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An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment

ADRIAN TOWSE · RACHEL SILVERMAN BONNIFIELD

Abstract

Anti-microbial drugs form the backbone of modern medicine. Yet their lifespan is naturally limited; over time, use of these drugs selects for mutations that survive exposure those same drugs, driving "anti-microbial resistance", or AMR. Already, drug-resistant infections kill an estimated 35,000 Americans and 1.27 million global citizens every year. In the absence of sufficient research and development (R&D) investment for new antimicrobials, deaths from drug-resistant infections could increase dramatically in the coming decade. However, the R&D pipeline for new antimicrobials remains sparse, constrained by an array of market failures that prevent private companies from capturing a sufficient private return on investment (ROI) despite the very high social value of new antimicrobials. Widespread recognition of these market failures among experts and policymakers has driven a search for creative solutions, and generated enthusiasm for the use of pull mechanisms which could help incentivize antibiotic development. One particularly promising pull approach—so-called "subscription models"—would offer guaranteed annual payments to successful antibiotic developers *delinked* from sales volumes. A subscription approach is included in the pending PASTEUR Act, which is legislation introduced by lawmakers in the US House of Representatives and Senate and endorsed in President Biden's 2023 budget request.

In this paper, we consider the expected return on investment for such a program—that is, an ambitious new program to incentivize antibiotic development via a US government subscription-based pull mechanism (though not necessarily the PASTEUR Act, per se). We construct an illustrative subscription program from first principles, with parameters drawn (where possible) from the literature and some simplifying and deliberately conservative assumptions about program design and remuneration. We model the 10- and 30-year costs and benefits of such an initiative, both from the US domestic perspective and from a global welfare perspective. We find that the program is likely to generate a very high social ROI in both the short and long-term. From the US domestic perspective—considering both the value of averted death/disease and associated hospital costs—ROI is calculated at 6:1 over a 10-year time horizon and 28:1 over a 30-year time horizon. From the global perspective—exclusively considering the health value of DALYs (Disability Adjusted Life Years) averted—ROI grows to 27:1 over a 10-year time horizon and 125:1 over the full 30-year program duration. Sensitivity analysis suggests that the overall high returns are robust under a wide variety of alternative assumptions and scenarios. Based on these high social returns, we encourage the US Congress to urgently finance and authorize a subscription program for new antimicrobials, with particularly consideration for the PASTEUR Act.

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Adrian Towse
Office of Health Economics

Rachel Silverman Bonnifield
Center for Global Development

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CENTER FOR GLOBAL DEVELOPMENT
2055 L Street, NW Fifth Floor
Washington, DC 20036

1 Abbey Gardens
Great College Street
London
SW1P 3SE

www.cgdev.org

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1. Introduction: Anti-Microbial Resistance (AMR): A current challenge and a near-future crisis

1.1 The historical context

Anti-microbial drugs—treating viral, bacterial, fungal, and parasitic infections—form the backbone of modern medicine. The discovery and global distribution of these drugs[1], alongside global introduction of effective childhood vaccinations, has helped dramatically decrease the global burden of infectious disease. In the US, the top three causes of death in 1900 were pneumonia, TB, and diarrhoea/enteritis. By 1999 only pneumonia/ influenza (a virus) remained in the top 10, at number six, far behind heart disease and cancer. In addition, the widespread availability and high efficacy of antibiotics facilitate surgeries, chemotherapy, organ transplants, and other treatments for non-communicable diseases—all of which would be far riskier, and perhaps impossible, if not for effective drugs against the pathogens which may be introduced in the process or for which an immune system weakened by the intervention has a limited ability to fight.

Yet the lifespan of these drugs is naturally limited by evolutionary processes. Exposure to an anti-microbial—either through clinical use or presence in the environment—creates selective pressure; microbes will randomly mutate over time, and drug-resistant variants will be more likely to survive exposure to an anti-microbial drug. This phenomenon is generally referred to as "anti-microbial resistance", or AMR. Resistance risk is increased by overuse and inappropriate use of antimicrobials, including monotherapies, premature treatment discontinuation, and use to promote growth in livestock, as well as the inadvertent release into the ecosystem that can accompany these uses. Humans are engaged in a race against this resistance—we need to ensure that novel antimicrobials are available to replace old therapies as their efficacy wanes. To do so, we need to slow the emergence of resistance while also maintaining a robust development pipeline for new antimicrobial drugs.

Already, drug resistance is a major cause of disease and death, both in the United States (US) and around the world. The US CDC (CDC, 2019a) estimates that AMR from antibiotic resistance bacterial and fungal infections causes 35,000 deaths per year in the US; a recent global estimate (the "GRAM study,"[2] formally referenced as Antimicrobial Resistance Collaborators, [ARC] 2022) calculated a global death toll of 1.27 million for 2019 for antibiotic resistant bacterial infections.[3] Resistance is seen to develop for all classes of antimicrobial agent; this paper focuses on antibacterial resistance and excludes resistance to agents for viral, fungal, and parasitic infections.

1 Sulphonamides were introduced in 1932. Penicillin was discovered in 1928, initially developed for medical use in the 1940s, when it was produced in substantial quantities to treat sick and wounded soldiers. Streptomycin, discovered in 1943, an aminoglycoside, was the first antibiotic effective against tuberculosis (TB) in humans. Other important classes of antibiotics include macrolides, first introduced in 1952, cephalosporins in 1962, and carbapenems in 1975. No new classes have been discovered since the 1980s. (CDC, 1999; Davies, 2013.)

2 The acronym GRAM is explained on the website of the Institute of Health Metrics and Evaluation here: Our approach | Institute for Health Metrics and Evaluation (healthdata.org)

3 There is some controversy about estimation techniques, discussed in further detail in Appendix A.

But these current figures represent the tip of the iceberg vis-à-vis the global challenge. Mortality and morbidity rates, naturally, will rise as resistance increases, with the knock-on consequences for health system costs and economic activity. There are three main pathways of impact. First, common infections will become less easily treated, causing more people to fall ill and die. Second, first-line antimicrobials are generally well-tolerated and easily administered; current second-and third-line antibiotics often come with more serious side-effects, and require intravenous administration or hospitalization. Finally, and perhaps most frightening, is the "nightmare scenario" in which modern medicine collapses because surgeries, chemotherapy, and other common interventions are no longer viable due to infection risk.

A critical issue is therefore the speed with which rates of growth of resistance will grow and their potential to lead to much higher death rates, health system and wider economic effects. The O'Neill Report (2016) reported that "a continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product." A 2017 World Bank Report predicted global GDP being 1.1%–3.8% lower by 2050, comparable to the 3.6% global loss of GDP during the 2008–9 financial crisis (World Bank, 2017).

It is helpful to unpack the overall burden of resistance to antibacterial drugs, as this umbrella term refers to a range of pathogens and pathogen-drug combinations. At present, a small number of pathogens and pathogen-drug combinations account for the bulk of mortality and morbidity arising from resistance to antibacterial drugs (see Appendix A). Though there will inevitably be some differences of priority between different parts of the world, a recent exercise (ARC, 2022) identified a target list of 20 pathogen-drug resistant combinations. At present, estimates suggest that six pathogens account for over 70% of global deaths attributable to resistance to antibacterial drugs (ARC, 2022).

1.2 The research and development (R&D) pipeline

Despite this large and growing burden, the R&D pipeline for new antimicrobials remains sparse.[4] Using internal data from the US Food and Drug Administration (FDA), alongside public data published on the FDA website, Dheman et al. (2020) offer "a longitudinal analysis of [US] investigational new drug applications (INDs) for new, systemic antibacterial drugs under active development between 1980 and 2019," summarized by Rex and Outterson (2021):

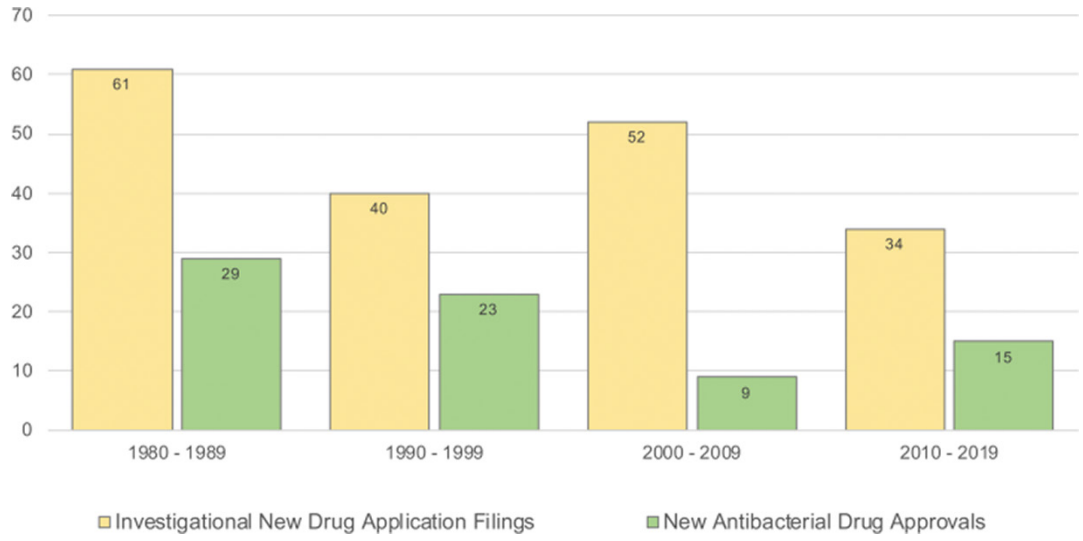
> "The key messages from Dheman et al. are all bad news for public health:
> (1) the number of new antibacterials in clinical development is (again) falling,

4 A useful survey of the state of product development pipelines is set out in a blog by Rex and Outterson (2021) (https://amr.solutions/2020/06/30/fda-analysis-of-40-years-of-antibacterial-development-dheman-et-al/) drawing on recent papers, (Darrow et al. 2020; Dheman et al. 2020; and Kinch et al. 2014). In addition, WHO conducts regular reviews of the pipeline—see Butler et al. (2022) for the most recent WHO analysis.

> (2) the risk of failure is rising, (3) the speed of clinical development is slowing, and (4) most large companies with the capability to market agents on a global scale have exited clinical development."

We reproduce below Figure 1 from Dheman et al. 2020. It shows that "antibacterial drug development activity rebounded substantially from 2002 to 2009, primarily led by involvement of small pharmaceutical companies", leading to more approvals in the following decade. However, this trend has now reversed; new antibacterial INDs during 2010–2019 fell to their lowest level since 1980. As of writing, it has been three years since the last approval of a new antibiotic by the FDA (Cefiderocol in November 2019).

FIGURE 1. Number of approved systemic antibacterial new molecular entities and investigational new drug filings: 1980–2019



There is also a disconnect between global AMR priorities, i.e., the new antibacterials likely to have most value, and the targets of drug development. Dheman et al. 2020 found that only "8 of the 25 drugs currently in development [in the US] have expected activity against at least 1 of [the WHO top 3] critical pathogens". As of June 2019, Pew Charitable Trusts reported that just 42 antibiotics were in clinical development globally, with about half (24) targeting bacteria on CDC or WHO priority lists (The Pew Charitable Trusts, 2019). Theuretzbacher et al. (2019) state that "the pipeline of antibiotics that target gram-negative bacteria is dominated by derivatives of existing classes of antibiotics" and "does not sufficiently address the problem of extensively drug-resistant gram-negative bacteria".[5] This is confirmed by the 2022 WHO pipeline study (Butler et al. 2022) which found 45 "traditional" antibacterial agents in development and 31 "non-traditional" agents. Of the total of 76, just over half (54%) targeted WHO priority pathogens, and only 4 of the 76 had new modes of action. The WHO

5 Specifically, the authors found that the pipeline does not sufficiently address the bacteria A. baumannii, P. aeruginosa, and Enterobacteriaceae, all of which are on the Priority Pathogens List (see Figure 1 in Appendix 2).

analysis also reported that since 2017, i.e., in the last 5 years, 12 new antibacterial drugs have been approved globally, but only one belongs to a new bacterial class, and only one is targeted at a Gram-negative priority pathogen.

1.3 The market failure for new antimicrobials

The large and growing burden of AMR, paired with the insufficient R&D pipeline for new antimicrobials, begs an obvious question: why are market mechanisms failing to address this challenge? At the most basic level, the market failure arises because private companies are unable to capture a sufficient private return on investment (ROI), despite the very high social value of new antimicrobials.

Underlying this disconnect are several distinct challenges:

- **Initial Sales Volumes Are Low:** Given the imperative to conserve novel antimicrobial efficacy, new antimicrobials should only be used for the small subset of patients where existing first-, second-, and third-line therapies have failed. This keeps initial sales volumes low (Outterson et al. 2022). Although sales volumes tend to rise over time for most pharmaceuticals, antimicrobial stewardship measures will tend to limit the rise in sales volumes.[6]
- **Most Social Value is Incurred After Patent Expiry:** Traditional private-sector business models invest in up-front R&D with the expectation of substantial revenue/profit during the patent exclusivity period, during which they can demand a price premium over marginal cost and demand is high. But for new antimicrobials, usage of the drug will increase over a long time horizon—with most social value likely realized only after this period has ended and generic competitors are able to enter the market (see for example the modelling in Towse et al., 2017). This means that the expected ROI for a private developer is relatively low relative to the long-term social value of the new antimicrobial.
- **Clinical Value is Difficult to Demonstrate:** To receive regulatory approval, novel antimicrobials are required to demonstrate evidence of clinical evidence of safety and efficacy. Unless there are no active agents for the infection under study (hopefully a very rare situation), the only ethical approach is to demonstrate non-inferiority to best available therapy in randomized controlled trials (RCTs) against infections that are expected to be drug susceptible. (For a discussion of the issues, see Rex et al. (2019).) In vitro microbiological data and pharmacokinetic/pharmacodynamic data are used to determine dosing for cure against resistant pathogens. Given we want new drugs available before we have a resistance crisis, it is preferable from a societal standpoint that it take a long time to recruit

6 WHO in 2017 introduced the Access, Watch, Reserve ("AWaRe") classification of antibiotics in its Essential Medicines List. Outterson et al. (2022) point out that the majority of new antibiotics launched over the last decade are designated as "Reserve" under WHO AWaRe, which is good for public health, but reinforces the challenges to getting revenue during the period of patent protection.

a sufficiently large cohort of highly drug-resistant patients into a clinical trial.[7] The evidence for the superiority of the new agents is thus indirect and relies heavily on non-clinical data but payers and their HTA bodies, however, are not used to accepting superior efficacy evidence from laboratory data (rather than from an RCT).

- **Traditional Reimbursement Approaches Undervalue New Antimicrobials:** Traditional reimbursement policy mechanisms, including Health Technology Assessment (HTA), focus on the benefit to the immediate patient, and on the cost to the health system. Yet much of the benefits from new antibiotics lie outside these dimensions and so are not taken account of in pricing and reimbursement decisions. These have been termed the STEDI principles (Spectrum, Transmission, Enablement, Diversity, and Insurance) by Outterson and Rex, (2020):[8]
    - Spectrum value, which emerges from antibiotics that cover a narrower spectrum of pathogens, preventing 'collateral damage' to the microbiome and reducing the build-up of AMR;
    - Transmission value, which arises from preventing the spread of the infection among the wider population by treating individual patients;
    - Enablement value, which arises, for example, from protecting the safety of surgical procedures that rely on prophylactic or post-operation antibiotics, or of using drugs that suppress the immune system risking infection;
    - Diversity value, which arises from attenuating the 'selection pressure' on existing antibiotics and preserving the efficacy of these existing treatments against resistant pathogens; and
    - Insurance value, which arises from having access to an effective treatment available in case of a catastrophic event, such as an outbreak of multi-drug resistant pathogen.

In addition, rewarding novel modes of action is argued by some to be important (Karlsberg Schaffer et al., 2017; BCG, 2022) which adds value by reducing cross-resistance among classes of antibiotics, and fostering R&D of 'follow-on' products with the same mechanism of action.

- **Common Hospital Payment Mechanisms Disincentivize Use of Novel (More Expensive) Antimicrobials:** Most hospitals, whether publicly or privately owned, are under pressure to keep costs down. One common form of payment mechanisms is the Diagnostic Resource Group (DRG), whereby the hospital is paid a pre-set amount to deal with a particular health problem. When antibiotics are needed, this model incentivizes cost-efficiency—that is, using the most affordable antimicrobial, which may not be the most effective (or ultimately

7 For a discussion of the issues see Rex et al. (2017).

8 The STEDI term is usually attributed to Rothery et al., 2018. A comprehensive outline is set out in Karlsberg Schaffer et al., 2017 and Neri et al., 2019. As Rex states in https://amr.solutions/2020/04/14/pull-incentives-for-antibiotics-how-much-and-why/
STEDI "was proposed by Outterson and Rex, *Translat Res* 2020, based on a list of attributes first proposed by Karlsberg et al., 2017."

cost-effective) for drug resistant infections. Use of the wrong antibiotic also creates risk that the patient will develop a multi-drug resistant infection. Some health systems have sought to introduce payments that supplement the DRG, including billing rules introduced in 2019 by the US Centers for Medicare and Medicaid Services (CMS) to better compensate use of more expensive antibiotics (Rex 2019); however, it is not yet clear whether these reforms have effectively counteracted perverse incentives in practice.

- **Point of Care Diagnostic Tests Are Not Being Used to Reduce Drug Resistance:** More rapid diagnostic testing will reduce the need for presumptive prescribing, and so both reduce the use of antibiotics that will not work and ensure better targeting of drugs that will work. This will reduce the growth of drug resistance. There are challenges with the incentives for the development of diagnostics in general (Garau et al. 2013; Garrison and Towse, 2014)—notably around the use of cost-based (rather than value-based) reimbursement, and the lack of intellectual property protection or data exclusivity, which impact incentives to collect evidence. In the specific case of antibiotic use, these problematic incentives are exacerbated by the challenge of assessing new antibiotics' value relative to older antimicrobials.
- **The Science is Difficult:** A paper by Prasad et al. (2022) analysed reasons for failure of gram-negative antibiotic development over the last decade (2010–20) and found toxicology failures to be the main challenge, i.e. the relative poor predictive power of preclinical toxicity studies when compared to other drug classes.[9] Payne et al. (2015) offer a detailed description of the scientific challenges facing antibacterial discovery, drawing on the experience of GSK and of other companies.
- **Regulatory Approval Processes for New Antimicrobials are Time-Consuming:** As a broad class, there is "no evidence … that antimicrobial progress through the regulatory approval process in the USA is more time-consuming than non-antimicrobial development" (Darrow et al. 2020). However, antibacterial drugs more specifically "fall behind these other groups in their use of every type of expedited designation" (Rex and Outterson 2021).

As a result, even companies which are successful in developing and bringing a novel antibiotic to market generally fail to recoup their investments. Several small biotech companies have gone bankrupt even after market entry of new antimicrobial products; according to Outterson (2022), sponsors of 7 of the last 18 antibiotics have either gone bankrupt or have market capitalizations well below the sunk costs of R&D. These failures are cautionary tale for investors and entrepreneurs who might otherwise be interested in tackling a globally relevant challenge.[10]

9 Rex sets out how this is being addressed by some of the "push" initiatives (https://amr.solutions/2022/06/14/leaky-pipelines-when-is-a-molecule-a-drug/)

10 See Achaogen (https://amr.solutions/2019/04/22/scary-scarier-scariest-achaogen-ft-editorial-cbs-60-minutes-on-amr/) and Melinta (https://amr.solutions/2020/01/07/melinta-part-2-bankruptcy-is-not-the-end-post-approval-costs-for-an-antibiotic/); other developers have been sold for a pittance, as in the case of Tetraphase (Tetraphase sold for $14m … and $600m goes up in smoke! • AMR.Solutions).

2. A pull mechanism for new antimicrobials: Rationale and design

2.1 Incentivizing novel antimicrobial R&D: The case for "pull" mechanisms

The market failure for novel antimicrobials, described in the previous section, is well-understood by policymakers and economists. Broadly, there are two ways to overcome these market failures and better incentivize development of needed antibiotics. The first is "push funding" which seeks to subsidize or reduce R&D costs and/or increase the likelihood of a successful development. The second is "pull funding," which increases the quantity or predictability of revenue contingent on successful antibiotic development and market entry. (A full discussion of push and pull funding in the context of antimicrobial development is provided in Appendix B).

There are several "push" incentives and initiatives—both proposed and in implementation—intended to strengthen the pipeline of new antibiotics.[11] These push initiatives facilitate continued R&D for antibiotics despite a lack of private-sector market incentives. Push approaches can also be politically attractive to government funders, as the governments' financial burden is self-limiting; research initiatives get underway with immediate effect; and funding typically offers direct support to domestic universities, non-profits, or companies.

However, important critiques have been raised about the effectiveness and efficiency of push financing—both for drug development broadly, and for antimicrobials specifically. As summarized in Kosiak and Silverman, 2021, push funding can have negative distortionary effects on pharmaceutical R&D. These problems generally fall into three categories:

> "First, push funding requires governments or other funders to "pick winners" to receive funding. This can be seen as an unjustified corporate subsidy, especially if the government or public subsequently is expected to pay for the final product at market prices. Practically, "picking winners" also risks distorting the market and driving out competitors, thereby potentially decreasing the likelihood of innovation success. Second, push funding distorts market incentives in ways that may cause inefficiency. Since push funding is "free" for the recipient, they may use such funds to support and continue projects with a very low likelihood of success, well after the point at which they would be discontinued if market forces applied. Third, the role of governments or philanthropies are often vulnerable to the sunk cost fallacy when they serve as co-investors in development of a product or technology, e.g., "we paid for this so we might as

11 These include CARBX and the AMR Action Fund, among others.

> well use it," even if the resulting technology is low-value and inappropriate for the target population" (Kosiak and Silverman, 2021).

For the antimicrobial sector specifically, important efforts have been taken to at least partially address some of these challenges; for example, CARB-X requires cost-sharing for the development programs in which it invests, and does terminate projects with limited prospects for ultimate clinical success. However, these institutions acknowledge that push financing approaches on their own, even if otherwise successful, are insufficient to incentivise market entry and commercialization (Rex and Outterson, 2021; Outterson 2021). In this view, purely "push" initiatives offer no pathway or incentive for commercialization of R&D; therefore, push initiatives, on their own, are unlikely to result in new "marketed" antibiotics, even if they generate success in early drug development and clinical trials. The GAO has echoed this view, finding in a 2020 report that "postmarket incentives are needed to overcome the economic challenges" (GAO, 2020a).

Pull mechanisms, in contrast to push alone, leverage "the promise of future sales and/or other revenue to indirectly justify up-front expenditures in R&D, thereby "pulling" innovations to market. Pull funding maintains incentives for innovation success; removes (or at least reduces) the government's role in "picking winners" *before* clinical safety and efficacy are demonstrated (though of course, the government will ultimately need to select the recipients of pull financing); and allows the funder to serve as a more impartial arbiter of whether the resultant innovation is socially valuable" (Kosiak and Silverman, 2021). Pull financing is only received contingent upon successful market entry, thereby also ensuring R&D incentives extend through licensing and commercialization.

The weight of the evidence—both empirical and theoretical—suggests that substantial pull incentives will be needed to adequately address this challenge with a sufficiently robust pipeline of novel antibiotic candidates.

2.2 The case for a subscription revenue model

Within the broader category of "pull incentives" are many different specific funding mechanisms. A few basic design considerations must be considered:

- How will products be selected and evaluated?
- Does a pull payment exist in *addition* to sales revenue; does it *guarantee* sales revenue; or does it *entirely replace* sales revenue?
- Will the pull payment be in one installment, or staggered over a multi-year implementation period?
- Will the pull payment be paid in cash or some other store of in-kind value such as a transferable intellectual property rights or a priority review voucher?

- What contractual conditions apply to qualify for receipt of the pull incentive, e.g. for stewardship, access and price?

In the case of novel antimicrobials, these design choices for a pull incentive should be tailored to be optimally responsive to two distinct objectives:

1) To increase the magnitude and predictability of a developer's revenue, contingent on successful market entry of a novel antibiotic; and
2) To remove perverse incentives for inappropriate use and overuse of the novel antibiotic once it comes market by *delinking* developer revenue from sales volumes.

Given these objectives, several funding models with different permutations of the design parameters described above have been proposed and evaluated (for further details, see Appendix B). The three leading candidates are as follows:[12]

- Market Entry Rewards (MERs)—essentially prizes—offer lump-sum payment or bringing a new antibiotic to market, i.e. achieving registration. Though MERs can in theory *supplement* versus *replace* sales revenue, in the case of antimicrobials specifically—where one objective is to delink revenue from sales volumes—it would make sense for the drug to be sold at cost or cost-plus after that point, thereby eliminating volume-based incentives. Estimates for the required magnitude of an MER range from roughly $1.5 billion to $4.8 billion for a partially delinked global MER (the company keeps sales revenue) with a best estimate of $2.2 billion (Outterson 2021a). (See Appendix B for further discussion).
- Transferable Intellectual Property Rights (TIPR), also known as "Wildcard patents", Transferable Exclusivity Extensions (TEEs) or Transferable Exclusivity Vouchers (TEVs). These reward successful market entry of a new antimicrobial with a sellable "voucher", which enables the recipient to extent patent protection on a different product for a specified period (Ferraro et al., 2017). This approach is sometimes attractive from a budgetary perspective, as the government need not allocate funding up-front; such programs appear "costless" from an appropriations perspective. However, the social cost of extended patent exclusivity can be very high if it sustains high drug prices beyond the counterfactual end of patent exclusivity; many of these costs will be borne by the US government via Medicaid and Medicare, and the total "hidden" fiscal cost can be substantial. For such a program to work in the context of AMR, voucher receipt would also need to be contingent on relinquishing the patent or at-cost sales—thereby addressing the second (delinkage) objective.
- "Netflix-style" subscription models delink annual fixed payments for the drug from the volume of sales. The payer (for example, CMS) would offer the developer a fixed annual payment over a long time horizon (e.g. 10 years); in exchange, the payer would receive an

12 Japan and Canada are currently considering a fourth option, which would guarantee revenue for novel antimicrobials in line with their "fair share" of a global R&D incentive. See Appendix B for further discussion.

unlimited quantity of the drug at marginal cost. This offers the successful developer a substantial guaranteed revenue stream over a long time horizon (e.g. 10 years) without requiring volume-based sales of a drug to individual patients.

Three recent reviews of pull options in the context of incentives for new antibiotics confirm that MERs, TIPR / TEEs, and subscription models are the most promising approaches, with a general preference for the latter. Brennan et al. (2022) argue that a subscription program would stimulate new creative financing mechanisms to provide capital for small companies. BCG (2022) assess the various models (Exhibit 10 p15) and conclude that the subscription model is the strongest option; that conclusion shared by Dutescu and Hillier (2021) following their extensive literature review. In the US context, we agree with the relative consensus that a subscription model over 10 years is preferable to a one-off MER or TEE.[13]

2.3 An illustrative subscription revenue model for the US government: Design and parameters

For the US, we consider an illustrative Netflix-style subscription model that would offer fixed, predictable revenue to antibiotic developers' contingent upon successful market entry. The payment would be made each year for a decade and would entitle the US government to procure an unlimited quantity of the drug on behalf of its citizens. After the subscription period is concluded, the US government would be entitled to continue procuring the drug at a heavily discounted price, approaching the marginal cost of production.

We consider the following parameters for the program:[14]

- The program should seek to generate a total of 18 new antibiotics over three decades to treat the six priority pathogens— or three drugs for each priority pathogen. This is intended to ensure that there are multiple treatment options available for each priority pathogen and to defray the design risk from a pull mechanism that would pick only one winner. That translates to an expected value of 6 new antibiotic launches each decade.[15] We note that our estimate for the numbers of new drugs needed may be too low. The O'Neill report argued for 15 drugs in 10 years (1.5 new drugs per annum) and we could target new drugs for each of

13 More broadly, we agree with the relative consensus that a subscription model is theoretically superior to the other options described here. However, we recognize that political and fiscal constraints, as well as other feasibility considerations, will vary across jurisdictions. In particular, the EU is actively considering a TEE model. The industry trade association EFPIA has set out a strong case for TEE in the EU (EFPIA 2020) and commissioned reports on its benefits and feasibility from CRA (Wilsden et al. 2022) and OHE (Berdud et al., 2019). There is room for variation in the approach chosen across jurisdictions, so long as consistent selection approaches are maintained and actors contribute their "fair share" towards global antimicrobial R&D through their chose mechanism. We also recognise that an MER or a TEE does not have to take the form of a one-off event. Contractual arrangements can be put in place to ensure issues around, for example, real world data collection, supply, and stewardship are addressed.

14 Please see Appendices for detailed justification of these program parameters.

15 As there is no consensus view on this in the literature, this is necessarily an arbitrary but broadly reasonable program ambition.

the 20 pathogen-drug combinations in the Priority List in Appendix A. There also may be a case for "front-loading", i.e. having more new drugs in the first decade, to make up for lack of investment, before reverting to a lower but sustained number for subsequent decades.

- Pulling one new antimicrobial to market (with full delinkage) would require a 10-year subscription model with total value of $4.5 billion. This is an upward adjustment for inflation of the central "best" estimate of $4.2bn in the range modelled by Outterson (2021) of $3.3 to $8.9 billion.[16] The US share of this total is proportionate to its share of GDP among the G7 + European Union, or 46%. This means that the US should pay $2.1 billion total per new drug, amortized over the ten-year subscription duration.
- Patent protection expires at the end of the subscription period, allowing for generic competition to push prices toward marginal cost.
- The US should commit to this program for the next 30 years to enable long-term investments in R&D. The ten-year cost of the program (without discounting) is $6.8 billion; the 30-year cost is $32 billion. Annual costs would peak and stabilize at a recurrent $1.24 billion per year, starting in year 10. This annual payment would account for 0.8% of US government spending on pharmaceuticals in 2019, and 0.3% of total US expenditure (public and private) on pharmaceuticals.[17]

As these parameters are selected for illustrative purposes only, we note that there are some important simplifications and design choices that may not be optimal within a real-world program:

- In our simplified model, the US government offers a fixed, consistent payment for all antimicrobials without consideration of their relative efficacy and value. In practice, a subscription model should vary remuneration under the program based on a novel drug's specific characteristics and utility.
- We imagine that the US share of the total pull incentive will be equivalent to its share of GDP within the G7 + EU (46%).[18] Alternative cost-sharing approaches might be desirable to distribute the burden of R&D more broadly; these could include the US share of OECD GDP (40%), or the US share of global GDP (24%). A weakness of all such approaches is that they require substantial policy commitments by other countries; it may therefore be desirable to consider a scenario where the US continues to pay an outsized share of costs in line with

16 Outterson (2021a) also models an "acquisition scenario," which calculates the pull incentive required for an acquired Phase II-ready asset; this can be thought of as accounting for complementary push funding that supports the candidate through preclinical development and Phase I trials. For this scenario, the Outterson calculates that a total subscription payment between $2.2 billion and $4.8 billion would be required, with a central "best" estimate of $3.1 billion. We opt to use the full delinkage numbers for the sake of producing a conservative ROI estimate, but we note there is some debate about whether this higher average payment would be required given early-stage push investments.

17 Office of the Inspector General reports U.S. prescription drug expenditures totalled $370 billion in 2019. Spending through Department of Health and Human Services (HHS) programs accounted for 41 percent ($151 billion) of this total., available at https://oig.hhs.gov/reports-and-publications/featured-topics/drug-spending/#:~:text=According%20to%20data%20from%20the,151%20billion)%20of%20this%20total.

18 Using World Bank data for 2021.

its current market share (84%) for novel antimicrobials (Rahman et al. 2021), or even a last-resort "free-rider" scenario where the US bears the entirety of the R&D cost. We model these alternative scenarios within a sensitivity analysis, discussed in further below.

These parameters suggest a program that is broadly similar to the proposed PASTEUR Act, which is legislation introduced by lawmakers in the US House of Representatives and Senate, initially within the CURES 2.0 Bill (2021)—and which would provide both the requisite financing and authority to implement the program we describe. (A very similar proposal is also included within President Biden's 2023 Budget Request for the Department of Health and Human Services (U.S. Department of Health and Human Services, 2022).) The PASTEUR Act, as revised in September 2022 (Senate Congressional Record), would allocate $6 billion over 10 years to subscription payments for new antibiotics. For each novel antimicrobial, the bill text would authorize a minimum total subscription value of $750 million and a maximum total subscription value of $3 billion, with payment varying based on the efficacy and degree of innovation for each new agent. Our mean cost estimate for the US share of a subscription payment ($2.1 billion per drug, on average) is thus aligned with the payment parameters suggested under the proposed PASTEUR Act.

The revised PASTEUR Act text also specifies that the Secretary of Health and Human Services is to establish a "Subscription Contract Office" which will sit within the HHS to oversee "eligibility, requirements, and contract amount." However, the text delegates many of the program details to HHS; for example, the Secretary is to promulgate regulations that define the eligibility/application processes for "critical need antimicrobial drugs" and set pricing and contracting approaches within the broad parameters specified.

3. Modelling the return on investment for a US government subscription purchasing program

3.1 Return on investment: United States domestic perspective

In this section we consider the costs and value of such a pull mechanism from the perspective of the United States government—both in the short term (10 years) and over a longer time horizon (30 years). We consider only drug costs and health benefits/reductions in healthcare costs associated with reduced AMR deaths. We do not include the STEDI values, discussed further in Appendix C, as we do not have enough data to support an estimate.

The detailed calculations are set out in Appendix C and available in a supplementary Excel model. We make the following assumptions across all our modelling:

- Each new drug is held in reserve for 4 years and then reduces deaths by 5% each year; starting from year 5 onwards, effectiveness falls by 2% year on year, due to the build-up of resistance;

- We assume that the US share of this financing will be proportionate to its current GDP share in the G7 plus EU (46%) with the remainder paid by other countries;
- We use a discount rate of 1.5% for health effects, and 3.5% for costs; and
- We assume the rate of growth of resistance is 2%. Absent new drugs, annual deaths increase by 2% each year.[19]

For the U.S. specifically, we make the following key assumptions (described and justified in detail in Appendix C):

- Current annual US deaths from AMR are 35,000 (CDC 2019a);
- Approximately 27,800 deaths, i.e. around 79% of these deaths, come from the six leading pathogens which would be targeted by a pull incentive (CDC 2019a, as analyzed in Appendix Table A1);
- We derive the DALY value of each death from data presented in the GRAM study (ARC 2022), which suggests an average 17 DALY loss associated with each HIC death from AMR; this implies that 27,800 AMR-related deaths are equivalent to a loss of 472,600 DALYs;
- Each DALY is worth $100,000,[20] giving an estimate of $1.7 million per death and implying that current AMR-attributable health losses for those six infections can be valued at $47.3 bn per year;
- Patent protection expires at the end of the subscription period, allowing for generic competition to push prices toward marginal cost; and
- We derive averted health system costs from Nelson et al. (2021a), who estimate total AMR-related healthcare costs of $4.6 billion in the US—or $131,000 associated with each of 35,000 annual deaths. We assume that a reduction in deaths and associated illnesses which result from new drugs will lead to a proportionate reduction in healthcare expenditure.

The results of the modelling exercise are presented in Table 1.

TABLE 1. Domestic US costs and benefits, over 10 years and over 30 years

	Total Cost (Discounted)	Lives Saved	DALYs Saved	DALY Value	Healthcare Savings (Discounted)	DALY + Healthcare Savings (Discounted)	Benefit: Cost Ratio
10-Year	$5.4 bn	20,000	340,000	$30.0 bn	$2.0 bn	$32.0 bn	6:1
30-Year	$17.9 bn	383,000	6,510,000	$470.7 bn	$24.0 bn	$494.8 bn	28:1

19 As described in Appendix C, there are no reliable projections about the growth of AMR deaths, and indeed CDC data suggested a decrease in AMR-related mortality within the US between 2013 and 2019. Nevertheless, our expectation (modelled here) is that there will be an eventual increase in AMR-related deaths in the absence of new therapeutic options. In the sensitivity analysis we model an alternative scenario of no growth in AMR deaths; the benefits are smaller in this scenario, but the program still offers a positive return over 10- and 30-year time horizons.

20 Demand-side estimates have been recently estimated at $100,000 per QALY (Phelps, 2019). An alternative supply-side opportunity cost approach (Vanness et al. 2021) estimated $104,000 per QALY. As these two measures give us similar numbers of $100,000 per QALY, we can ignore the question as to which basis is most relevant. We equate QALYs and DALYs for the purpose of this exercise.

The modelling gives the following results:

- In the absence of new drugs, attributable deaths to our six pathogens would increase from 27,800 to over 50,000 in year 30, with a cumulative total of 1,150,000 deaths.
- Over its full 30-year time horizon, the program averts 383,000 deaths, 6.5 million DALYs, and $24.0 billion in healthcare costs. The discounted value of DALYs averted is $470.8 billion and discounted costs are $17.9 billion. This equates to a 30-year ROI of 28 to 1.
- Over a shorter 10-year period the benefits are lower, as we assume it takes 4 years post-launch before a drug is used. The program takes time to build up momentum; after 10 years we only have six new drugs. During this shorter time frame, the program averts 20,000 deaths, 340,000 DALYs, and $2.0 billion in healthcare costs. The discounted value of DALYs averted is $30.0 billion and discounted costs are $5.4 billion. This equates to a 10-year ROI of 6 to 1.

The returns are very large over 30 years, with benefits exceeding the costs by a factor greater than twenty-eight. Over 10 years, benefits exceed costs by a multiplier of around six. This reflects the fact that costs are incurred throughout the program, whereas the benefits are cumulative, with many occurring decades into the future as a sustainable program is put in place.

3.2 Return on investment: Global perspective

In order to estimate a return on investment, the key additional assumptions are as follows. (See Appendix C for full description and justification.)

- We assume that 25% of the deaths outside of "high income" countries could be tackled by improved access to the suite of existing antibiotics;
- We consider the entire global cost of the incentive program, including complementary incentives that would be implemented elsewhere in the world;
- At the global level, we assume the new drugs can impact the MDR infections and deaths of the 73% of infections caused by our six pathogens (ARC 2022);
- We use $18,000 as the cost per DALY (roughly global average GDP on PPP, in effect assuming 1 x GDP value);
- We derive the DALY value of each death from data presented in the GRAM study (ARC 2022), which suggests an average 37.7 DALY loss associated with each global death from AMR, reflecting the younger average age of death across LMICs; and
- We did not find reliable estimates of health costs at the global level. Therefore, we omit this from our analysis and consider only the value of direct health benefits.

We summarise the results of the modelling in Table 2.

TABLE 2. Global costs and benefits, over 10 years and over 30 years

	Total Cost (Discounted)	Lives Saved	DALYs Saved	Value of DALYs Saved	Benefit: Cost Ratio
10-Year	$11.7 bn	518,000	19.5 million	310.6 billion	27:1
30-Year	$38.9 bn	9,933,000	374.5 million	4,874.2 billion	125:1

- Over its full 30-year time horizon, the program averts 9.9 million deaths and 374.5 million DALYs. The discounted value of DALYs saved is $4.9 trillion and discounted costs are $36.33 billion. This equates to a 30-year ROI of 125 to 1.
- Over the shorter 10-year period, the program averts 518,262 deaths and 19.5 million DALYs. The discounted value of DALYs saved is $310.6 billion and discounted costs are $11.7 billion. This equates to a 10-year ROI of 27 to 1.

We have excluded the economic impact and health system costs from ROI calculations, as we have little confidence in the underlying analysis. More work needs to be done on estimates of health costs and effects and economic effect in the global estimates. We have relied on the World Bank estimates (2017) for which underlying assumptions are not explained. However, the DALY value of averted deaths is more than sufficient to produce a high ROI without even considering these secondary benefits.

3.3 Sensitivity analysis

Given the lack of confidence in some of our underlying parameters, we model a range of different scenarios via a sensitivity analysis (Table 3). Broadly, our high-level result (e.g. a high ROI from the proposed program) is robust to many different assumptions and scenarios. From both the US and global perspectives, the biggest sensitivity is related to the efficacy of drugs that result from this initiative against AMR-related deaths. From the US government's perspective specifically, another substantial sensitivity is the total share of the pull mechanism that it would need to finance—but the program would generate a positive return on investment even in a scenario where the US paid the entirety of the pull incentive. Likewise, the program remains highly beneficial even if there is no counterfactual growth in AMR deaths over the next 30 years.

TABLE 3. Sensitivity analysis of ROI estimates under different scenarios (benefit to cost ratio)

Scenario	10-Year, US[a]	30-Year, US[a]	10-Year, Global[b]	30-Year, Global[b]
Base Case	6:1	28:1	27:1	125:1
"Free Rider"—US Share 100%	3:1	13:1	27:1	125:1
US Market Share—US Share 84%	3:1	15:1	27:1	125:1
US GDP Share (Within OECD)—US Share 40%	7:1	31:1	27:1	125:1
US GDP Share (Global)—US Share 24%	11:1	53:1	27:1	125:1

Scenario	10-Year, US[a]	30-Year, US[a]	10-Year, Global[b]	30-Year, Global[b]
No Growth in AMR Deaths (0% Per Year)	5:1	18:1	23:1	82:1
Fast Growth in AMR Deaths (5% Per Year)	8:1	52:1	34:1	237:1
Slower Resistance Growth to New Antimicrobials (1% Per Year)	6:1	30:1	27:1	136:1
Faster Resistance Growth to New Antimicrobials (5% Per Year)	6:1	22:1	25:1	100:1
Lower Drug Efficacy Scenario (2% Death Reduction Per Drug at Peak Efficacy)	2:1	11:1	11:1	50:1
Larger Share of Global AMR Burden Addressed Via Improved Access (50%)	6:1	28:1	19:1	89:1

[a] Includes health benefits and averted healthcare costs

[b] Includes health benefits only

4. Policy implications

4.1 Total advanced commitment required

Based on our parameters, total (nominal) program cost would peak at $1.24 billion per year in the US. However, the 10-year phasing of payments means that the first 10 years of a program incur cumulative nominal costs of $6.8 billion. Our calculations therefore suggest that the proposed $6 billion budget of the PASTEUR act (over 10 years) is roughly adequate, though slightly lower than our budget estimate. Renewal in the program's second decade would need to be at an increased level ($12.4 billion over ten years) to sustain the necessary launch of new drugs.

While there are other options available under existing legislation, as we note in Appendix B, it is difficult to see how a program of the requisite size needed could be initiated without new Congressional legislation. The high social return demonstrated in our calculations offers a strong rationale for Congress to authorize and fully fund the proposed PASTEUR Act, which is broadly aligned with our model parameters.

We acknowledge, however, that our bottom-line cost estimate is subject to key sensitivities. The most important ones are:

- The number of new antibiotics needed to address the priority pathogens, which would impact total costs but not the ROI (assuming the efficacy of new antibiotics is held constant);
- The total (global) incentive payment required to incentivize the desired innovation, including whether the pull renumeration level accounts for complementary push financing; and
- The US share of the total incentive payment.

The accompanying spreadsheet allows direct exploration of these sensitivities and others, including how they impact ROI calculations.

4.2 Specific design considerations

Beyond the basic program description used as the basis of our ROI calculation, there are several important program design conditions that are relevant to the effectiveness of the proposed subscription program. These include:

1. **The long-term credibility of the program:** To incentivize the desired investments in R&D, potential antimicrobial developers must have confidence that the incentive program will endure political changes in control of the White House and Congress. The incentive program will thus be most effective if it benefits from strong bipartisan support.
2. **The performance basis for payments:** While we estimate an "expected" payment for new drugs, in practice the subscription payment for each drug should vary commensurate with its efficacy and overall health value. To do so, the US government would need to establish a credible and predictable process for value assessment of each new drug. Both the system and the valuation of each new drug will need to be periodically revisited on the basis of new evidence.
3. **Revision of priority pathogen list:** The US government will need to periodically reassess and revise the list of priority pathogens based on evolutionary trends in drug resistance and the launch of new drugs. However, it is important that such a process does not penalize drugs in late-stage development via abrupt removal from the priority pathogen list.
4. **Complementary sources of financing:** Our US government cost calculations in this paper assume, in our base case, that the remainder of the required incentive payments (54%) will be covered by complementary programs in other countries. The US government should consider building support for globally coordinated action through negotiations in international fora—most relevantly the G7, OECD, and G20. As we have discussed, several other countries are discussing or piloting incentives.

4.3 Overall assessment

Our findings suggest a very high return on investment from a potential US subscription program to incentivize the development of new antimicrobials. Our estimates are robust to many different scenarios and parameters, with high impact both within the US and around the world in averting deaths, reducing morbidity, and helping contain healthcare expenditure. These findings offer a strong rationale for the U.S. Congress to pass and fully fund the PASTEUR Act, and for the US government to press for co-ordinated international action across its G7 and G20 partners.[21]

21 The June 2022 communique from the G7 meeting included the words "strengthen research and innovation for new antibiotics in international partnerships, and incentivise the development of new antimicrobial treatments with a particular emphasis on pull incentives."

Appendix A. Estimates of the burden of disease

This Appendix sets out:

- overall estimates of the burden of disease, globally and in the US.
- estimates as to which types of pathogen are the most important to address.

We begin by setting out the health impact and then look at the economic impact, for example on the health system, notably hospitals, and on the wider economy.

1. Estimates of the health burden of disease, globally and in the US

Global perspective

The 2014 O'Neill Review, (O'Neill, 2014) commissioned by the UK Government, estimated that AMR could cause 10 million deaths a year by 2050, based on a report by KPMG (KPMG 2014) that it had commissioned. A critical commentary (de Kraker et al., 2016) notes that this study follows the approach of the 2009 ECDC and EMA report (ECDC 2009) which produced a widely quoted estimate that "Each year, about 25 000 patients die in the EU from an infection with the selected multidrug-resistant bacteria."

de Kraker et al., 2016 argue that this approach may overstate the impact of AMR because (i) too much weight is given to sampling from tertiary hospitals (ii) blood cultures used to estimate drug resistant infections are given to the sickest or those not responding to empiric therapy. These estimates of bloodstream infections (BSI) are them multiplied using a ratio to pick up other types of drug resistant infections: lower respiratory tract infections (LRTIs), surgical site infections (SSIs), urinary tract infections (UTIs), third-generation cephalosporin-resistant E. coli and K. pneumoniae, and MRSA. These rates then have to be translated into mortality rates.

In the case of the O'Neill estimate four scenarios are then used to project future AMR deaths: an absolute rise in resistance levels of 40% for all species under study or 100% resistance, with both of these scenarios combined with either stable or doubled infection rates. de Kraker et al. (2016) argue that "there is no empirical data supporting any of these scenarios. Furthermore, each scenario assumes that the mortality risk per infection will remain unchanged, despite evidence that mortality rates associated with BSIs and sepsis are decreasing due to improved supportive care."

A systematic review of 214 studies estimating the burden of AMR was undertaken by Naylor et al. (2018). The authors concluded that "there is considerable variability in burden estimates, which can lead in-turn to inaccurate intervention evaluations and poor policy/investment decisions."

The most recent study was published in the Lancet in February 2022 (ARC, 2022). They estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019.

The study sought to use the same methodology as the Global Burden of Disease studies (see https://www.healthdata.org/gbd/about). It used two counterfactuals:

- All drug resistant infections are replaced by susceptible infections— this estimates only deaths and DALYs *directly attributable* to resistance.
- All drug-resistant infections are replaced by no infection—this estimates all deaths and DALYs *associated* with resistant infection.

The headline results for 2019 were:

- 1·27 million deaths (95% uncertainty interval (0·911m–1·71m) were directly *attributable* to resistance (ie, based on the counterfactual scenario that drug-resistant infections were instead drug susceptible) in the 88 pathogen–drug combinations evaluated in this study;
- On the basis of a counterfactual scenario of no infection, 4·95 million deaths (3·62–6·57) were *associated* with bacterial AMR;
- For the "super region" "High Income" (which includes the US, Canada, and Western Europe) the figures were 0.141m (0.0986m–0.197m) *attributable* and 0.604m (0.0434m–0.824m) *associated*;
- By implication, for the rest of the world, the figures were 1.129m *attributable* and 4.346m *associated*.

Rates of deaths per 100,000 were:

- Globally 16.4 per 100,000 (11.8–22.0) *attributable* and 64.0 per 100,000 (46.8–84.9) *associated*;
- For the "super region" "High Income" (which includes the US, Canada, and Western Europe) 13.0 per 100,000 (9.1–18.2) *attributable* and 55.7 per 100,000 (40.1–76.0) *associated*.

These results suggest that:

- Using *attributable* deaths, i.e. the counterfactual of susceptible infection, AMR would have been the 12th leading GBD Level 3 cause of death globally, ahead of both HIV and malaria;
- Using *associated* deaths, the counterfactual of no-infection, AMR would have been the third leading GBD Level 3 cause of death in 2019.

The authors note that "the highest rates of death were in sub-Saharan Africa and south Asia." They argue that this reflects "both the prevalence of resistance and the underlying frequency of critical infections." Other challenges include poor sanitation and hygiene and:

- "Scarcity of laboratory infrastructure making microbiological testing unavailable to inform treatment to stop or narrow antibiotics";
- "The inappropriate use of antibiotics driven by insufficient regulations and ease of acquisition";
- "Inadequate access to second-line and third-line antibiotics;" and
- "Counterfeit or substandard antibiotics that can drive resistance."

This suggests that in some parts of the world *increased availability of existing second-line antibiotics will reduce death rates*. This point is echoed in a Comment piece by Laxminarayan (2022) who points out that "uronically, the burden of resistance partly reflects the insufficient access to antibiotics. The problem of excessive and inappropriate use of antibiotics co-exists with the problem of insufficient access even in the same geographical areas. Pneumococcal pneumonia is easily treatable with antibiotics, but the burden estimated by Murray and colleagues reflects the lack of access to even inexpensive drugs such as penicillin. Some of the AMR burden in sub-Saharan Africa is probably due to inadequate access to antibiotics and high infection levels, albeit at low levels of resistance, whereas in south Asia and Latin America, it is because of high resistance even with good access to antibiotics. Over two-thirds of attributable deaths were due to resistance to first-line antibiotics including fluoroquinolones and â-lactam antibiotics (carbapenems, cephalosporins, and penicillins)."

Laxminarayan also points out that "Even the lower end of 911,000 deaths estimated by Murray and colleagues is higher than the number of deaths from HIV, which attracts close to US$50 billion each year."

Focusing on Europe and the US

We can compare these global estimates with a report from the WHO and ECDC. Citing a Lancet paper (Cassini et al. 2019), this report estimates of 33,110 attributable deaths from AMR in the EU/EEA area in 2015 (i.e. including the UK). Given a population of over 514m this is equivalent to around 6.44 attributable deaths per 100,000 people.

The US CDC report (CDC 2019a) has a "Threat Estimate 2019", which estimates 35,000 deaths due to bacterial resistance in the US, or 10.66 per 100,000.

Another US study funded by IDSA and The Pew Charitable Trusts, (Nelson et al. 2021a) estimated the burden of six multidrug-resistant infections (methicillin-resistant Staphylococcus aureus (MRSA); extended-spectrum cephalosporin resistance in Enterobacteriaceae suggestive of extended spectrum â-lactamase (ESBL) production, vancomycin-resistant Enterococcus (VRE), carbapenem-resistant (CR) Acinetobacter species, carbapenem-resistant Enterobacteriaceae (CRE), or multidrug-resistant (MDR) Pseudomonas aeruginosa) among the U.S. Medicare population. They estimated 11,852 (8,719–14,985) AMR deaths in 2017 for 58.4m Medicare patients, giving a rate of 20.3 per 100,000. We discuss this study in more detail later in this Appendix.

We thus have:

- A global estimate from the ARC (2022) of 1.27 million deaths (95% uncertainty interval 0.911m–1.71m) directly *attributable* to resistance in 2019, which is globally 16.4 per 100,000 (11.8–22.0);
- For the USA we have several numbers:
    - From the same global study, for the "super region" "High Income" (which includes the US, Canada, and Western Europe) we have a death rate of 13.0 per 100,000 (9.1–18.2) for 2019.
    - The CDC give an estimate for the US in 2019 of 10.66 per 100,000 or 35,000 deaths.
    - The EDSA / Pew study estimated a rate of 20.3 per 100,000 for Medicare patients.

For the purposes of this exercise, we use the CDC estimate of 10.66 per 100,000 or 35,000 deaths and the global estimate from the ARC of 16.4 per 100,000 and 1.27m deaths.

Estimates related to pathogen prioritization

There are a number of priority pathogen lists, notably from the WHO (2017), the Indian Government (2021) (working with WHO India), the CDC (2019, 2013), and the ISDA (Rice LB. 2008, Boucher HW et al. 2009). These lists have been combined and compared by Rex (2021).

The ARC (2022) also set out disaggregated data on the types of pathogen that are of most concern in terms of death and mobidity. The six leading pathogens for deaths *associated* with resistance were:

1. Escherichia coli
2. Staphylococcus aureus
3. Klebsiella pneumoniae
4. Streptococcus pneumoniae
5. Acinetobacter baumannii
6. Pseudomonas aeruginosa.

These were responsible for 929,000 (660,000–1,270,000) (73%) of the deaths *attributable* to AMR and 3,57 million (2·62–4·78) (72%) of the deaths *associated* with AMR in 2019.

Seven pathogen–drug combinations each caused more than 50,000 deaths *attributable* to AMR in 2019:

1. Methicillin-resistant S aureus
2. Multidrug-resistant, excluding extensively drug-resistant, tuberculosis
3. Third-generation cephalosporin-resistant E coli
4. Carbapenem-resistant A baumannii
5. Fluoroquinolone-resistant E coli

6. Carbapenem-resistant K pneumoniae
7. Third-generation cephalosporin-resistant K pneumoniae.

The authors conclude that "Resistance to fluoroquinolones and â-lactam antibiotics (i.e., carbapenems, cephalosporins, and penicillins)—antibiotics often considered first line for empirical therapy of severe infections—accounted for more than 70% of deaths attributable to AMR across pathogens."

They also point out that "Only five of the seven pathogen–drug combinations that we estimated to have caused the most deaths attributable to bacterial AMR in 2019 are currently on the [2017 WHO Priority List] list; MDR tuberculosis and fluoroquinolone-resistant E coli are not included. Additionally, meticillin-resistant S aureus—the leading pathogen–drug combination in our analysis for attributable deaths in 2019—is listed as "high" but not "critical" priority. WHO has explained that the absence of MDR tuberculosis from its priority list is because it has already been established globally as a top priority for innovative treatments, but this exclusion remains a source of considerable debate. Although many factors were considered in producing the WHO priority list, these new estimates of the global burden of specific pathogen–drug combinations can inform future work on WHO priority pathogen–drug combinations."

We have mapped the findings of the ARC (2022) onto the summary of priority pathogen lists prepared by Rex (2021). The results are set out in Figure A1 below. We can see that there are some differences between the lists, and there is a need to absorb the implications of the ARC (2022) work for existing lists. However, there is a significant degree of consensus on the priorities for drug development.

FIGURE A1. Mapping of priority pathogen lists

Pathogen (WHO category)	Antimicrobial Resistance Collaborators (2022)	WHO (2017)	Indian* (2021)	CDC (2019)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Top 7 "attributable deaths" Top 6 pathogen	Critical	Critical	Urgent (carbapenem-R)	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Top 6 pathogen	Critical	Critical	Serious (MDR)	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Top 7 "attributable deaths": • third-generation cephalosporin-resistant E coli • third-generation cephalosporin-resistant K pneumoniae • carbapenem-resistant K pneumoniae 2x Top 6 pathogens	Critical	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R		High	High	Serious (VRE)	Serious (VRE)	Yes
Staphylococcus aureus, methicillin-R, vancomycin-I/R	Top 7 "attributable deaths" Top 6 pathogen	High	High	Serious (MRSA)	Serious (MRSA) Concerning (VRSA)	Yes
Helicobacter pylori, clarithromycin-R		High				
Campylobacter spp., fluoroquinolone-R		High		Serious (drug-R)	Serious (drug-R)	
Salmonellae spp., fluoroquinolone-R		High	High (drug-R)	Serious (drug-R, Typhi & non-typhoidal)	Serious (drug-R)	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R		High		Urgent (drug-R)	Urgent (drug-R)	
Neisseria meningitidis, 3rd-gen ceph-R, fluoroquinolone-R			Medium			
Streptococcus pneumoniae, penicillin-NS	Top 6 pathogen	Medium	Medium	Serious (drug-R)	Serious (drug-R)	
Haemophilus influenzae, ampicillin-R		Medium	Medium			
Shigella spp., fluoroquinolone-R		Medium	Medium	Serious (drug-R)	Serious	
Staphylococcus, coagulase-neg, Van/Lzd-R			Medium			
Clostridium difficile				Urgent	Urgent	
Candida spp. fluconazole-R				Urgent (C. auris) Serious (Drug-resistant)	Serious (Flu-R)	
M. tuberculosis	Top 7 "attributable deaths" (MDR TB)			Serious (drug-R)	Serious (drug-R)	
Fluoroquinolone-resistant E coli	Top 7 "attributable deaths" Top 6 pathogen					
Group A *Streptococcus*				Concerning (erythro-R)	Concerning (erythro-R)	
Group B *Streptococcus*				Concerning (clinda-R)	Concerning (clinda-R)	
Aspergillus fumigatus				Watch (azole-R)		
Mycoplasma genitalium				Watch (drug-R)		
Bordetella pertussis				Watch (drug-R)		

*Note that the Indian PPL sometimes differs slightly from WHO in terms of precise patterns of qualifying R.

2. Estimates of the economic impact

The report by the Global AMR R&D Hub & WHO (2022) cites the World Bank Report (World Bank, 2017) which "predicted losses of up to 3.8% of gross domestic product (GDP) globally by 2050." The World Bank set out two scenarios ("low AMR impacts and high AMR impacts"). The results show, respectively global GDP being 1.1% and 3.8% lower by 2050, with annual impacts by 2030 of $1 trillion and $3.4 trillion.

It notes that the "high AMR impact" results are comparable to those of the 2008 crash, albeit with greater impact on low-income countries. The Report states:

> "In the high-AMR scenario, health care expenditures in 2050 would be as much as 25 percent higher than the baseline values for low-income countries, 15 percent higher for middle-income countries, and 6 percent higher for high-income countries. Globally, annual expenditures in 2050 would be 8 percent higher than in the base case. The additional expenditures in 2050 would be $1.2 trillion annually in the high-AMR scenario. In the low-AMR scenario, the additional health care expenditure in 2050 would be $0.33 trillion annually" (World Bank, 2017; p. 22).

The World Bank also estimates that nearly 8 million additional people will fall into extreme poverty by 2030 in the low-AMR case; and more than 28 million people will fall into extreme poverty by 2050 in the high-AMR case.

However, no explanation of the assumptions underpinning these estimates is given, in particular the assumptions made about the rate of growth of resistant infections. We can also note that the Report addresses AMR and not the narrower focus of this paper, which is on antibacterial drug resistant infections. It is not obvious, therefore, how these numbers can be adapted for use to estimate the economic impact of antibacterial resistance.

The Global AMR R&D Hub & WHO (2022) report includes a summary of studies that have estimated the economic impact of AMR across countries and regions. The numbers are as follows:

- **EU:** 1.518–9 billion EUR per year, due to increased health expenditure and productivity losses (European Commission, 2017; Llor and Bjerrum 2014; Prestinaci et al., 2015);
- **OECD:** 2.9 trillion USD cumulative losses by 2050 due to AMR (Cecchini et al., 2015);
- **US:** 55 billion USD per year, including 22–20 billion USD in excess for direct healthcare costs, plus lost productivity ~35 billion USD a year (CDC, 2013);
- **Canada:** 120 billion CAD in hospital costs, and 388 billion CAD in lost GDP by 2050 (Commission of Canadian Academies, 2019; Government of Canada, 2022); and
- **Japan:** 55bn–192.47bn USD 2050 annual loss (WB, 2017; Global Coalition on Aging, 2022).

Two of these reports cited (Cecchini et al., 2015; Commission of Canadian Academies, 2019) do provide useable data on health care costs and productivity effects. The CDC has a more recent report (CDC, 2019a) with a companion paper (Nelson et al. 2021b) which has usable data.

The paper we cited earlier (Naylor et al., 2018) highlighted the variability in burden estimates arising from the use of different methodologies, finding "excess healthcare system costs ranged from non-significance to $1 billion per year, whilst economic burden ranged from $21,832 per case to over $3 trillion in GDP loss" They found the median quality scores for payer/provider and economic burden studies to be 0.56 and 0.53 [out of 1] respectively.

The 11 studies estimating economic burden included the two commissioned by and reported on in O'Neill (2014), from KPMG LLP (2014) and from RAND Europe (2014). Prior to the publication of the World Bank 2017 paper, these were the most cited estimates of global economic impact. Both studies included resistance to HIV treatments (a viral infection) and to malaria treatments (a parasitic infection) as well as to treatments for TB and for three bacteria. RAND Europe assumed three resistance rates 5%, 40%m and 100% after 15 years. KPMG modelled an absolute increase in resistance of 40%, and a resistance rate of 100% in two scenarios (i) using current infection rates and (ii) doubling current infection rates. O'Neill (2014) summarised their findings as "continued rise in resistance by 2050 would lead to 10 million people dying every year and a reduction of 2% to 3.5% in Gross Domestic Product (GDP). It would cost the world up to 100 trillion USD."

As the results are not disaggregated to enable us to look at antibacterial resistance, and (as already discussed) the assumptions about infection rates and resistance have been criticised as implausible (de Kraker et al., 2016), these estimates of economic effect do not provide a basis for use.

CDC evidence on the growth of resistance

In the context of rates of growth, we can look at the comparisons in the CDC (2019a) report of cases and deaths as between 2013 and 2019. We set these out below. We have mapped the ARC 2019 list of the top 6 pathogens causing global deaths onto the relevant CDC categories reported in CDC (2019a). The overlap is not exact, for example ESBL-producing Enterobacteriaceae includes more than Escherichia coli. However, it is a good approximation.

Several points are apparent:

- For 3 of the 5 pathogens for which comparable data is reported by the CDC, both cases and deaths in 2019 are lower than in 2013;
- Death rates for 4 out of the 5 pathogens for which comparable data is reported by the CDC are lower in 2019 than in 2013; and

- Overall deaths in 2019 for the 6 pathogens total 27,800. This is 79% of the total AMR deaths of 35,000 estimated by the CDC for 2019. This is higher than, but similar to, the ARC 2019 estimate of 73% of AMR deaths globally that can be attributed to these 6 pathogens.

TABLE A1. Comparison of CDC cases and deaths 2019 v. 2013 for selected resistant germs

Resistant Germ	2019 Cases	2019 Deaths	2013 Cases	2013 Deaths	2019 Death Rate (%)	2013 Death Rate (%)
ESBL-producing Enterobacteriaceae	197,400	9,100	131,900	6,300	4.61	4.78
Carbapenem-resistant Enterobacteriaceae	13,100	1,100	11,800	1,000	7.63	8.47
Carbapenem-resistant Acinetobacter	8,500	700	11,700	1,000	8.24	8.55
Multidrug-resistant Pseudomonas aeruginosa	32,600	2,700	46,000	3,900	8.28	8.47
Methicillin-resistant Staphylococcus aureus	323,700	10,600	401,000	13,600	3.27	3.34
Subtotal of comparable cases 2019 v 2013	**575,300**	**24,200**	**602,000**	**25,800**	**4.21**	**4.28**
Drug-resistant Streptococcus pneumoniae	900,000	3,600	N/A	N/A	0.40	N/A
Total		**27,800**				

Hospital and other health system costs of resistance—US studies

As we noted, a US study, funded by the Infectious Diseases Society of America, (IDSA) and The Pew Charitable Trusts, Nelson et al. (2021a), estimated the burden of resistant infections on patients 65 years and over, among the U.S. Medicare population in the Veteran Affairs healthcare system over 12 years (2007–2018 inclusive) in a retrospective observational study with 87,509 patients with infections and 835,048 matched controls. They estimated the burden of six multidrug-resistant infections (methicillin-resistant Staphylococcus aureus (MRSA); extended-spectrum cephalosporin resistance in Enterobacteriaceae suggestive of extended spectrum â-lactamase (ESBL) production, vancomycin-resistant Enterococcus (VRE), carbapenem-resistant (CR) Acinetobacter species, carbapenem-resistant Enterobacteriaceae (CRE), or multidrug-resistant (MDR) Pseudomonas aeruginosa).

The results showed increased costs per patient for invasive hospital onset infection ranging from $22,293 for MRSA to $57,390 for CR, and attributable mortality ranging from 14.2% (MRSA) (1 in 7) to 24.1% for CR (1 in 4) and additional in-patient days for invasive hospital onset infections ranging from 2.33 for MDR to 4.43 for CRE. They then used these estimates to derive aggregate impact for the US Medicare population of both community onset and hospital onset infections. They estimate 11 852 (8719–14 985) AMR deaths in 2017. There were 58.4m Medicare patients in 2017, giving a death rate of 20.3 per 100,000. They estimate a total of 448,223 extra hospital in-patient days, costing $1,885m.

The authors argue that these estimates are consistent with the CDC's estimates (CDC, 2019). The CDC estimate 35,000 people died in the US in 2019 from antibiotic resistant infections. In a related paper Nelson et al. (2021b) the authors used Veteran Affairs data for a shorter period (2007–2015) than in Nelson et al. (2021a), multiplying it by the numbers of cases of these infections in a cohort of 722 US hospitals from 2017 published by Jernigan et al. (2021) to produce an estimate of total, population level health care costs in the US attributable to these six bacteria resistant infections. The health costs per case for invasive hospital onset infection range from $30,998 for MRSA to $74,306 for CR. Total 2017 national health care costs were estimated at $4.6 billion. Total health care expenditure was $3.5 trillion, making these costs 0.13% of total health care costs.

We can note that the CDC also argues that deaths are decreasing. It revises its 2013 estimate of 23,000 deaths upwards to 44,000. The conclusion of the CDC is that its estimate of 35,000 deaths in 2019 means a fall of 18 per cent. In a related study already referred to, Jernigan et al. (2021) found that incidence of antibiotic resistant infections fell for four of the six pathogens they tracked, through a cohort of 890 hospitals during the period 2012–2017 accounting for 41.6 million hospitalisations.

We note that the Nelson et al. (2021a) study uses multistate modelling to minimise time dependent bias. Wozniak et al. (2019) argue that "in our systematic review, we only identified two studies that used multi-state modelling to fully adjust for the time-varying nature of infection and consider this the recommended method which would generate the most unbiased estimates of cost of AMR. This would suggest the large majority of current costing studies are generating longer LOS estimates leading to an inflated estimate of the cost of AMR." One of these studies is for the US (Neidell et al., 2012). It reports on six antibiotic resistant pathogens acquired by 5,699 patients in four Manhattan hospitals between 2006 and 2008 finding additional health care costs were $15,626 per patient for hospital acquired infection and $25,573 for community acquired infection. Additional length of stay was 3.4 days for community acquired infection.

The US studies are robust and provide evidence that can be included in our analysis.

Hospital and other health system costs of resistance—non-US studies

The Council of Canadian Academies, (2019) estimated that 1 in 10 of hospitalised Canadians in 2018 acquired infections. The average cost of a resistant bacterial infection in hospital was estimated to be CAD$18,000 ($13,850). The report sets out the heterogeneity of costs across different types of resistant infections, reporting similar patterns in other countries, including the US studies reported above. They estimate that resistant bacterial infections cost Canadian hospitals CAN$1.4 billion ($1.1 billion) in 2018, about 0.6% of health care spending, more than 4 times the US estimate.

The study estimated economic losses arising from the mortality and morbidity due to resistant infections reduced Canada's GDP by $2.0 billion in 2018, about 0.13% of real (inflation-adjusted)

GDP. It uses a Dynamic Computational General Equilibirium Model. The key assumptions are the age profiles and labour market profiles of those affected by resistant infections, and the underlying productivity of the economy. In 2050, AMR will reduce Canada's GDP by an estimated $13 billion to $21 billion per year, if resistance to first-line antimicrobials remains constant at 26% or continues to rise to 40%, respectively. The Canadian economy will be 0.5 to 0.7% smaller in 2050 than otherwise.

The OECD study by Cechinni et al. (2015) attempts to estimate the impact of AMR on working age populations in order to generate an economic impact. At current resistance rates they estimate an annual GDP loss of −0.03% in 2020; −0.07 in 2030; and −0.16% in 2050, with a cumulative GDP loss of −$2.9 trillion. However, the modelling assumptions and data sources are not explained.

Appendix B. Push and pull mechanisms in the context of AMR

Pull mechanisms proposed

We can distinguish "push funding" which seeks to reduce R&D costs and/or increase the likelihood of a successful development, from "pull funding" which offers revenue in some form if a project is successful and normal "market forces" are not sufficient to get the innovation needed.

There are a number of "push" incentives and initiatives have been proposed and/or are being funded for new antibiotics. These include CARBX and the AMR Action Fund. These are important, in the sense that they enable R&D to continue, and they make important contributions to developing the science. Push funding also has a political attraction to governments as projects can immediately be pointed to, and there is a cap on the financial contribution. However, pull mechanisms are needed to complement them (Rex and Outterson, 2021). Without market demand, which will need to be created via a pull mechanism, these initiatives will not produce a single new "marketed" antibiotic.

Discussion of pull mechanisms for new drugs and vaccines began in the context of global health. With the Rockefeller Foundation and, more substantially, the Bill and Melinda Gates Foundation (BMGF), funding push initiatives in the form of Product Development Partnerships in areas such as TB, malaria and HIV/AIDS, interest grew in complementary pull incentives, notably in publications by Kremer and Glennerster (2004), the Center for Global Development (Levine et al., 2005), and working papers written for the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH, 2006). As a result, various pull incentives have been put in place in global health, notably the Advance Market Commitment (AMC) (Kremer et al., 2020).

More recently, a number of pull incentives have been proposed for antibiotics, which seek to introduce "pull" whilst addressing delinkage of reward from volume sales. The main proposals are:

- Prizes. The O'Neill Review (O'Neill, 2016) proposed Market Entry Rewards (MERs) which were essentially prizes for bringing a new antibiotic to market, i.e. achieving registration. The Review envisaged rewards of around $1.5bn per new molecular entity. This sum was designed to cover R&D costs with a one-off lump sum payment. The implication was that the product would then be supplied at cost price. Outterson (2021a) concludes from a detailed analysis that $3.1 billion is the best estimate of the size needed for a fully delinked MER. Prizes have also been proposed in global health, notably in the Health Impact Fund proposal (Hollis and Pogge, 2008), which is a form a voluntary patent buy-out, with the prize linked to the value of the new drug or vaccine.
- Transferable Intellectual Property Rights (TIPR), also known as "Wildcard patents", Transferable Exclusivity Extensions (TEEs) or Transferable Exclusivity Vouchers (TEVs). These work by transferring to the successful developer of an antibiotic a transferable

sellable voucher of some form which enables the recipient to extent patent protection on a different product for a specified period (Ferraro et al., 2017). If the developer can sell these to the highest bidder, then they have a valuable asset, given the monthly value of sales and profits of best-selling drugs in major markets such as the USA. However, there are two major disadvantages. The first is that sales are highly skewed. Any fixed period of TIPR is going to give some products very high rewards in order to ensure a reasonable reward (i.e. one that will cover average R&D costs) at the margin. Secondly, the generic / biosimilar industry is going to object to any mechanism which can delay plans for entry into the market;[22] there are also costs to the government and broader public of keeping drug prices high past the counterfactual point of patent expiry.

- Priority Review Voucher (PRV). This instrument can be sold and enables the holder to seek a priority review from the FDA for their drug "with a targeted review time of 6 months, rather than the 10-month standard review" GAO (2020b). It was introduced initially for companies obtaining FDA approval for drugs tackling Tropical Diseases to provide them with a means of getting additional revenue from selling a PRV. Subsequently, Congress extended the award of a PRV to two additional categories of drug.[23] The GAO found "From fiscal year 2009, when the first PRV was awarded, through fiscal year 2019, FDA awarded 31 PRVs, mostly for drugs to treat rare paediatric diseases ... 17 were sold to another drug sponsor for prices ranging from about $67 million to $350 million".[24] However, the four-month ceiling and the need to apply it to drugs not getting priority review status or breakthrough designation limits its value.[25]
- "Netflix-style" subscription models that delink payment for the drug from the volume of sales. These were initially introduced for Direct Acting Antivirals (DAAs) to treat Hepatitis C in Louisiana (Trusheim et al. 2018) and in Australia (Moon et al., 2019). The payment to the manufacturer (the subscription) was fixed and separate from volumes used. The intent was to enable payers to target the high prevalence of patients and move towards disease eradication. We can note that the benefit of subscription is to enable the payer to have *high* volume use independently of the payment to the manufacturer. Adaptation of this model to antibiotics involves using delinkage to reward developers because product use is low.

22 Both of these difficulties can in principle be addressed. The first by putting a "cap and collar" on the TIPR, i.e. setting the period of extended patent life by reference to an anchor sum and the average sales of the product to which it will be applied. The second, by requiring a notice period that rules out products that are very close to patent expiry.

23 "Rare pediatric diseases, such as Duchenne muscular dystrophy and certain types of cystic fibrosis, are serious and life-threatening diseases where the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years [and] Medical countermeasures include[ing] drugs and vaccines that can diagnose, prevent, protect from, or treat the effects of exposure to emerging infectious diseases, such as pandemic influenza, and to chemical, biological, radiological, or nuclear agents." (GAO 2020).

24 According to the GAO "As of September 30, 2019, available data show that drug sponsors had redeemed 16 of the 31 PRVs to obtain a shorter FDA review time for drugs to treat conditions and diseases such as human immunodeficiency virus (HIV), type 2 diabetes, and different forms of arthritis. These drug applications may not otherwise qualify for priority review."

25 The proposal was deemed a non-starter in Europe as there were no discernible differences in approval times.

Examples of Netflix-style subscription models

In the UK, NICE and NHS England have a program to implement a delinked payment-based system with two antibiotics (NICE, 2020). The results were announced in April 2022 (FT available at https://www.ft.com/content/c7cbebe4-8597-4340-8c55-56c4b423c1d1) An assessment of the 20 year value of these drugs was made by NICE including the "STEDI" elements of value that are important to assessing the value of new antibiotics. The NHS had offered to pay the maximum of the value identified or £10m per annum, whichever was the lower. In the event, NICE found the value of each drug to exceed £10m per annum. The FT reports that "Under the deal being struck by the NHS with Pfizer of the US and Shionogi of Japan, the drug companies will be paid a fixed fee of £10m a year." This is initially for a period of 3 years, renewable for up to 10 years. The figure of £10m "was set at a level that would give international companies an incentive to invest in antibiotic research and development, if other countries pay proportionate sums scaled to their gross domestic product." If the UK has [2.5%] of the relevant global market, this implied an overall global revenue of [$4bn] over 10 years.

We can note, however, that the assessment report prepared for NICE struggled to value the STEDI elements of value. In its reviews of both Cefiderocol, (NICE 2022a) and Ceftazidime with avibactam (NICE 2022b) the NICE Appraisal Committee accepted that the products were unlikely to offer spectrum or transmission value but found that the modelled results presented by its advisors did not fully capture the three other STEDI elements, enablement value, diversity value, and insurance value. The Committee also found that the modelled results had too low a population estimate in both cases. The Committee increased the estimate of population benefit to take account of both the uncaptured value three of the STEDI elements and a low estimate of likely patient numbers. This indicates that more work is required before the HTA-led value-based approach can be relied upon as a global model.[26,27]

In Sweden, there is a lump sum payment model pilot. This was set up following a report by the Swedish Public Health Agency and the TLV (the Swedish equivalent of NICE; Availability of antibiotics (folkhalsomyndigheten.se)). Five antibiotics are included in the pilot study.

Guaranteed annual minimum compensation of SEK 4,000,000 ($420,000) / year during the agreement period is offered. The scheme runs until the end of 2022 (Available at: https://www.folkhalsomyndigheten.se/contentassets/c09fd6d5d42243e097be216767686c08/questions_answers_agreements_signed_pilot_study_new_reimbursement_model.pdf). Note that the basis for

26 For further discussion of the challenges of estimating STEDI values, and work done so far see Morton et al. (2019); Gordon et al. (2020); Wilsden et al. (2022); Rothery et al. (2018); Neri et al. (2019) and Karlsberg Schaffer et al. (2017).

27 The UK exercise has been widely regarded as a success, albeit with lessons to be learned. One commentary, however, (Glover R.E. et al. 2022) criticised the model as supporting the antibiotic pipelines of large pharmaceutical companies rather than supporting "a resilient, innovative, commercial antibiotic ecosystem". These comments seem rather bizarre given the clarity of the selection criteria and the value-based population health approach to determining the size of the payments, with reassessment after three-years based on data collection.

the Swedish scheme is not reimbursement for R&D, but to keep products available in Sweden. It is thus intended to provide for a minimum level of revenue to do this. In exchange, the companies are required to have stockpiled that drug, so it is available for use in case of an outbreak of AMR.

The PASTEUR (Pioneering Antimicrobial Subscriptions To End Upsurging Resistance) Act in the US has been reintroduced in the US Congress, and has the following subscription model features[28] (for context see Outterson and Rex, 2020[29]). The key concepts are:

1. At IND (or a later time of the sponsor's choosing), the innovator can request designation as a Critical Need Antibiotic based on anticipated product properties. By this, investors will know precisely the potential value of the post-approval subscription contract from the US that will automatically be granted if the project receives FDA approval.
2. The value will be in the range $750m to $3bn based on the product attributes that are actually achieved.[30] This will be paid out over a period of up to 10 years or through the exclusivity period. In return, patients covered by federal insurance programs will receive these drugs at no cost.
3. Smaller transitional awards can be made while the system is being set up.
4. Hospitals get financial support to improve diagnostics and stewardship.
5. A $6bn fund is created to pay for the first wave of these antibiotics, i.e. over the first 10 years; a rolling review process is implied by the Act.

US pull mechanisms which do not require new primary legislation

Kosiak and Silverman (2021) set out a number of alternative "pull mechanisms" in a US context which do not require new primary legislation:

- Prizes can be offered by US federal government agencies under the America COMPETES Reauthorization Act of 2010. Prizes in excess of $1m need approval from the agency head, prizes in excess of $50m can only be offered after 30 days' notice to Congress. Some agencies have powers that pre-date this legislation. Use remains limited, with 125 awards totalling $69m in 2018. They argue that prizes have been seen as *complements* to push funding rather than *substitutes* and that organising an effective prize competition is complex. They also note the *opportunity cost* problem. The full cost of a Federal program has to be counted (scored) upfront when a legally binding commitment is made. This means the money cannot

28 For a six page summary see https://www.bennet.senate.gov/public/_cache/files/8/e/8e9d28e7-fb4f-4068-a5cf-748a97ae5059/542730D46434BBABF910C1C765BD2E30.pasteur-act-2021---section-by-section-061421.pdf

29 PASTEUR builds on a proposal by the Duke Margolis Center (Schneider et al. 2020) Delinking US Antibiotic Payments through a Subscription Model in Medicare.

30 We note that Rex and Outterson (2016) proposed "a payment model using a graded array of benchmarked rewards designed to encourage the development of antibiotics with the greatest societal value." It may well be that a points-based system based on this approach would be used to decide where in the $750m–$3bn payments for a particular antibiotic should lie.

be used for any other purpose, even if there is a significant chance the prize will never be awarded. If the prize is not awarded by the expiry of the appropriation, then the funds return to the Treasury.

- "Milestone Payments", like prizes, require a pre-specified goal to have been reached. However, these are usually linked to specific participants, and there is a series of payment linked goals leading up to the final objective. In 1958 Congress gave NASA "Other Transaction Authority" (OTA) for "advanced research projects". In 1989 this was extended to DARPA, and subsequently to other departments and agencies including HHS. 2020 legislation (Pilot Program on Strengthening the Defense Industrial and Innovation Base) encouraged greater use of OTAs. The most well known use is NASA's Space Act OTA with Space X which led to the Falcon 9 space launch vehicle. The Federal Acquisitions Regulations (FAR) also allow the use of performance payments, but on fixed price contracts and not, primarily, to enhance innovation. The trend of OTAs has been upwards, the DoD gave 94 in 2017 with obligations totalling $2.1bn by the end of that period.
- AMCs. There are three different sources of federal authority for AMCs:
    - Project BioShield, managed by the Biomedical Advanced Research and Development Authority (BARDA), permits the DHHS to purchase CBRN countermeasures, such as diagnostic tests, drugs and vaccines up to 8 years before completion. Milestone payments can be used for up to half of the award. Individual awards have ranged from $1m to $900m.
    - The Lantos Hyde Global Leadership Against HIV/AIDS, TB and Malaria Reauthorisation Act of 2008 allows negotiation of participation in AMCs with legally binding contracts to purchase vaccines to combat these and other, related, infections.
    - The Defense Production Act 1950 permits purchase commitments to enhance domestic preparedness and recovery from national emergencies.
    - Additionally Operation Warp Speed involved the negotiation of advance purchase contracts as well as the provision of push funding. The purpose of Operation Warp Speed was to coordinate HHS-wide efforts, including the NIH ACTIV partnership for vaccine and therapeutic development, the NIH RADx initiative for diagnostic development, and work by BARDA. Operation Warp Speed used BARDA as the financial interface between the U.S. federal government and the biomedical industry. The program was initially being funded with $10 billion, with additional funds allocated through BARDA. Funding was increased to about $18 billion by October 2020. However, Operation Warp Speed did receive substantial additional funding through primary Congressional legislation as part of comprehensive legislation to tackle the Covid 19 pandemic.

AMCs, to work, need large costly purchase commitments and, of course, the money may never be spent. This increases the opportunity cost/scoring problem. "No year" funding (no expiry date) helps with one of the problems. Having a "credit score" or likelihood of success to pro rate the value of the

prize would also help. Having a third party contract to provide the AMC, with the risk that the Federal government did not honour its commitment, is another route.

Finally, they point out, the US government could issue target product profiles, indicating an intent to purchase, appropriations permitting, if the profile were met. The DoD does this.

A recent GAO report (GAO, 2020a) outlined examples of agency use of current powers to tackle AMR. These included:

- BARDA "push" funding of, and support for CARB-X, to a committed total of $250m. CARB-X supports pre-clinical and Phase 1 research, and the development of new diagnostic tests;
- The DOD has used Other Transaction Authority to fund three projects for developing tests, and $271m for research on new treatments;
- BARDA has allocated "push" funding of $959m to developers of 24 antibiotic drugs since 2010; and
- NIH funds research for both tests and treatments.

The GAO also proposed the use of post-launch financial incentives, noting that "push" alone would not work. It identified four options: a lump sum MER; TIPRs; a subscription model; and add-on payments to hospitals outside of DRGs. However, the GAO also noted that CMS has already introduced top-up payments for new antibiotics, but with limited effect.

Three recent reviews of pull options in the context of incentives for new antibiotics confirm the assessment of the GAO and of our earlier analysis, that MERs, TIPR/TEEs, and subscription models are the most viable options. Brennan et al. (2022) argue that introducing the PASTEUR Act or an equivalent revenue guaranteeing program will stimulate new creative financing mechanisms to provide capital for small companies. BCG (2022) assess the various models (Exhibit 10 p15,) concluding that the subscription model is the strongest option, a conclusion shared by Dutescu and Hillier (2021) following their extensive literature review.

Appendix C. Estimating the cost, value and return on investment of a pull mechanism for new antibiotics

1. How many new antimicrobials do we need?

There is no agreed number of new drugs required or analysis as to how that number might be calculated. The estimate in the O'Neill Report (2016) is for 15 new drugs required in a decade, i.e. 1.5 new drugs per annum. The IDSA proposal (2010) is for "10 by 20", i.e. ten new drugs in a decade. However, it may be that this reflects a view that some "front-loading" is required, i.e. more initial activity is needed in order to get the resistance challenge under control.

In our calculations we make the following assumptions:

- We need three new drugs for each of the six priority pathogens, i.e. 18 new drugs. This is intended to ensure that there are multiple treatment options available for each priority pathogen and to defray the design risk from a pull mechanism that would pick only one winner. That translates to an expected value of 6 new antibiotic launches each decade. As there is no consensus view on this in the literature, this is necessarily an arbitrary but broadly reasonable program ambition. This estimate may be too low. The O'Neill report argued for 15 drugs in 10 years (1.5 new drugs per annum) and we could target new drugs for each of the 20 pathogen-drug combinations in the Priority List in Appendix A. There also may be a case for "front-loading", i.e. having more new drugs in the first decade, to make up for lack of investment, before reverting to a lower but sustained number for subsequent decades.
- Drug efficacy will last for 30 years before the build-up of resistance substantially erodes their clinical value. We assume a decline in efficacy against resistant infections of 2% per annum once the drug is actively being used. After 30 years, efficacy will have fallen by 45%;[31]
- This suggests a target of 0.6 new antibacterial drugs launches per year.[32]

It may be that 3 new drugs are not needed for each priority pathogen, but it is not feasible to create a pull mechanism with only one winner. Moreover, there are many other drug-pathogen resistant combinations highlighted by the ARC, (2022) and by the CDC (2019a) which are likely to increase in importance over time. A sustainable path of at least 0.6 expected new drugs per annum is likely to be needed.

31 We can note analysis by BCG (BCG, 2022) which the average time to first identified resistance is now only 2–3 years. Outterson (2021) uses an assumption of a 20-year life for new antibiotics, taken from Sertkaya et al. (2014). This would imply a much higher rate of decline in efficacy than we have assumed. For example, a 5% pa decline would reduce efficacy by 64% after 20 years. An alternative way of approaching this is to make assumptions about the proportion of cases that have resistance to the new drug. If this grows by 2% pa then after 30 years, 82% of cases will be resistant to the new drug. It is not clear to us which approach is appropriate, nor at what threshold of reduced efficacy a drug becomes of little clinical value.

32 An alternative approach could target three drugs for each of the 20 pathogen-drug combinations in the Priority List in Appendix A. This could imply a need for 60 new drugs—a much higher target launch rate of 2 per annum.

Our modelling uses expected values—that is, our most likely estimated outcomes, equivalent to the mean in a normal distribution. The incentive is therefore based on the assumption that we want an *expected* 0.6 new drugs per annum, i.e. a 50% chance that this will occur. If we wanted, for example, a 90% likelihood of *at least* 0.6 new drugs per annum, we would have to target a far higher expected number per annum, which would increase the expected cost of the pull incentive. We return to this point when we discuss the value of insurance.

2. The cost of a financing one new antimicrobial via "pull" mechanisms

A recent paper by Outterson (2021a) sets out an estimate of the needed size of a pull mechanism per drug based on the expected cost of drug development. He cites four previous estimates of the size of "pull" required (O'Neill 2015; Stern et al. 2017; Sertkaya et al. 2014; Årdal et al. 2018). Outterson argues that evidence indicates that these estimates were optimistic about costs, required rates of return and success rates, as well as making, arguably unrealistic, assumptions about push and/ or other sources of funding that reduced the necessary size of a "pull" payment. His numbers are higher than these numbers.

In the Supplementary Material to his paper, Outterson (2021b) sets out his estimates for each stage of drug development based on an extensive review of the literature on R&D cost for both antibiotics and for drugs more generally. One of the papers it references extensively is Towse et al. (2017) which also estimates both the cost of R&D and the size of the pull requirement per drug. The central estimate results from both of these papers are set out below:

- Outterson (2021a) models both a one-off Market Entry Reward (MER) and a 10-year subscription model using $2021. The required value of a one-off global market entry reward, but with the company keeping all subsequent sales revenue (a partially de-linked MER) is $2.2bn (with a range of $1.5bn to $4.8bn), and the total value of a fully delinked 10-year subscription model is $4.2bn (with a range of $3.3bn to $8.9bn). These are based on assumptions of: out of pocket costs of $447m; development time from IND to FDA approval of 96 months (8 years); clinical failure rates require 6 drugs to enter Phase 1 to get 1 FDA approval; the pre-clinical probability of success was 17%; a 10% required rate of return; 27% sales and administrative expenses (17% for an MEA); and cost of goods sold of 25%.
- Towse et al. (2017) models both a base case scenario and a 10-year subscription model using $2011. We can adapt the base case to give an estimated MER of $2.0bn,[33] and the total value of a 10-year subscription model is $3.1bn.[34] These are based on assumptions of: out of pocket costs of $354m; development time from IND to FDA approval of 6.8 years, with additional pre-clinical duration of 5 years; clinical failure rates requiring 5 drugs to enter Phase 1 to

33 We do this by taking the global capitalised cost at launch ($1581m), and adding in post launch study costs ($40m) and estimates of sales and administrative expenses and cost of goods sold from Table 9a ($430m)

34 We calculate this using the $2621m payments plus $430m of sales and administrative expenses and cost of goods sold.

get 1 FDA approval; the pre-clinical probability of success was 35%; a 10% required rate of return; 16% sales and administrative expenses; and cost of goods sold of $50 per treatment.

If we adjust the Towse et al. (2017) figures for inflation from 2011 to 2021 using the BLS CPI we would increase the amounts by approximately 20% to $2.2bn for the MER and $3.7bn for the subscription. These are comparable to Outterson, which has a lower bound of $3.3bn for the fully delinked subscription model. Both models assume no "push" funding. Given the similarity of these figures and the more recent timing of the analysis underpinning the Outterson (2021) numbers, we use these as our guide to estimate costs and returns on investment. Specifically, we use the Outterson (2021) estimate of $4.2bn discounted 10-year global subscription revenues per drug adjusted for inflation, which gives us a figure of $4.5bn

We also ignore any differential in payment to reflect the quality of the antibiotic, on the assumption that, on average, the cost is $4.5bn.

3. Estimating the total revenue requirements for a pull mechanism

If we combine our estimate of 18 drugs required over 30 years or 0.6 new drugs per annum, with the figure of $4.5bn global subscription revenues per drug, then we end up an estimate of $2.7bn per annum. We assume that the US share of this financing will be proportionate to its current share of GDP among the G7 + European Union countries—46%—with the remainder paid by other countries. The US share, at 46%, would sum to an estimate of $1.24 billion per annum when the program was in "steady state" i.e., delivering 0.6 new drugs per annum. This annual payment would account for 0.8% of US government spending on pharmaceuticals in 2019, and 0.3% of total US expenditure (public and private) on pharmaceuticals.[35]

4. Estimating the return on investment for this pull portfolio[36]

An ROI calculation is complicated for several reasons. (Note that we are not calculating the impact of individual new drugs, but estimating the impact of new drugs on the burden of antibiotic resistant mortality and morbidity, i.e. as a reduction in the DALYs estimated by the CDC (2019a) for the US and by the ARC (2022) globally.)

35 Office of the Inspector General reports U.S. prescription drug expenditures totalled $370 billion in 2019. Spending through Department of Health and Human Services (HHS) programs accounted for 41 percent ($151 billion) of this total., available at https://oig.hhs.gov/reports-and-publications/featured-topics/drug-spending/#:~:text=According%20to%20data%20from%20the,151%20billion)%20of%20this%20total.

36 The O'Neill report (O'Neill, 2016) did not attempt to establish a rate of return on its proposals noting that "the world can avert the worst of AMR by investing three to four billion USD a year to take global action. This is tiny in comparison to the cost of inaction." The World Bank report (World Bank, 2017) estimated an investment of $9bn per annum would generate benefits in excess of costs of 31% to 88% depending on the success of the strategy and on the underlying growth and impact of AMR. However, the World Bank report allocated very little expenditure to new drugs, and much of the gain was economic rather than health related.

- **Attribution:** Would any given drug have come to market without the pull mechanism? If so, what is the additional cost (if any) of the pull mechanism, versus the compensation that would be paid by the US government and others for the same drug in the absence of an explicit advance commitment? We assume that no new drugs would come in the absence of the pull mechanism. In effect, we assume that all new drugs, including those currently in development, receive, on average, a discounted payment of $4.5bn per annum over 10 years.
- **Time Horizon and Discount Rate:** Most benefits will come far in the future; the selected time-horizon and discount rate for the analysis are thus highly consequential for the result. We assume a discount rate for costs of 3.5% and a discount rate for health effects of 1.5%. This differential reflects the need to take account of the increasing value attached to health as living standards grow (Gravelle and Smith, 2001).
- **Geographic Scope:** Total ROI depends on the geographic scope selected—does the US government only value benefits incurred within its borders? Or does it also consider health and other gains abroad? We show separate estimates for the US and for global impact.
- **Scope of Value:** As discussed above, traditional HTA approaches only consider health benefit to the patient and cost-savings to the health system. ROI calculations will depend on which of the STEDI benefits (if any) are considered, and how they are valued. We discuss obtaining STEDI values below. However, we show results without elements of the STEDI values.
- **Risk Aversion:** One of the STEDI elements is the value of insurance. Are we choosing to target an expected value of (say) 18 drugs, or to target a high probability (e.g. 90% or higher) of generating *at least* 18 drugs? We have used expected value, but arguably society should be seeking greater confidence that new drugs will be forthcoming. We discuss include this element in the STEDI estimates.
- **The STEDI estimates:**
    - **Spectrum Value:** A new narrow spectrum drug will help to reduce the build-up of resistance as compared to an equally effective broad-spectrum antibiotic. It is thus worth more in terms of preserving activity for longer. However, it is not possible for us to factor this into our calculations at an aggregate level, and thus we underestimate the benefits. We can note that the benefits could come in terms of more DALYs averted or in a reduced need for new drugs if activity is preserved for longer.
    - **Transmission Value:** In individual HTA assessments this needs to be modelled using a dynamic transmission model. The modelling is similar to that undertaken in models estimating vaccine effectiveness, where the build-up of "herd immunity" is an important benefit of the vaccine. In our case, the reduced DALY burdens we are estimating will include deaths from the transmission of infection.
    - **Enablement Value:** This element is very important. Smith and Coast (2013) first raised this issue, giving the example of hip replacements. They estimated the non-availability of effective antibiotic prophylaxis as increasing post-operative infection rates to 40–50% with 30% of those infected dying. With a 15% death rate, the willingness to undergo hip replacement would likely fall substantially adding to morbidity levels, by

reducing activity in one of the most cost-effective of current interventions. Teillant et al. (2015) estimated that between 39% and 51% of pathogens causing surgical site infections and 27% of pathogens causing infections after chemotherapy were already resistant to standard prophylactic antibiotics in the USA. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120,000 additional surgical site infections and infections after chemotherapy per year in the USA and 6300 infection-related deaths. For a 70% reduction in efficacy, deaths would increase by 15,000. Procedures at risk included caesarean section, hip replacement, pacemaker implantation. appendectomy and cancer chemotherapy for leukaemia, lymphoma and myeloma. The CDC (2019a) set out interventions that may no longer possible including caesarean sections: 1.2m US women in 2017; organ transplants: 35,000 performed in the US in 2016; dialysis: more than 500,000 US patients in 2016; and cancer care: 650,000 US people receiving outpatient chemotherapy in 2016.

- **Diversity:** Depending on the strategy used to maximise the value to be got from the new antibiotic, its use now (as opposed to being saved as a last line treatment for MDR patients) is likely to preserve the activity of existing antibiotics for longer as they will be used less. This potential effect is similar to that of the spectrum effect set out above, except that the benefits come from longer use of existing antibiotics, rather than of the new antibiotic.
- **Insurance value:** There are two potential elements to this. Firstly, the most effective use of a new antibiotic may be to save it as a last line treatment. The value of this is greater than the expected number of lives saved/morbidity averted from when it is used. We can think of this as "option value"—we have something in the glass case, and we can break it open in the case of an emergency. Having a treatment available, even if it is not used or used infrequently, has substantial value. This value is greater than the value calculated using expected uncertainty models (which use assumptions about the expected number of lives saved by having the option) if the health system is risk averse on behalf of the population it serves.

  The other element of insurance value is having enough effective antibiotics in reserve in the event of a major outbreak of, or growth in, drug resistant infection. At a more mundane level this is about supply, and the scheme introduced by the Swedish government involves delinked subscription payments to manufacturers in exchange for commitments over security of supply. However, the effective antibiotics must exist. There is potential for outbreaks of resistant infection that can have a substantial impact on the health system. Resistant infections can lead to ward closures and in some cases force hospitals to suspend activity, with serious knock-on implications for the health of non- infected patients in need of other treatments and procedures. We have a variant of the effects of enablement value. The riskiness of infection is so great that the hospital is not willing to admit patients.

We can model this as a likelihood of outbreaks of this type and estimate the adverse health effects if effective antibiotics are not available. However, again, an element of risk aversion is relevant. It is not just the expected value, but the desire of the health system to avoid this situation. Fischer and Ghelardi (2016) model use of the precautionary principle as the value of insurance against adverse outcomes when self-insurance is not an option. In this case the government is risk averse and willing to pay much more to avoid a catastrophic outcome. Such an outcome may well be a build-up of resistant infection such that the ability to supply procedures and the demand for them (enablement value) are both very substantially reduced, with a very large effect on the health and wellbeing of citizens.

We have not attempted to model this effect, but it can be done so in two ways:

- The first is on the demand side estimating a risk premium. This requires an estimate of the potential size of the adverse effect and an assumption about the risk function of the government (such as Constant Absolute Risk Aversion (CARA);
- The second is on the supply side, as in what is a reasonable precautionary action and how much will it cost? In our case, the obvious precautionary activity is to invest much more (i.e. over and above expected values of needed drugs) in getting new drugs, such that the likelihood of untreatable resistant outbreaks is much reduced. Thus, in our calculations discussed earlier we are assuming a 50% chance of getting the numbers of drugs we think are needed. We may get more, or less. If we wanted, say, a 90% chance of getting at least this number of drugs, we would need to invest more, or offer subscription commitments that incentivized more investment.

- There are also several other important parameters that must be estimated or selected, each with substantial uncertainty:
  - *Average AMR deaths per year*;
  - The *average DALYs lost per AMR death*;
  - The *growth rate of resistant infection* and therefore of AMR deaths;
  - The *proportion of total AMR morbidity and mortality* that would be averted by the target portfolio of new drugs; and
  - The *knock-on effects* on health costs and on broader economic activity.

We discuss selection of these parameters in more detail. We model two different scenarios:

1) Domestic US Costs and Benefits, narrowly defined over 10 years and over 30 years;
2) Global Costs and Benefits, broadly defined, over 10 years and over 30 years.

We also carry out sensitivity analysis and report the results in the main paper.

5. Domestic US costs and benefits

We focus initially on the US. We have set out above the CDC (2019a) estimate of deaths of around 35,000 per annum from antibiotic resistance.

As we show in Table A1, the proportion of these deaths that come from six leading pathogens which would be targeted by a pull incentive is 27,800. This is around 79% (as compared to the 73% estimate in the ARC 2022 paper for global deaths). We need to translate these deaths into lost DALYs. There are three possible ways in which we can do this:

- We can use the ratios from the study by the ARC, 2022. They find 1.27m deaths equivalent to 47.6m Years of Life Lost (YLLs) and 47.9 million Disability Adjusted Life Years (DALYs). We have 37.7 QALYs lost per death. We can note that the figures for High Income Countries are 141,000 deaths, 2.39 million YLLs and 2.41 million DALYs lost, giving 17 DALYs lost per death. This reflects the higher age of patients when they get sick in high income countries.
- We can use the ratios from Cassini et al. (2019) study of deaths due to antibiotic resistant bacteria in the EU and EEA in 2015. The estimate was of 671,689 relevant infections, 33,110 attributable deaths and 874,541 DALYs. This is an average of 26.4 DALYs per attributable death. YLLs accounted for 85.3% of the DALYs lost, an average of 22.5 DALYs per death.

We use the most conservative of these estimates, the ARC, 2022 figure of 17 DALYs lost per death for the US and 37.7 DALYs for the global scenario. In a US setting, this would convert 27,800 deaths into 472,600 DALYs.

We can value a DALY on one of two bases. Firstly, the value we attach to health, in the sense of our willingness to pay for more health gain, a demand-side estimate. This has been recently estimated at $100,000 per QALY (Phelps, 2019). An alternative approach is to look at how else those health funds could be used within the health care system, i.e. supply-side opportunity cost. Vanness et al. (2021) estimated $104,000 per QALY as the cost of health foregone when people drop out of insurance when premiums increase. As these two measures give us similar numbers of $100,000 per QALY, we can ignore the question as to which basis is most relevant. We equate QALYs and DALYs for the purpose of this exercise.

So, if we assume that each DALY is worth $100,000, this gives an estimate of $1.7 million per death; we thus have a total annual lost health "value" of antibiotic resistance attributable to these six infections of $47.26 billion.

Let us assume that each new drug reduces deaths from the six infections by 5% at its peak. Thus, if we were to have 18 new drugs functioning at this level of effectiveness, then 90% of deaths from these six AMR infections would be averted. However, each new drug does not have any impact for the first four years after its launch. In year 5 it reduces infections by 5%. From year 6 onwards it loses effectiveness

at a rate of decline of 2% per annum.[37] By year 30, all of our 18 new drugs have entered the market. At year 30, the cumulative portfolio is reducing resistant bacterial infections and deaths by about 60%, although the program is continuing in order to renew the portfolio, as earlier new drugs become less effective, given our assumption of a 2% per annum reduction in efficacy as resistance builds to new drugs.

We are assuming that the rate of growth of resistance is around 2%. We assume that the annual death rate increases by 2% in the absence of new antibiotics. In the absence of new drugs, attributable deaths to our six pathogens would increase from 27,800 in year 0 to over 50,000 in year 30, a cumulative total of 1,150,000 deaths.

The program would avert 383,000 deaths over 30 years, with a benefit of 6.5 million DALYs, worth a discounted value of $471 billion.

Over a shorter 10-year period the benefits are much lower, as we are assuming that it takes 4 years post-launch before a drug is used, and the program takes time to build up momentum (after 10 years we only have six new drugs.) Around 20,000 deaths are avoided and the value of the discounted DALY benefits is $30 billion.

We assume the reduction in deaths and in morbidity also lead to reductions in health costs. Nelson et al. (2021a) estimated costs of $4.6 billion. This is $131,000 associated with each of 35,000 deaths. We can assume that a reduction in infections and deaths, consequential on each new drug, will have an effect on health care costs that is proportionate to their impact on deaths.

The discounted health costs saved are $24.0 billion over 30 years, and $2.0 billion over 10 years. We have not included an estimate of wider economic effects, in particular, of productivity effects. We have not found any reliable estimate of these effects, indeed we have not come across an age profile of those dying of, or suffering from, drug resistant bacteria. We can note the average effect of 17 DALYs averted, and life expectancy in the US of 79 years in 2019,[38] implies an average age for those dying in their early 60s[39] when the current retirement age (for social security purposes) is 66 years old. This means that the economic effects in the US may be relatively small.

The costs of the program, 0.6 drugs per annum, at a US share of $2.1 bn per drug,[40] gives a discounted 30-year total of $17.9 billion. This gives a return of ($471 billion + $24 billion)/$17.9bn, or 28 times.

37 As noted earlier, we are modelling a reduction in effectiveness of 2% per annum from year 5, which reduces effectiveness by year 35 to 55%.

38 CDC https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2020/202012.htm

39 It is not as straightforward as taking 17 away from 79 because (i) the 17 DALYs includes health loss from those who recover and do not die, and (i) people do not live in full health, i.e. 1 life year gives less than 1 DALY.

40 Note that this in principle is spread over 10 years. However, it is discounted, therefore we have included it at point of product launch.

Over a shorter 10-year period, the costs are $5.4 billion, giving a return of $30 billion + $2 billion/ $5.4 billion, or 6 times. This shows that costs are front loaded, and the benefits occur decades into the future as a sustainable program is put in place.

Global costs and benefits

The global return on investment is harder to estimate. The ARC (2022) identify "inadequate access to second-line and third-line antibiotics" as a driver of higher burden in LMICs, a point echoed by Laxminarayan (2022). The SECURE initiative has been developed by GARDP and WHO, with support from UNICEF and the Clinton Health Access Initiative (CHAI) to provide participating countries with access to both new antibiotics designed to address drug-resistant infections, but also essential older antibiotics not widely available or subject to frequent supply chain disruptions (GARDP, 2022).

We therefore assume that 25% of the deaths outside of "high income" countries could be tackled by improved supply of existing antibiotics. High income deaths are 141,000, giving 1.129m. If we assume only 75% of these need access to new antibiotics, we have 846,750, add back the 141,000 and we have a revised total of 987,750 deaths. Again, we assume the new drugs can impact the MDR infections and deaths of the 73% of infections caused by our six pathogens. This is 721,058. Again, we assume these deaths are increasing at a rate of 2% per annum. Thus, we have 30 million deaths over the 30-year period which the new drugs could impact.

We assume that our 18 drugs have clinical utility across the globe. As in the case of the US alone, we assume that each new drug reduces infections by 5% at its peak. However, each new drug does not have any impact for the first four years after its launch. In year 5 it reduces infections by 5%. From year 6 onwards it loses effectiveness due to the growth of resistance by 2% per annum. By year 30, all of our 18 drugs have entered the market. At year 30, the cumulative portfolio is reducing resistant bacterial infections and deaths by 61%, although the program is continuing, in order to renew the portfolio, as earlier new drugs become ineffective, given our assumption of a 30-year life for a drug.

The program averts 9.9 million deaths over 30 years, with a benefit of 374 million DALYs, worth $4.87 trillion. Over a shorter 10-year period the benefits are lower, as we are assuming that it takes 4 years post-launch before a drug is used, and the program takes time to build up momentum (after 10 years we only have six new drugs.) Even so, 518,000 deaths are avoided, and the value of the discounted DALY benefits is $310.6 billion.

The World Bank Report (2017) estimated global health expenditure being between $0.33 trillion and $1.2 trillion higher by 2050. We use the figure of $0.333 trillion, but assume it is reached by 2030. The ARC (2022) total numbers growing at 2% per annum would give a gross global figure of 2.30m deaths in 2030. This gives us a potential health cost saving of $0.333trillion/2.30m per death averted. This is $144,000 per death. As we find this figure implausible—and in the absence of other reliable estimates—we omit consideration of healthcare savings in our primary modelling.

The World Bank Report (2017) estimated also estimated global GDP being between $1 trillion and $3.4 trillion lower by 2050. We use the figure of $1 trillion, but assume it is reached by 2030. The ARC (2022) total numbers growing at 2% per annum would give a figure of 2.30m deaths in 2030. This gives us a potential economic loss of $1 trillion/2.30m per death averted. This is $434,780 per death. This seems high and may reflect higher assumptions about death rates than are found in the ARC study with our 2% per annum growth rates. We do not consider these figures sufficiently reliable for our modelling and have thus excluded potential economic effects from our primary calculations.

There are a number of key sensitivities in this calculation. The most important ones, for which we have least information are:

- The numbers of new drugs needed; and
- How effective the drugs would be at addressing AMR.

Other key assumptions for which we have some evidence include:

- The DALYs gained per death averted; and
- The $ value of a DALY in the US, and globally.

We have ignored, for lack of data, key aspects, including:

- The STEDI elements of value arising from avoiding the build up of AMR; and
- Whether the payer is risk averse. (As we noted above, all of these calculations assume risk neutrality. They are based on expected outcomes.)

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