994–99.

Årdal, Christine, Yohann Lacotte, and Marie-Cécile Ploy. 2021. *Improving Access to Essential Antibiotics*. EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections.

Årdal, Christine, Kevin Outterson, Steven J. Hoffman, Abdul Ghafur, Mike Sharland, Nisha Ranganathan, Richard Smith, Anna Zorzet, Jennifer Cohn, Didier Pittet, Nils Daulaire, Chantal Morel, Zain Rizvi, Manica Balasegaram, Osman A. Dar, David L. Heymann, Alison H. Holmes, Luke S. P. Moore, Ramanan Laxminarayan, and Marc Mendelson. 2016. "International Cooperation to Improve Access to and Sustain Effectiveness of Antimicrobials." *Lancet* 387(10015):296–307.

Årdal, Christine, John-Arne Røttingen, Aleksandra Opalska, Arjon J. Van Hengel, and Joseph Larsen. 2017. "Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance." *Clinical Infectious Diseases* 65(8):1378–82.

Baraldi, Enrico, Olof Lindahl, Miloje Savic, David Findlay, and Christine Årdal. 2018. "Antibiotic Pipeline Coordinators." *Journal of Law, Medicine & Ethics* 46(S1):25–31.

Bax, Richard, and Samantha Green. 2015. "Antibiotics: The Changing Regulatory and Pharmaceutical Industry Paradigm." *Journal of Antimicrobial Chemotherapy* 70(5):1281–84.

BEAM (Biotech Companies from Europe Innovating in Anti-Microbial Resistance Research) Alliance. 2017. *BEAM Alliance Position Paper 2017: Key Guidelines to Implement Effective Measures toward SMEs to Revive the Antibacterial R&D Field.* Paris.

BEAM Alliance. 2019. *Incentivising a Sustainable Response to the Threat of AMR.* Paris.

BEAM Alliance. 2020. *Reflection Paper on the AMR Action Fund.* Paris.

BEAM Alliance. 2021. *Reflection Paper on the Roadmap towards the Revision of the Pharmaceutical Legislation.* Paris.

BEAM Alliance. 2022. *Pull Incentive Mechanisms Suitable for SMEs Developing AMR Products.* Paris.

Bennet, Michael, Todd Young, Mike Doyle, and Drew Ferguson. 2021. *The Pioneering Antimicrobial Subscriptions to End Up surging Resistance (PASTEUR) Act of 2021.* https://www.bennet.senate. gov/public/_cache/files/4/b/4b47a465-62c8-425a-96c4-0b335c857fb0/EE07F7E3051917ECFD81 F2FBBFD39147.pasteur-act-one-pager-061421.pdf.

Bhatti, Taimur, Ka Lum, Silas Holland, Stephanie Sassman, David Findlay, and Kevin Outterson. 2018. "A Perspective on Incentives for Novel Inpatient Antibiotics: No One-Size-Fits-All." *Journal of Law, Medicine & Ethics* 46(S1):59–65.

Boluarte, Till, and Ulrik Schulze. 2022. "The Case for a Subscription Model to Tackle Antimicrobial Resistance." Boston Consulting Group (blog), February 11. https://www.bcg.com/en-us/ publications/2022/model-for-tackling-antimicrobial-resistance.

Boyer, Beth, Adam Kroetsch, and David Ridley. 2022. *Design of a Transferable Exclusivity Voucher Program.* Washington, DC: Duke-Margolis Center for Health Policy.

Brennan, Maressa, Mark P. Williams, and Ivy Hsu. 2022. *Models for Financing Antibiotic Development to Address Antimicrobial Resistance.* Washington, DC: Milken Institute.

Brogan, David M., and Elias Mossialos. 2016. "Systems, Not Pills: The Options Market for Antibiotics Seeks to Rejuvenate the Antibiotic Pipeline." *Social Science & Medicine* 151:167–72.

Cama, J., R. Leszczynski, P. K. Tang, A. Khalid, V. Lok, C. G. Dowson, and A. Ebata. 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.

Ciabuschi, Francesco, Enrico Baraldi, Olof Lindahl, and Simone Callegari. 2020. "Supporting Innovation against the Threat of Antibiotic Resistance: Exploring the Impact of Public Incentives on Firm Performance and Entrepreneurial Orientation." *Journal of Business Research* 112:271–80.

Clift, Charles. 2019. *Review of Progress on Antimicrobial Resistance: Background and Analysis.* London: Chatham House, the Royal Institute of International Affairs.

Daniel, Gregory W., Mark B. McClellan, Monika Schneider, Jingyuan Qian, Gabriela Lavezzari, and Ellen De Graffenreid. 2017. *Value-Based Strategies for Encouraging New Development of Antimicrobial Drugs*. Washington, DC: Duke-Margolis Center for Health Policy.

Daniel, Gregory W., Monika Schneider, Marianne Hamilton Lopez, and Mark B. McClellan. 2018. "Implementation of a Market Entry Reward within the United States." *Journal of Law, Medicine & Ethics* 46:50–58.

DRIVE-AB. 2016. "Incentives to Stimulate Antibiotic Innovation: The Preliminary Findings of DRIVE-AB." Working paper. Geneva.

Duke-Margolis Center for Health Policy. 2020. "Without Effective and Novel Antibiotics Resistant Infections Threaten Us All." Issue brief. Washington, DC.

Dutescu, Ilinca A., and Sean A. Hillier. 2021. "Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study." *Infection and Drug Resistance* 14:415–34.

Edwards, S. E., and C. M. Morel. 2019. "Learning from Our Mistakes: Using Key Opportunities to Remove the Perverse Incentives That Help Drive Antibiotic Resistance." *Expert Review of Pharmacoeconomics & Outcomes Research* 19(6):685–92.

EFPIA (European Federation of Pharmaceutical Industries and Associations). 2022. "A New EU Pull Incentive to Address Anti-microbial Resistance (AMR)." Brief. Brussels.

Eichberg, Michael J. 2015. "Public Funding of Clinical-Stage Antibiotic Development in the United States and European Union." *Health Security* 13(3):156–65.

Giubilini, Alberto. 2019. "Antibiotic Resistance as a Tragedy of the Commons: An Ethical Argument for a Tax on Antibiotic Use in Humans." *Bioethics* 33(7):776–84.

Glasziou, Paul, Jonathan Dartnell, Ruby Biezen, Mark Morgan, and Jo-Anne Manski-Nankervis. 2022. "Antibiotic Stewardship: A Review of Successful, Evidence-Based Primary Care Strategies." *Australian Journal of General Practice* 51(1–2):15–20.

Glover, Rebecca E., Andrew C. Singer, Adam P. Roberts, and Claas Kirchhelle. 2021. "NIMble Innovation—a Networked Model for Public Antibiotic Trials." *Lancet Microbe* 2(11):e637–44.

Gotham, Dzintars, Lorenzo Moja, Maarten van der Heijden, Sarah Paulin, Ingrid Smith, and Peter Beyer. 2021. "Reimbursement Models to Tackle Market Failures for Antimicrobials: Approaches Taken in France, Germany, Sweden, the United Kingdom, and the United States." *Health Policy* 125(3):296–306.

Hey, Spencer Phillips, and Aaron S. Kesselheim. 2017. "Reprioritizing Research Activity for the Post-Antibiotic Era: Ethical, Legal, and Social Considerations." *Hastings Center Report* 47(2):16–20.

IACG (UN Interagency Coordination Group on Antimicrobial Resistance). 2018. "Antimicrobial Resistance: Invest in Innovation and Research, and Boost R&D and Access." Discussion paper. Geneva: World Health Organization.

Kliemann, Breno S., Anna S. Levin, M. Luísa Moura, Icaro Boszczowski, and James J. Lewis. 2016. "Socioeconomic Determinants of Antibiotic Consumption in the State of São Paulo, Brazil: The Effect of Restricting Over-the-Counter Sales," edited by R. A. de Mello. *PLOS ONE* 11(12):e0167885.

Lanini, Simone, John P. A. Ioannidis, Francesco Vairo, Michel Pletschette, Gina Portella, Virginia Di Bari, Alessia Mammone, Raffaella Pisapia, Stefano Merler, Boniface Nguhuni, Martin Langer, Antonino Di Caro, Sarah J. L. Edwards, Nicola Petrosillo, Alimuddin Zumla, and Giuseppe Ippolito. 2019. "Non-inferiority versus Superiority Trial Design for New Antibiotics in an Era of High Antimicrobial Resistance: The Case for Post-marketing, Adaptive Randomised Controlled Trials." *Lancet Infectious Diseases* 19(12):e444–51.

Lim, Jane Mingjie, Shweta Rajkumar Singh, Minh Cam Duong, Helena Legido-Quigley, Li Yang Hsu, and Clarence C. Tam. 2020. "Impact of National Interventions to Promote Responsible Antibiotic Use: A Systematic Review." *Journal of Antimicrobial Chemotherapy* 75(1):14–29.

Lomazzi, Marta, Michael Moore, April Johnson, Manica Balasegaram, and Bettina Borisch. 2019. "Antimicrobial Resistance—Moving Forward?" *BMC Public Health* 19(1):858.

Lum, Ka, Taimur Bhatti, Silas Holland, Mark Guthrie, and Stephanie Sassman. 2018. "Diagnosis Confirmation Model: A Value-Based Pricing Model for Inpatient Novel Antibiotics." *Journal of Law, Medicine & Ethics* 46(S1):66–74.

Monnier, Annelie A., Jeroen Schouten, Gianpiero Tebano, Veronica Zanichelli, Benedikt D. Huttner, Céline Pulcini, Christine Årdal, Stephan Harbarth, Marlies E. Hulscher, and Inge C. Gyssens. 2019. "Ensuring Antibiotic Development, Equitable Availability, and Responsible Use of Effective Antibiotics: Recommendations for Multisectoral Action." *Clinical Infectious Diseases* 68(11):1952–59.

National Institute for Health and Care Excellence. 2020. "Frequently Asked Questions: Developing and Testing Innovative Models for the Evaluation and Purchase of Antimicrobials." Brief. London: NHS England. https://amr.solutions/wp-content/uploads/2020/03/2020-04-03-NHS-England-Procurement-FAQs-FINAL.pdf.

Neri, Margherita, Grace Hampson, Christopher Henshall, and Adrian Towse. 2019. *HTA and Payment Mechanisms for New Drugs to Tackle AMR*. OHE Research Paper. London: Office of Health Economics.

OECD (Organisation for Economic Co-operation and Development), WHO (World Health Organization), FAO (Food and Agriculture Organization of the United Nations), and OIE (World Organisation for Animal Health). 2017. *Tackling Antimicrobial Resistance Ensuring Sustainable R&D*. Paris: OECD.

Outterson, Kevin. 2014. *New Business Models for Sustainable Antibiotics*. Centre on Global Health Security Working Group Papers. London: Chatham House. https://carb-x.org/wp-content/uploads/2018/02/2014_02_15_New-Business-Models-Sustainable-Antibiotics.pdf.

Outterson, Kevin. 2021. "Estimating the Appropriate Size of Global Pull Incentives for Antibacterial Medicines." *Health Affairs* 40(11):1758–65.

Outterson, Kevin, and Anthony McDonnell. 2016. "Funding Antibiotic Innovation with Vouchers: Recommendations on How to Strengthen a Flawed Incentive Policy." *Health Affairs* 35(5):784–90.

PCAST (President's Council of Advisors on Science and Technology). 2014. *Report to the President on Combating Antibiotic Resistance*. Washington, DC: Executive Office of the President.

Perfect, John R. 2017. "The Antifungal Pipeline: A Reality Check." *Nature Reviews Drug Discovery* 16(9):603–16.

Pew Charitable Trusts. 2013. "GAIN: How a New Law Is Stimulating the Development of Antibiotics." Issue brief. Philadelphia. https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2013/11/07/gain-how-a-new-law-is-stimulating-the-development-of-antibiotics.

Pew Charitable Trusts. 2021. "Tracking the Global Pipeline of Antibiotics in Development, March 2021." Issue brief. Philadelphia. https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development.

Renwick, Matthew, David Brogan, and Elias Mossialos. 2014. *A Critical Assessment of Incentive Strategies for Development of Novel Antibiotics*. LSE Health, London School of Economics and Political Science. Vol. 44.

Review on Antimicrobial Resistance. 2014. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*. London.

Review on Antimicrobial Resistance. 2016. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. London.

Rex, John H., and Kevin Outterson. 2016. "Antibiotic Reimbursement in a Model Delinked from Sales: A Benchmark-Based Worldwide Approach." *Lancet Infectious Diseases* 16(4):500–505.

Savic, Miloje, and Christine Årdal. 2018. "A Grant Framework as a Push Incentive to Stimulate Research and Development of New Antibiotics." *Journal of Law, Medicine & Ethics* 46(S1):9–24.

Schneider, M., N. Harrison, and M. McClellan. 2020. *Recommended Post-market Incentive Strategies to Support the Development of Innovative Antibiotics*. Washington, DC: Duke-Margolis Center for Health Policy.

Sertkaya, Aylin, Amber Jessup, and Hui-Hsing Wong. 2017. "Promoting Antibacterial Drug Development: Select Policies and Challenges." *Applied Health Economics and Health Policy* 15(1):113–18.

Simpkin, Victoria L., Matthew J. Renwick, Ruth Kelly, and Elias Mossialos. 2017. "Incentivising Innovation in Antibiotic Drug Discovery and Development: Progress, Challenges and Next Steps." *Journal of Antibiotics* 70(12):1087–96.

So, Anthony D., and Tejen A. Shah. 2014. "New Business Models for Antibiotic Innovation." *Upsala Journal of Medical Sciences* 119(2):176–80.

Tang, Qi, Peipei Song, Jiajia Li, Fanlei Kong, Long Sun, and Lingzhong Xu. 2016. "Control of Antibiotic Resistance in China Must Not Be Delayed: The Current State of Resistance and Policy Suggestions for the Government, Medical Facilities, and Patients." *BioScience Trends* 10(1):1–6.

Theuretzbacher, Ursula, Christine Årdal, and Stephan Harbarth. 2017. "Linking Sustainable Use Policies to Novel Economic Incentives to Stimulate Antibiotic Research and Development." *Infectious Disease Reports* 9(1):6836.

Toth, Damon J. A., Matthew H. Samore, and Richard E. Nelson. 2021. "Economic Evaluations of New Antibiotics: The High Potential Value of Reducing Healthcare Transmission through Decolonization." *Clinical Infectious Diseases* 72(Supplement_1):S34–41.

Towse, Adrian, Christopher K. Hoyle, Jonathan Goodall, Mark Hirsch, Jorge Mestre-Ferrandiz, and John H. Rex. 2017. "Time for a Change in How New Antibiotics Are Reimbursed: Development of an Insurance Framework for Funding New Antibiotics Based on a Policy of Risk Mitigation." *Health Policy* 121(10):1025–30.

Wang, Xuemei, Yuqing Tang, Chenxi Liu, Junjie Liu, Youwen Cui, and Xinping Zhang. 2020. "Effects of Restrictive-Prescribing Stewardship on Antibiotic Consumption in Primary Care in China: An Interrupted Time Series Analysis, 2012–2017." *Antimicrobial Resistance & Infection Control* 9(1):159.

Yoshikawa, Yuki, Isabelle Feldhaus, Ece Özçelik, Tiago Cravo Oliveira Hashiguchi, and Michele Cecchini. 2021. "Financial Strategies Targeting Healthcare Providers to Promote the Prudent Use of Antibiotics: A Systematic Review of the Evidence." *International Journal of Antimicrobial Agents* 58(6):106446.

Zhang, Tingting, Helen Lambert, Linhai Zhao, Rong Liu, Xingrong Shen, Debin Wang, and Christie Cabral. 2022. "Antibiotic Stewardship in Retail Pharmacies and the Access-Excess Challenge in China: A Policy Review." *Antibiotics* 11(2):141.

## *Papers from systematic review—uncited*

Access to Medicine Foundation (AMF). 2021. *Biotechs are Saving the World from Superbugs. Can They Also Save Themselves?* Amsterdam.

Ahmad, Raheelah, Nina Jiayue Zhu, Andrew J. M. Leather, Alison Holmes, and Ewan Ferlie. 2019. "Strengthening Strategic Management Approaches to Address Antimicrobial Resistance in Global Human Health: A Scoping Review." *BMJ Global Health* 4(5):e001730.

AMR Industry Alliance. 2022. *Progress Report: AMR Industry Alliance 2021 Survey.*

Årdal, Christine, Enrico Baraldi, Ursula Theuretzbacher, Kevin Outterson, Jens Plahte, Francesco Ciabuschi, and John-Arne Røttingen. 2018. "Insights into Early Stage of Antibiotic Development in Small- and Medium-Sized Enterprises: A Survey of Targets, Costs, and Durations." *Journal of Pharmaceutical Policy and Practice* 11(1):8.

Årdal, Christine, Yohann Lacotte, Suzanne Edwards, and Marie-Cécile Ploy. 2021. "National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation." *Antibiotics* 10(6):749.

Årdal, Christine, Marie-Cécile Ploy, and Yohann Lacotte. 2021. *A Strategy for Implementing Multi-Country Incentives in Europe to Stimulate Antimicrobial Innovation and Access.* EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections.

Association of the British Pharmaceutical Industry (ABPI). 2021. *AMR: Key Messages.* https://www.abpi.org.uk/publications/antimicrobial-resistance-amr-key-messages/.

Auer, Clemens Martin, Vinzent Rest, and Katharina Hawlik. 2019. "Public Investments in R&D for New Antibiotics: A Call for Smart and Bold Leadership." In *AMR Control 2019–20.* World Alliance Against Antibiotic Resistence.

Baraldi Enrico, Francesco Ciabuschi, Simone Callegari, and Olof Lindahl. 2019. "Economic Incentives for the Development of New Antibiotics." Report commissioned by the Public Health Agency of Sweden.

Baraldi, Enrico, Francesco Ciabuschi, Jens Eklinder, Carl Kronlid, Ross Leach, Olof Lindahl, Ka Lum, Kevin Outterson, Jens Plahte, Kellie Ryan, John-Arne Røttingen, Susan Wood, and Christine Årdal. 2016. "Solutions from Other Industries Applicable to the Antibiotic Field." DRIVE-AB 1–36.

Baraldi, Enrico, Charles Clift, Cornelia Körber, and Ursula Theuretzbacher. 2014. "DRIVE-AB Stakeholder Meeting: European Small and Medium Enterprises Focused on Antibacterial Drug Research and Development." http://drive-ab.eu/wp-content/uploads/2015/02/DRIVE-AB-SME-stakeholder-meeting-report.pdf.

BEAM Alliance. 2019. *Supporting Financial Investments on R&D to De-risk Antimicrobial Development.* Paris.

Behdinan, Asha, Steven J. Hoffman, and Mark Pearcey. 2015. "Some Global Policies for Antibiotic Resistance Depend on Legally Binding and Enforceable Commitments." *Journal of Law, Medicine & Ethics* 43(Suppl 3):68–73.

Berman, Daniel, Sujith J. Chandy, Oliver Cansdell, Krishnee Moodley, Balaji Veeraraghavan, and Sabiha Y. Essack. 2022. "Global Access to Existing and Future Antimicrobials and Diagnostics: Antimicrobial Subscription and Pooled Procurement." *Lancet Global Health* 10(2):e293–97.

Bhavnani, Sujata M., Kevin M. Krause, and Paul G. Ambrose. 2020. "A Broken Antibiotic Market: Review of Strategies to Incentivize Drug Development." *Open Forum Infectious Diseases* 7(7):ofaa083.

Claeys, Kimberly C., Teri L. Hopkins, Ana D. Vega, and Emily L. Heil. 2018. "Fluoroquinolone Restriction as an Effective Antimicrobial Stewardship Intervention." *Current Infectious Disease Reports* 20(5):7.

Daniel, Gregory W., Mark B. McClellan, Gabriela Lavezzari, Monika Schneider, and Juan Qian. 2016. *Tracking the Progress of Economic Incentives for Antimicrobial Drug Development in the U.S. and Across the Globe*. Washington, DC: Duke-Margolis Center for Health Policy.

Elder, David P., Martin Kuentz, and René Holm. 2016. "Antibiotic Resistance: The Need for a Global Strategy." *Journal of Pharmaceutical Sciences* 105(8):2278–87.

EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections. 2021. Policy Brief: Incentivizing Antibiotic Access and Innovation.

Farha, Maya A., and Eric D. Brown. 2019. "Drug Repurposing for Antimicrobial Discovery." *Nature Microbiology* 4(4):565–77.

Ferraro, Jimena S., Adrian Towse, and Jorge Mestre-Ferrandiz. 2017. "Incentives for New Drugs to Tackle Anti-Microbial Resistance." Office of Health Economics Research. OHE Briefing: 1–43.

Gallini, Nancy. 2017. "Do Patents Work? Thickets, Trolls and Antibiotic Resistance." *Canadian Journal of Economics* 50(4):893–926.

GARDP. 2019. *Delivering on the Sustainable Access of Antibiotics: Moving from Principles to Practice Workshop Report*.

Gauld, Natalie J., Irene S. L. Zeng, Rosemary B. Ikram, Mark G. Thomas, and Stephen A. Buetow. 2017. "Antibiotic Treatment of Women with Uncomplicated Cystitis before and after Allowing Pharmacist-Supply of Trimethoprim." *International Journal of Clinical Pharmacy* 39(1):165–72.

Hobæk, Bård, and Anne Kveim Lie. 2019. "Less Is More: Norwegian Drug Regulation, Antibiotic Policy, and the 'Need Clause.'" *The Milbank Quarterly* 97(3):762–95.

Hoffman, Steven J., Grazia M. Caleo, Nils Daulaire, Stefan Elbe, Precious Matsoso, Elias Mossialos, Zain Rizvi, and John-Arne Røttingen. 2015. "Strategies for Achieving Global Collective Action on Antimicrobial Resistance." *Bulletin of the World Health Organization* 93(12):867–76.

Houchens, Christopher, and Joe Larsen. 2017. *The Role of the Biomedical Advanced Research and Development Authority (BARDA) in Promoting Innovation in Antibacterial Product Development*. AMR Control.

IACG (UN Interagency Coordination Group on Antimicrobial Resistance). 2019. "Draft Recommendations of the Ad Hoc Interagency Coordination Group on Antimicrobial Resistance." Geneva: World Health Organization.

IFPMA. 2016. "Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance." https://www.ifpma.org/wp-content/uploads/2016/01/Industry_Declaration_on_Combating_Antimicrobial_Resistance_Jan2017-1.pdf.

IFPMA. 2021. "Global Principles on Incentivizing Antibiotic R&D." https://www.ifpma.org/wp-content/uploads/2021/02/IFPMA-Global-Principles-on-Incentivizing-Antibiotic-RD.pdf.

Jaczynska, Ella, Kevin Outterson, and Jorge Mestre-Ferrandiz. 2015. "Business Model Options for Antibiotics: Learning from Other Industries." Chatham House, The Royal Institute of International Affairs, and the Big Innovation Centre.

Kållberg, Cecilia, Christine Årdal, Hege Salvesen Blix, Eili Klein, Elena M. Martinez, Morten Lindbæk, Kevin Outterson, John-Arne Røttingen, and Ramanan Laxminarayan. 2018. "Introduction and Geographic Availability of New Antibiotics Approved between 1999 and 2014," edited by J. Lexchin. *PLOS ONE* 13(10):e0205166.

Kieny, Marie-Paule. 2015. "Creating an Intergovernmental Consortium for New Antibiotics: A New Development Model." AMR Control.

Malan, Lucille, Quinten Labuschagne, Erich Brechtelsbauer, Debra A. Goff, and Natalie Schellack. 2018. "Sustainable Access to Antimicrobials; A Missing Component to Antimicrobial Stewardship—A Tale of Two Countries." *Frontiers in Public Health* 6:324.

Martens, Evan, and Arnold L. Demain. 2017. "The Antibiotic Resistance Crisis, with a Focus on the United States." *Journal of Antibiotics* 70(5):520–26.

McKellar, Michael R., and A. Mark Fendrick. 2014. "Innovation of Novel Antibiotics: An Economic Perspective." *Clinical Infectious Diseases* 59(suppl_3):S104–7.

Médecins Sans Frontières (MSF). 2018. "Open Statement on the Launch of the Global AMR R&D Collaboration Hub." https://www.msf-me.org/media-centre/news-and-stories/msf-open-statement-launch-global-amr-rd-collaboration-hub.

Médecins Sans Frontières (MSF). 2018. "Response by MSF Access Campaign to the Consultation on IACG Discussion Paper, 'Antimicrobial Resistance: Invest in Innovation and Research, and Boost R&D and Access.'" https://msfaccess.org/sites/default/files/2018-11/AMR_TechBrief_IACGInnovationRnDAccess_ENG_2018.pdf.

Moradi, Ghobad, Mohammad Mehdi Gouya, Babak Eshrati, Minoo Mohraz, Bakhtiar Piroozi, Leila Molaei, and Bakhtiar Piroozi. 2018. "National Action Plan of the Islamic Republic of Iran for Combating Antimicrobial Resistance during 2016–2021." *Medical Journal of the Islamic Republic of Iran* 32:65.

Morel, Chantal M., Olof Lindahl, Stephan Harbarth, Marlieke E. A. de Kraker, Suzanne Edwards, and Aidan Hollis. 2020. "Industry Incentives and Antibiotic Resistance: An Introduction to the Antibiotic Susceptibility Bonus." *Journal of Antibiotics* 73(7):421–28.

Nagel, Tobi. 2018. "Delivering Phage Products to Combat Antibiotic Resistance in Developing Countries: Lessons Learned from the HIV/AIDS Epidemic in Africa." *Viruses* 10(7):345.

Nair, M., M. P. Zeegers, G. M. Varghese, and S. Burza. 2021. "India's National Action Plan on Antimicrobial Resistance: A Critical Perspective." *Journal of Global Antimicrobial Resistance* 27:236–38.

Outterson, Kevin, Unni Gopinathan, Charles Clift, Anthony D. So, Chantal M. Morel, and John-Arne Røttingen. 2016. "Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality." *PLOS Medicine* 13(6):1–7.

Outterson, Kevin, John H. Powers, Gregory W. Daniel, and Mark B. McClellan. 2015. "Repairing the Broken Market for Antibiotic Innovation." *Health Affairs* 34(2):277–85.

Piddock, Laura J. V, Jean-Pierre Paccaud, Seamus O'Brien, Michelle Childs, Rohit Malpani, and Manica Balasegaram. 2021. "A Nonprofit Drug Development Model Is Part of the Antimicrobial Resistance (AMR) Solution." *Clinical Infectious Diseases* 74(10):1866–71.

Plahte, Jens, and John-Arne Røttingen. 2015. "Antibiotic Innovation—Some Lessons from the WHO Processes on Public Health, Innovation and Intellectual Property." AMR Control.

Rello, Jordi, Eleonora Bunsow, and Antonio Perez. 2016. "What If There Were No New Antibiotics? A Look at Alternatives." *Expert Review of Clinical Pharmacology* 9(12):1547–55.

Renwick, Matthew J., David M. Brogan, and Elias Mossialos. 2016. "A Systematic Review and Critical Assessment of Incentive Strategies for Discovery and Development of Novel Antibiotics." *Journal of Antibiotics* 69(2):73–88.

Renwick, Matthew, and Elias Mossialos. 2018. "What Are the Economic Barriers of Antibiotic R&D and How Can We Overcome Them?" *Expert Opinion on Drug Discovery* 13(10):889–92.

Renwick, Matthew J., Victoria Simpkin, and Elias Mossialos. 2016. "Targeting Innovation in Antibiotic Drug Discovery and Development: The Need for a One Health—One Europe—One World Framework." Copenhagen (Denmark): European Observatory on Health Systems and Policies.

Review on Antimicrobial Resistance. 2015. *Securing New Drugs for Future Generations: The Pipeline of Antibiotics*. London.

Review on Antimicrobial Resistance. 2015. *Survey of Actors Involved in the Development of Antimicrobials: High Level Results*. London.

Review on Antimicrobial Resistance. 2016. Press Notice: *Global Pharmaceutical Industry Calls on Governments to Work with Them to Beat the Rising Threat of Drug Resistance.* London.

Roope, Laurence S. J., Richard D. Smith, Koen B. Pouwels, James Buchanan, Lucy Abel, Peter Eibich, Christopher C. Butler, Pui San Tan, A. Sarah Walker, Julie V Robotham, and Sarah

Wordsworth. 2019. "The Challenge of Antimicrobial Resistance: What Economics Can Contribute." *Science* 364(6435).

Sciarretta, Kimberly, John-Arne Røttingen, Aleksandra Opalska, Arjon J. Van Hengel, and Joseph Larsen. 2016. "Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations from the Transatlantic Task Force on Antimicrobial Resistance: Table 1." *Clinical Infectious Diseases* 63(11):1470–74.

Schäberle, Till F., and Ingrid M. Hack. 2014. "Overcoming the Current Deadlock in Antibiotic Research." *Trends in Microbiology* 22(4):165–67.

Schneider, Monika, Nicholas R. Harrison, Gregory W. Daniel, and Mark B. McClellan. 2020. *Delinking US Antibiotic Payments through a Subscription Model in Medicare.* Washington, DC: Duke-Margolis Center for Health Policy.

Schneider, Monika, Nicholas R. Harrison, and Mark B. McClellan. 2020. "Population-Based Payments May Help Ensure Access to Life-Saving Antibiotics for Medicare Beneficiaries." Health Affairs Blog.

Shionogi & Co LTD. 2020. "Antimicrobial Resistance (AMR) Position Paper." https://www.shionogi. com/content/dam/shionogi/global/sustainability/amr/pdf/E_Shionogi_AMR_Position_ Paper.pdf.

Singer, Andrew C., Claas Kirchhelle, and Adam P. Roberts. 2020. "(Inter)Nationalising the Antibiotic Research and Development Pipeline." *Lancet Infectious Diseases* 20(2):e54–62.

Spellberg, Brad, John Bartlett, Rich Wunderink, and David N. Gilbert. 2015. "Novel Approaches Are Needed to Develop Tomorrow's Antibacterial Therapies." *American Journal of Respiratory and Critical Care Medicine* 191(2):135–40.

Stern, Selma, Simon Chorzelski, Laura Franken, Simon Völler, Heinrich Rentmeister, and Benjamin Grosch. 2017. "Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development." Berlin: The Boston Consulting Group (BCG).

Sumpradit, Nithima, Suriya Wongkongkathep, Kumthorn Malathum, Noppavan Janejai, Wantana Paveenkittiporn, Thitipong Yingyong, Teerasak Chuxnum, Amornrat Vijitleela, Phairam Boonyarit, Chutima Akaleephan, Weerawat Manosuthi, Varaporn Thienthong, Julaporn Srinha, Supaporn Wongsrichai, Thitiporn Laoprasert, Pornpimon Athipunyakom, Nathaya Kriengchaiyaprug, Kingdao Intarukdach, Sukanya Numsawad, Nuntiya Somjetanakul, Sirima Punnin, and Niyada Kiatying-Angsulee. 2021. "Thailand's National Strategic Plan on Antimicrobial Resistance: Progress and Challenges." *Bulletin of the World Health Organization* 99(09):661–73.

Swaminathan, Soumya, and Kamini Walia. 2016. "Strengthening Research and Innovation to Address the Challenge of Antimicrobial Resistance." AMR Control.

Tacconelli, Evelina, Andreas Peschel, and Ingo B. Autenrieth. 2014. "Translational Research Strategy: An Essential Approach to Fight the Spread of Antimicrobial Resistance." *Journal of Antimicrobial Chemotherapy* 69(11):2889–91.

Task Force for Combating Antibiotic-Resistant Bacteria. 2015. "National Action Plan for Combating Antibiotic-Resistant Bacteria." Washington, DC: The White House. https://obamawhitehouse. archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_ bacteria.pdf.

United Nations General Assembly. 2016. *Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance.*

Wang, Ying, Yulei Zhu, Xiaoliang Liu, Xinglu Xu, Wenqing Fang, and Xin Li. 2020. "The Effects of County Public Hospital Reform on the Consumption and Costs of Antibiotics: Evidence from a Quasinatural Experiment in Jiangsu, China," edited by S. Yokota. *BioMed Research International* 2020:1–14.

Wattal, Chand, and Neeraj Goel. 2014. "Tackling Antibiotic Resistance in India." *Expert Review of Anti-infective Therapy* 12(12):1427–1440.

Wellcome Trust. 2018. "House of Commons Health & Social Care Select Committee: Inquiry on Antimicrobial Resistance (AMR). Response by the Wellcome Trust." https://wellcome.org/sites/ default/files/antimicrobial-resistance-inquiry.pdf.

Wellcome Trust. 2020. "The Global Response to AMR: Momentum, Success, and Critical Gaps." Report. https://wellcome.org/reports/global-response-amr-momentum-success-and-critical-gaps.

Wellcome Trust. 2020. "The Growing Crisis in Antibiotic R&D: Opportunities for G20 Member Action to Support Sustainable Innovation." Discussion paper. https://wellcome.org/sites/default/files/ the-growing-crisis-for-antibiotic-r-and-d.pdf.

World Economic Forum and Wellcome Trust. 2018. *Antimicrobial Resistance: Tackling the Gap in R&D Resources with Pull Incentives.* Geneva.

World Health Organization. 2015. *Global Action Plan on Antimicrobial Resistance.* Geneva.

## Other Sources

Armstrong, Gregory L., Laura A. Conn, and Robert W. Pinner. 1999. "Trends in Infectious Disease Mortality in the United States During the 20th Century." *JAMA* 281(1):61–66.

Baraldi, Enrico, Francesco Ciabuschi, Ross Leach, Chantal Morel, and Alexandra Waluszewski. 2016. "Exploring the Obstacles to Implementing Economic Mechanisms to Stimulate Antibiotic Research and Development: A Multi-Actor and System-Level Analysis." *American Journal of Law & Medicine* 42(2–3):451–486.

Burki, Talha Khan. 2017. "Tuberculosis missing from WHO bacteria list. *Lancet Respiratory Medicine* 5(4):252.

CARB-X. "Stewardship & Access Plan (SAP) Development Guide." 2021. www.carb-x.org/about/stewardship-and-access.

FDA. 2020. "Limited Population Pathway for Antibacterial and Antifungal Drugs—the LPAD Pathway." https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway.

GARDP. 2019. "GARDP and Entasis Therapeutics Initiate Global Phase 3 Trial of Zoliflodacin, a First-in-Class Oral Antibiotic for the Treatment of Gonorrhoea." Press release. https://gardp.org/news-resources/gardp-and-entasis-therapeutics-initiate-global-phase-3-trial-of-zoliflodacin-a-first-in-class-oral-antibiotic-for-the-treatment-of-gonorrhoea/.

GARDP. 2021. "GARDP, CHAI and Shionogi Announce MOU to Increase Access to Antibiotic to Treat Antimicrobial Resistant Infections in Low- And Middle-Income Countries." Press release. https://gardp.org/news-resources/gardp-chai-shionogi-announce-mou/.

Global AMR R&D Hub. n.d. Accessed May 3, 2022. https://globalamrhub.org.

Hall, William, Anthony McDonnell, and Jim O'Neill. 2018. *Super-bugs: An Arms Race against Bacteria*. Cambridge, MA: Harvard University Press.

Harring, Niklas, and Eva M. Krockow. 2021. "The Social Dilemmas of Climate Change and Antibiotic Resistance: An Analytic Comparison and Discussion of Policy Implications." *Humanities and Social Sciences Communications* 8(125).

Hoffman, Steven J., and Kevin Outterson. 2015. "What Will it Take to Address the Global Threat of Antibiotic Resistance?" *Journal of Law, Medicine & Ethics* 43(2):363–8.

Hollis, Aidan, and Peter Maybarduk. 2015. "Antibiotic Resistance is a Tragedy of the Commons that Necessitates Global Cooperation." *Journal of Law, Medicine & Ethics* 43(S3):33–7.

Larsen, Joe. 2016. "Economic Incentives for Antibiotic Development: An Overview." US Department of Health & Human Services. https://www.hhs.gov/sites/default/files/joseph-larsen-paccarb-remediated.pdf.

McCaughan, Michael. 2020. "Medicare's Antibiotic Boost: Six Qualify for Add-On Payment." Informa Pharma Intelligence. https://pink.pharmaintelligence.informa.com/PS143180/Medicares-Antibiotic-Boost-Six-Qualify-For-Add-On-Payment.

McDonnell, Anthony, and Klempere, Katherine. 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). https://www.cgdev.org/blog/drug-resistant-infections-are-one-worlds-biggest-killers-especially-children-poorer-countries.

McDonnell, Anthony, John H. Rex, Herman Goossens, Marc Bonten, Vance G. Fowler Jr, and Aaron Dane. 2016. "Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks." *Clinical Infectious Diseases* 63(suppl_2):S57–59.

Murray, Christopher J. L., Kevin Shunji Ikuta, Fablina Sharara, Lucien Swetschinski, Gisela Robles Aguilar, Authia Gray, Chieh Han, Catherine Bisignano, Puja Rao, Eve Wool, Sarah C. Johnson, Annie J. Browne, Michael Give Chipeta, Frederick Fell, Sean Hackett, Georgina Haines-Woodhouse, Bahar H. Kashef Hamadani, Emmanuelle A. P. Kumaran, Barney McManigal, Ramesh Agarwal, Samuel Akech, Samuel Albertson, John Amuasi, Jason Andrews, Aleskandr Aravkin, Elizabeth Ashley, Freddie Bailey, Stephen Baker, Buddha Basnyat, Adrie Bekker, Rose Bender, Adhisivam Bethou, Julia Bielicki, Suppawat Boonkasidecha, James Bukosia, Cristina Carvalheiro, Carlos Castañeda-Orjuela, Vilada Chansamouth, Suman Chaurasia, Sara Chiurchiù, Fazle Chowdhury, Aislinn J. Cook, Ben Cooper, Tim R. Cressey, Elia Criollo-Mora, Matthew Cunningham, Saffiatou Darboe, Nicholas P. J. Day, Maia De Luca, Klara Dokova, Angela Dramowski, Susanna J. Dunachie, Tim Eckmanns, Daniel Eibach, Amir Emami, Nicholas Feasey, Natasha Fisher-Pearson, Karen Forrest, Denise Garrett, Petra Gastmeier, Ababi Zergaw Giref, Rachel Claire Greer, Vikas Gupta, Sebastian Haller, Andrea Haselbeck, Simon I. Hay, Marianne Holm, Susan Hopkins, Kenneth C. Iregbu, Jan Jacobs, Daniel Jarovsky, Fatemeh Javanmardi, Meera Khorana, Niranjan Kissoon, Elsa Kobeissi, Tomislav Kostyanev, Fiorella Krapp, Ralf Krumkamp, Ajay Kumar, Hmwe Hmwe Kyu, Cherry Lim, Direk Limmathurotsakul, Michael James Loftus, Miles Lunn, Jianing Ma, Neema Mturi, Tatiana Munera-Huertas, Patrick Musicha, Marisa Marcia Mussi-Pinhata, Tomoka Nakamura, Ruchi Nanavati, Sushma Nangia, Paul Newton, Chanpheaktra Ngoun, Amanda Novotney, Davis Nwakanma, Christina W. Obiero, Antonio Olivas-Martinez, Piero Olliaro, Ednah Ooko, Edgar Ortiz-Brizuela, Anton Yariv Peleg, Carlo Perrone, Nishad Plakkal, Alfredo Ponce-de-Leon, Mathieu Raad, Tanusha Ramdin, Amy Riddell, Tamalee Roberts, Julie Victoria Robotham, Anna Roca, Kristina E. Rudd, Neal Russell, Jesse Schnall, John Anthony Gerard Scott, Madhusudhan Shivamallappa, Jose Sifuentes-Osornio, Nicolas Steenkeste, Andrew James Stewardson, Temenuga Stoeva, Nidanuch Tasak, Areerat Thaiprakong, Guy Thwaites, Claudia Turner, Paul Turner, H. Rogier van Doorn, Sithembiso Velaphi, Avina Vongpradith, Huong Vu, Timothy Walsh, Seymour Waner, Tri Wangrangsimakul, Teresa Wozniak, Peng Zheng, Benn Sartorius, Alan D. Lopez, Andy Stergachis, Catrin Moore, Christiane Dolecek, and Mohsen Naghavi. 2022. "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis." *Lancet* 399(10325):629–55.

Outterson, Kevin, and John H. Rex. 2020. "Evaluating For-Profit Public Benefit Corporations as an Additional Structure for Antibiotic Development and Commercialization." *Translational Research* 220:182–190.

Public Health Agency of Sweden. 2020. "Questions and Answers on Procurement in Pilot Study for New Reimbursement Model." https://www.folkhalsomyndigheten.se/contentassets/c09fd6d5d42243e097be216767686c08/qa-new-reimbursement-model.pdf.

Røttingen, John-Arne, Sadie Regmi, Mari Eide, Alison J. Young, Roderik F. Viergever, Christine Årdal, Javier Guzman, Danny Edwards, Stephen A. Matlin, and Robert F. Terry. 2013. "Mapping of Available Health Research and Development Data: What's There, What's Missing, and What Role Is There for a Global Observatory?" *Lancet* 382(9900):1286–1307.

Schneider, Monika. 2020. "New Rules Expand Application of the NTAP Program for Innovative Antibiotics." *Contagion* 5(2). https://www.contagionlive.com/view/new-rules-expand-application-of-the-ntap-program-for-innovative-antibiotics.

Statista. n.d. *Total Global Spending on Pharmaceutical Research and Development from 2012 to 2026.* Accessed May 3, 2022. https://www.statista.com/statistics/309466/global-r-and-d-expenditure-for-pharmaceuticals/.

US National Library of Medicine. n.d. ClinicalTrials.gov. Accessed May 2, 2022. https://clinicaltrials.gov.

World Health Organization (WHO). 2021. "2021 aWaRe Classification." Excel spreadsheet. https://apps.who.int/iris/bitstream/handle/10665/327957/WHO-EMP-IAU-2019.11-eng.xlsx?ua=1.

World Health Organization (WHO). n.d. "SECURE: Expanding Sustainable Access to Antibiotics." Accessed June 1, 2022. https://www.who.int/groups/secure-expanding-sustainable-access-to-antibiotics.

World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE). 2021. "Monitoring Global Progress on Antimicrobial Resistance: Tripartite AMR Country Self-Assessment Survey (TrACSS) 2019–2020. Global analysis report." https://www.who.int/publications/i/item/monitoring-global-progress-on-antimicrobial-resistance-tripartite-amr-country-self-assessment-survey-(tracss)-2019-2020.

# Appendix 1. Search protocol

For years 2014+: (1) AND (2) AND (3) AND (4) AND (5)

For all years: (1) AND (2) AND (3) AND (4) AND (6)

*Where (1)–(6) are as follows:*

(1)  Antibiot*[Title] OR antimicrobial[Title] OR antibacterial[Title] OR anti-infective [Title] OR antiviral[Title] OR antifungal[Title]
*N.B. Where Medical Subject Headings (MeSH) terms can be used, "anti-infective" covers all these.*

(2)  Resistan*[Title/Abstract]
*Our review was designed to focus on purchasing systems for novel antimicrobials—i.e., ones that have been developed in response to rising resistance rates. Thus, this term was included in our search strategy.*

(3)  Procurement[Title/Abstract] OR""R&""[Title/Abstract] OR Research[Title/Abstract] OR Development[Title/Abstract] OR Funding[Title/Abstract] OR Innovation[Title/Abstract] OR Pipeline[Title/Abstract] OR "Market Entry"[Title/Abstract]
*This landscape analysis was designed to capture literature discussing changes or improvements to the antimicrobial market via changes to the procurement system. Thus, "procurement," or related terms, had to be included in the titles or abstracts of articles. While we are interested in the stewardship aspects of interventions, the scope of our review included only stewardship interventions that acted via changes to antimicrobial purchasing. Thus, we did not feel it necessary to include "stewardship" as a term on its own—this would have yielded many results that were out of scope.*

(4)  Incentive*[Title/Abstract] OR Policy[Title/Abstract] OR Policies[Title/Abstract] OR Strateg*[Title/Abstract] OR Program*[Title/Abstract] OR""Business model""[Title/Abstract] OR Mechanism*[Title/Abstract]
*The analysis was designed to review proposed changes to procurement systems, rather than simply describe the current situation. Thus, we included these terms to ensure that only literature actively suggesting new policies was included.*

(5)  Success*[Title/Abstract] OR Implementation[Title/Abstract] OR Uptake[Title/Abstract] OR Effect*[Title/Abstract] OR Efficacy[Title/Abstract]
*For many years, there have been discussions about potential interventions to antimicrobial procurement systems. However, there has been very little concrete movement. These terms were included to ensure we captured any interventions implemented in recent years.*

(6)   LMIC*[Title/Abstract] OR "Low-Income Countr*"[Title/Abstract] OR "Middle-Income Countr*"[Title/Abstract] OR Africa[Title/Abstract] OR Burundi[Title/Abstract] OR Somalia[Title/Abstract] OR Mozambique[Title/Abstract] OR Madagascar[Title/Abstract] OR Afghanistan[Title/Abstract] OR "Central African Republic"[Title/Abstract] OR "Sierra Leone"[Title/Abstract] OR Congo[Title/Abstract] OR Niger[Title/Abstract] OR Liberia[Title/Abstract] OR Malawi[Title/Abstract] OR Eritrea[Title/Abstract] OR Chad[Title/Abstract] OR Sudan[Title/Abstract] OR Gambia[Title/Abstract] OR Guinea-Bissau[Title/Abstract] OR "Burkina Faso"[Title/Abstract] OR Rwanda[Title/Abstract] OR Uganda[Title/Abstract] OR Mali[Title/Abstract] OR Ethiopia[Title/Abstract] OR Yemen[Title/Abstract] OR Togo[Title/Abstract] OR Guinea[Title/Abstract] OR Tajikistan[Title/Abstract] OR Tanzania[Title/Abstract] OR "South Sudan"[Title/Abstract] OR Lesotho[Title/Abstract] OR Zimbabwe[Title/Abstract] OR Kyrgyz*[Title/Abstract] OR Zambia[Title/Abstract] OR Syria*[Title/Abstract] OR Nepal[Title/Abstract] OR Pakistan[Title/Abstract] OR Benin[Title/Abstract] OR Haiti[Title/Abstract] OR Myanmar[Title/Abstract] OR Comoros[Title/Abstract] OR Senegal[Title/Abstract] OR Cambodia[Title/Abstract] OR Cameroon[Title/Abstract] OR Mauritania[Title/Abstract] OR Uzbekistan[Title/Abstract] OR Kenya[Title/Abstract] OR Nicaragua[Title/Abstract] OR India[Title/Abstract] OR Timor-Leste[Title/Abstract] OR "East Timor"[Title/Abstract] OR Nigeria[Title/Abstract] OR Bangladesh[Title/Abstract] OR "Sao Tome and Principe"[Title/Abstract] OR Angola[Title/Abstract] OR Honduras[Title/Abstract] OR "Cote d'Ivoire"[Title/Abstract] OR "Ivory Coast"[Title/Abstract] OR "Solomon Islands"[Title/Abstract] OR Ghana[Title/Abstract] OR Lao*[Title/Abstract] OR Vietnam[Title/Abstract] OR "Papua New Guinea"[Title/Abstract] OR Bhutan[Title/Abstract] OR Iran[Title/Abstract] OR Kiribati[Title/Abstract] OR Morocco[Title/Abstract] OR Egypt[Title/Abstract] OR Cabo Verde[Title/Abstract] OR Bolivia[Title/Abstract] OR Vanuatu[Title/Abstract] OR Tunisia[Title/Abstract] OR Djibouti[Title/Abstract] OR Eswatini[Title/Abstract] OR Philippines[Title/Abstract] OR Ukraine[Title/Abstract] OR Algeria[Title/Abstract] OR El Salvador[Title/Abstract] OR "West Bank"[Title/Abstract] OR Gaza[Title/Abstract] OR "Sri Lanka"[Title/Abstract] OR Mongolia[Title/Abstract] OR Indonesia[Title/Abstract] OR Micronesia[Title/Abstract] OR Samoa[Title/Abstract] OR Belize[Title/Abstract] OR Armenia[Title/Abstract] OR Georgia[Title/Abstract] OR Jordan[Title/Abstract] OR Azerbaijan[Title/Abstract] OR Kosovo[Title/Abstract] OR Guatemala[Title/Abstract] OR Namibia[Title/Abstract] OR Moldova[Title/Abstract] OR Suriname[Title/Abstract] OR Jamaica[Title/Abstract] OR Iraq[Title/Abstract] OR Fiji[Title/Abstract] OR "Marshall Islands"[Title/Abstract] OR Libya[Title/Abstract] OR Paraguay[Title/Abstract] OR Tonga[Title/Abstract] OR Albania[Title/Abstract] OR Lebanon[Title/Abstract] OR Ecuador[Title/Abstract] OR "North Macedonia"[Title/Abstract] OR Colombia[Title/Abstract] OR "Equatorial Guinea"[Title/Abstract] OR Tuvalu[Title/Abstract] OR "South Africa"[Title/Abstract] OR Peru[Title/Abstract] OR "Bosnia and Herzegovina"[Title/Abstract] OR Belarus[Title/Abstract] OR Maldives[Title/Abstract] OR Botswana[Title/Abstract] OR Gabon[Title/Abstract] OR Thailand[Title/Abstract] OR Guyana[Title/Abstract] OR Turkmenistan[Title/Abstract] OR

"Dominican Republic"[Title/Abstract] OR Dominica[Title/Abstract] OR "St. Vincent"[Title/Abstract] OR Serbia[Title/Abstract] OR Brazil[Title/Abstract] OR Montenegro[Title/Abstract] OR Mexico[Title/Abstract] OR "St. Lucia"[Title/Abstract] OR Cuba[Title/Abstract] OR Kazakhstan[Title/Abstract] OR Turkey[Title/Abstract] OR Argentina[Title/Abstract] OR Grenada[Title/Abstract] OR Bulgaria[Title/Abstract] OR Mauritius[Title/Abstract] OR China[Title/Abstract] OR Malaysia[Title/Abstract] OR Russia*[Title/Abstract] OR Costa Rica[Title/Abstract] OR Seychelles[Title/Abstract] OR Panama[Title/Abstract]

*While there has been previous research on interventions to improve antimicrobial procurement systems, little work has specifically focused on feasibility of these in low- and middle-income countries. Therefore, we chose to specifically include these terms in our search. Terms were included to capture all countries classified as low-income, lower-middle-income or upper-middle-income, according to the World Bank Development Indicators.*

# Appendix 2. List of key organizations/initiatives searched for grey literature

- Access to Medicine Foundation
- BEAM (Biotech Companies from Europe Innovating in Anti-Microbial Resistance Research) Alliance
- British Society for Antimicrobial Chemotherapy
- CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator)
- Center for Disease Dynamics, Economics & Policy (CDDEP)
- Chatham House, the Royal Institute of International Affairs
- DRIVE-AB (Driving Reinvestment in Research and Development and Responsible Antibiotic Use)
- Duke-Margolis Center for Health Policy
- European & Developing Countries Clinical Trials Partnership (EDCTP)
- Global Antibiotic Research and Development Partnership (GARDP)
- Global Antimicrobial Resistance Innovation Fund (GAMRIF)
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- High-Level Meeting of the UN General Assembly on Antimicrobial Resistance
- Infectious Diseases Society of America (IDSA)
- Innovative Medicines Initiative (IMI)
- Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)
- Médecins Sans Frontières (Doctors Without Borders)
- National Health Service (England)
- Pew Charitable Trusts
- ReAct
- REPAIR (Replenishing and Enabling the Pipeline for Anti-Infective Resistance) Impact Fund

- Review on Antimicrobial Resistance (AMR Review)
- Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)
- UN Interagency Coordination Group on Antimicrobial Resistance
- UNICEF
- US Biomedical Advanced Research and Development Authority (BARDA)
- US President's Council of Advisors on Science and Technology (PCAST)
- US President's Malaria Initiative
- Wellcome Trust
- World Bank
- World Health Organization (WHO)

# Appendix 3. Questions used to guide interviews with stakeholders

- What are the two or three biggest policy problems contributing to antimicrobial resistance?
- This project is focused particularly on how antimicrobials are procured, particularly in low- and middle-income countries. Do we need a new system for purchasing antimicrobials?
  - *If yes:*
    - Why is this change necessary?
    - What would this system look like?
    - What drugs would this apply to (all antimicrobials, just new, only hospital, only outpatient)?
  - *If no:*
    - What are the strengths of the current purchasing system?
    - Are any small modifications needed?
- What are the barriers to building consensus and implementing policy change in your area of expertise (geographic, field, industry)?
- Is there any research that we can either undertake or fund that would help move the policy process along?
- Anyone else should we speak to?

# Appendix 4. A breakdown of papers by intervention discussed

| Intervention | Paper Count* | LMIC Authors* | 2013 | '14 | '15 | '16 | '17 | '18 | '19 | '20 | '21 | '22 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MER | 76 | 5 | 0 | 3 | 6 | 12 | 10 | 14 | 10 | 8 | 7 | 6 |
| Subscription | 39 | 2 | 0 | 0 | 1 | 5 | 0 | 1 | 6 | 9 | 12 | 5 |
| PASTEUR | 14 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 8 | 4 |
| NHS England Pilot | 28 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 7 | 12 | 4 |
| Sweden Pilot | 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 9 | 3 |
| PAVE | 6 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 0 | 1 | 1 |
| Extended exclusivity | 50 | 3 | 1 | 5 | 5 | 11 | 8 | 6 | 2 | 3 | 7 | 2 |
| TEV | 37 | 2 | 0 | 2 | 2 | 7 | 5 | 4 | 6 | 1 | 5 | 5 |
| GAIN | 36 | 3 | 1 | 3 | 2 | 9 | 8 | 4 | 1 | 3 | 3 | 2 |
| AMC | 16 | 1 | 0 | 1 | 1 | 4 | 2 | 4 | 0 | 0 | 2 | 2 |
| DCM | 6 | 1 | 0 | 0 | 1 | 1 | 1 | 2 | 0 | 0 | 1 | 0 |
| Pay or play | 14 | 1 | 0 | 0 | 0 | 3 | 2 | 3 | 5 | 0 | 1 | 0 |
| Tax incentives | 33 | 1 | 0 | 1 | 3 | 8 | 6 | 6 | 3 | 1 | 2 | 3 |
| Increased reimbursement | 37 | 0 | 0 | 4 | 3 | 3 | 4 | 4 | 3 | 7 | 6 | 3 |
| DRG carve-out | 27 | 0 | 0 | 1 | 2 | 1 | 2 | 3 | 4 | 7 | 5 | 2 |
| Grants | 87 | 7 | 0 | 5 | 10 | 15 | 11 | 10 | 11 | 8 | 12 | 5 |
| Restrictive prescribing | 22 | 8 | 0 | 1 | 3 | 4 | 2 | 1 | 4 | 2 | 3 | 2 |
| Financial incentives for prescribers/ disincentives to over-prescribe | 12 | 2 | 0 | 1 | 0 | 2 | 0 | 1 | 5 | 0 | 2 | 1 |
| Trials/approvals reform | 68 | 6 | 1 | 5 | 6 | 10 | 7 | 8 | 11 | 6 | 10 | 4 |
| 21st Century Cures Act | 12 | 0 | 0 | 0 | 1 | 3 | 3 | 2 | 0 | 1 | 1 | 1 |
| Long-term supply continuity | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 |

*Most papers in the literature discuss more than one intervention. The sum of paper count is 644, 4.6 times the number of papers included in this review.