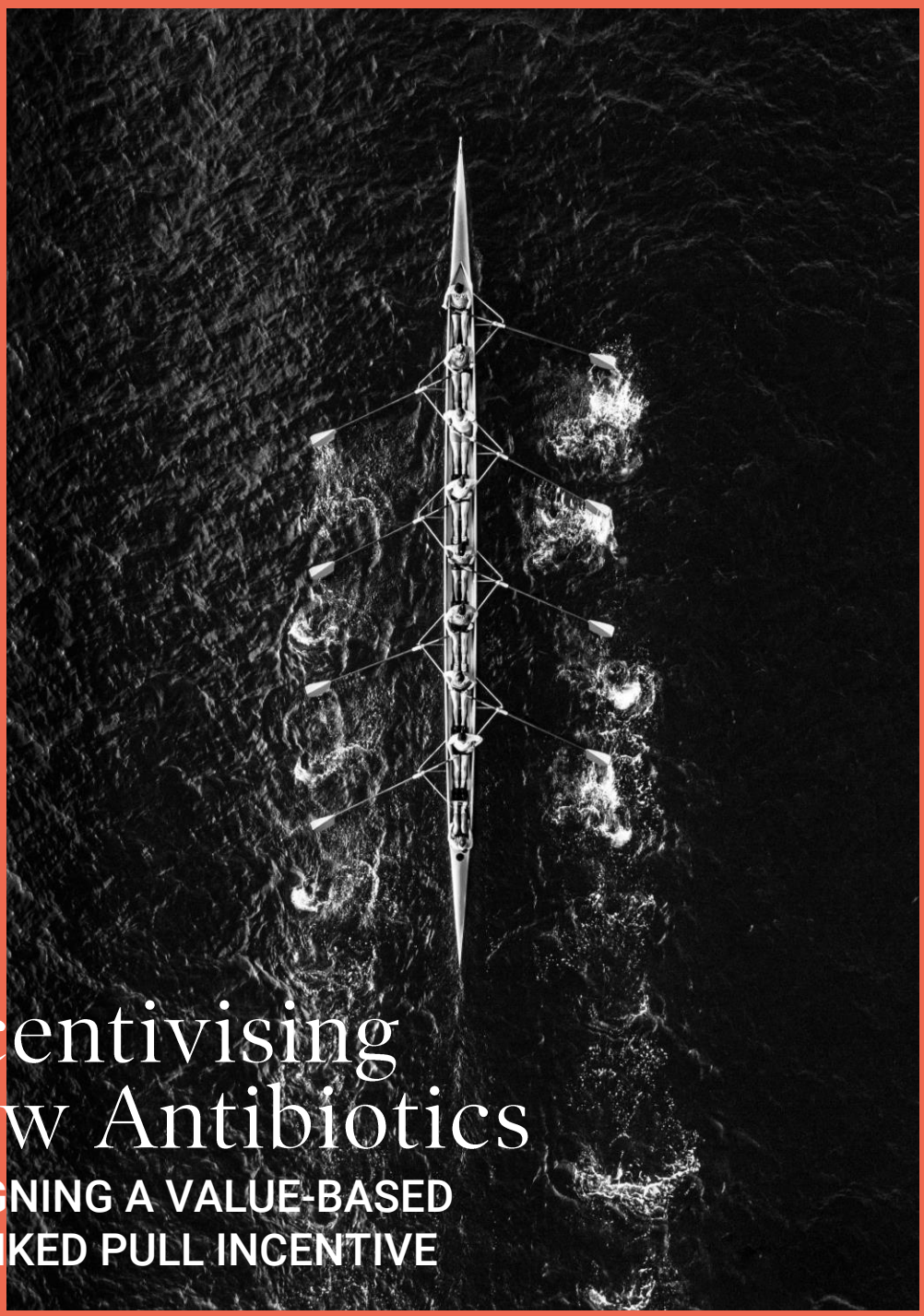
OHE



Incentivising New Antibiotics

DESIGNING A VALUE-BASED DELINKED PULL INCENTIVE

CONTRACT RESEARCH REPORT
MARCH 2023

Simon Brassel
Isobel Firth
Edward Oliver
Grace Hampson
Adrian Towse
Lotte Steuten

ohe.org

MARCH 2023

Incentivising New Antibiotics

DESIGNING A VALUE-BASED DELINKED PULL INCENTIVE

Simon Brassel
Office of Health Economics, London

Isobel Firth
PredictBy, Barcelona*

Edward Oliver
Adelphi Values, London*

Grace Hampson
Office of Health Economics, London

Adrian Towse
Office of Health Economics, London

Lotte Steuten
Office of Health Economics, London

Please cite this report as:
Brassel S., Firth I., Oliver E., Hampson G., Towse A., Steuten L. 2023. Incentivising New Antibiotics: Designing a Value-Based Delinked Pull Incentive. OHE Contract Research Report, London: Office of Health Economics. Available at: https://www.ohe.org/publications/incentivising-new-antibiotics-designing-value-based-delinked-pull-incentive-antbiotics/

Corresponding Author:
Lotte Steuten
lsteuten@ohe.org

* Isobel Firth and Edward Oliver were employees of the Office of Health Economics when performing this research.

For further information please contact:

Professor Graham Cookson
Chief Executive, OHE
Honorary Visiting Professor in Economics at City, University of London

Tel +44 (0)207 747 1408
Email gcookson@ohe.org

About OHE Consulting Reports

Many of the studies OHE Consulting performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications. Publication is at the client's discretion.

Studies published by OHE as OHE Consulting Reports are subject to internal quality assurance and undergo external review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views of OHE as an organisation.

Funding and Acknowledgements

This consulting report was commissioned and funded by The Association of the British Pharmaceutical Industry (ABPI).

Table of Contents

Executive Summary ..... **iv**

1 Introduction **1**

2 Methods **2**

3 Requirements for a global pull incentive mechanism **3**

4 Calculating the fair share of a global pull incentive for antibiotics **5**

4.1 Previous estimates of the size of a global pull incentive for an antibiotic 5

4.2 Current best estimate of the size of a global antibiotic pull incentive 6

4.2.1 Fully delinked, phase 2-ready asset, subscription over 10 years 6

4.2.2 Fully delinked, subscription over 10 years 6

4.2.3 Partially delinked, upfront payment 6

4.2.4 Assumptions of estimates 7

4.3 Which countries should share the burden of paying the global pull? 7

4.4 Experience from NHS England estimates in the England AMR Pilot 8

4.5 Scenarios for estimating a country's share of the global pull incentive 8

4.6 Recommendations for the subscription fee 9

5 Which antimicrobials should be eligible for payment through a pull mechanism? **11**

5.1 International experience 11

5.2 Areas of agreement and debate 12

5.3 Recommendations for eligibility screening 13

6 Setting the value-based subscription fee for a novel antibiotic **15**

6.1 The broader value of antibiotics and the STEDI framework 15

6.2 How a scoring system could set the subscription fee within the scheme 16

6.3 Areas of agreement and debate 18

6.4 Recommendations for value assessment 18

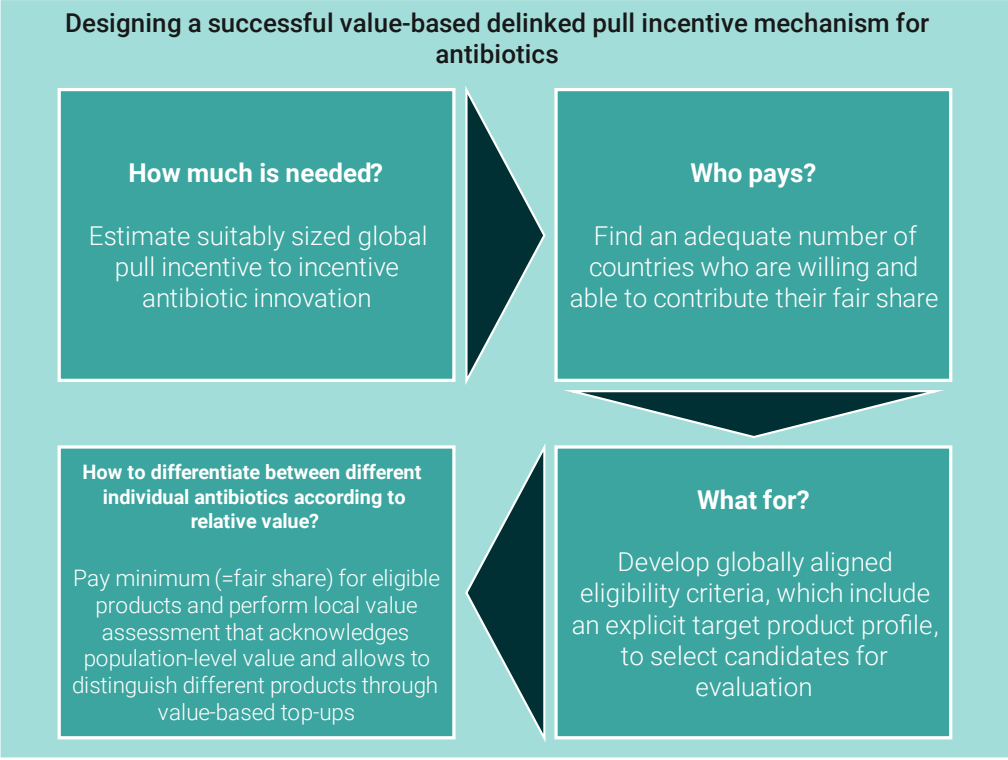
7 Conclusions **21**

8 References **22**

Executive Summary

The market of antibiotics is characterised by pervasive market failure. Currently, manufacturers cannot recoup their investments in novel antibiotics as antimicrobial stewardship limits sales volumes while generic competition drives down prices and current health technology assessment (HTA) processes fail to recognise the broader value that antibiotics may deliver. Consequently, many large pharmaceutical companies left the antibiotics space while smaller players went bankrupt. The current situation puts our society on a vulnerable trajectory of ever-growing antibiotic resistance while the effectiveness of existing antibiotics diminishes, and very few new antibiotics become available.

Multiple solutions have been proposed to fix the market failure and future-proof antibiotic innovation. One option is a globally aligned, value-based, *fully-delinked pull incentive*. Under such a mechanism, payers pay manufacturers a pre-specified subscription fee – based on the value of the antibiotic - over a pre-specified period, regardless of the volume of antibiotics used. To succeed, such a mechanism must provide a sufficiently large incentive shared by enough countries, assess and reward the most needed products and distinguish higher from lower value products (see Box 1). Important questions on how to achieve this, however, remain.



BOX 1: DESIGN ELEMENTS FOR A SUCCESSFUL VALUE-BASED DELINKED PULL INCENTIVE FOR ANTIBIOTICS

This report is based on desk research and a workshop between policymakers, payers, health economists and experts in AMR from the UK and internationally that was facilitated in November 2022. It aims to answer critical aspects of the questions outlined above.

How much is needed?

Companies make investment decisions partly based on expectations of global revenues. Therefore, the size of a global pull incentive should be calculated by aggregating revenue from all countries where the product is sold. The best estimate for a 10-year 'subscription' type payment that would cover the entire development process for a novel antibiotic asset and generate a large enough global incentive fully delinked from sales volumes is $4.2 billion (Outterson, 2021). A country's fair share towards such an incentive can be based on its relative wealth and, therefore, its ability to pay as proxied by its gross domestic product (GDP).

Who pays?

The individual contribution to the global pull incentive of a specific country depends on the number of countries that contribute. Which countries eventually will do so depends on many factors. At a minimum, these should be the seven wealthiest nations (G7) based on their GDP. However, the burden for these countries would significantly be reduced if, for example, the twenty wealthiest nations and the European Union (G20 + EU) by the size of GDP contributed.

With the NICE-NHS England Antimicrobial Resistance Pilot, the UK led the movement to fix the broken antibiotic market by example. While the maximum payment within the pilot was capped at £10M/year, the UK's fair share of an overall incentive would be around £23M/year for ten years if only the G7 countries contributed. If, however, all G20 countries (and remaining EU countries) contributed to such an incentive, the UK's fair share would be lower, around £12M/year for ten years. Therefore, it is now more urgent than ever for other countries to follow suit so that the UK's effort will be worthwhile, and the mechanism becomes financially sufficient and sustainable on a global level.

What for?

Eligible products should be selected primarily based on globally aligned criteria, including the unmet need to be addressed and a target product profile (TPP) setting out desired product characteristics and required efficacy estimates. Unmet needs should be defined using WHO priority pathogens levels and incorporate local unmet needs (if these were to be different). Following the eligibility screening process, the company and payer would enter into a contract guaranteeing the company a minimum subscription fee if the criteria and the TPP are met. In the medium to long run, the criteria can change to reflect changing unmet needs and requirements for changes in antibiotic development portfolios.

How to differentiate between different individual antibiotics according to relative value?

Value assessment must be local, and its methodology must distinguish between higher and lower-value products. The system should enable a value-based top-up based on a minimum subscription fee within a reasonable range to incentivise higher-value products. This will enable differential value to be rewarded within a subscription system intended to provide acceptable average returns on research and development (R&D) for antibiotics meeting the eligibility criteria.

The recent review by NICE has shown the complexity of doing a fully quantitative estimate of benefit (e.g., by calculating quality-adjusted life years (QALYs)) and the time and resources required. In the short run, the subscription fee for individual products could be set using a categorical, points-based scoring system.

The value of an antibiotic is, amongst other things, dependent on the use strategy. Therefore, the HTA agency and the company must define how the antibiotic will be used in the health system to maximise societal value over time so that appropriate evidence to support this broader value

assessment can be developed. The evaluation should use the STEDI value framework (incl. spectrum, transmission, enablement, diversity, and insurance value) to help capture the broader value profile of an antibiotic.

Depending on the use strategy adopted for the evaluation, some STEDI-categories are mutually exclusive or partly duplicative. Hence, any points-based system will need to use robust multi-criteria decision analysis in which duplication and mutual exclusivity are addressed. Any assessment using QALYs or points should allow for a reassessment after a period of time in which it is possible to consider additional real-world evidence on key parameters from local settings.

In the medium term (3-5 years), the methodology underlying the scoring mechanism to establish the subscription fee should be refined. In the long run (>5 years), a full population-level economic evaluation linked to QALYs incorporating an antibiotic's STEDI value should be aimed for. To achieve this, investment in research is needed in the short term to develop communities of practice around economic modelling for antibiotics with a view to generating methods and finding evidence sources that will enable population benefits to be estimated using QALY-based modelling with appropriate adjustment for risk aversion.

1 Introduction

Antibiotics, a subgroup of antimicrobials, are vital medicines. In the presence of antimicrobial resistance (AMR[1]), however, their ability to treat infections is reduced, with alarming impacts on our future health and wealth (Antimicrobial Resistance Collaborators, 2022; World Bank, 2017). Despite this bleak outlook, the current pipeline for new antibiotics is weak, with over 80% of new antibiotics belonging to existing classes where resistance is already high (WHO, 2022). This situation puts our society on a vulnerable trajectory of ever-growing antibiotic resistance while the effectiveness of existing antibiotics diminishes.

The main reason for the status quo is the pervasive market failure in antibiotics. On the supply side, antibiotic research and development carries a greater risk of failure than other pharmaceutical products because many promising compounds have high toxicity (Prasad et al., 2022). This greater risk, however, is not rewarded: expected sales volumes are likely to be low as antimicrobial stewardship practices limit the use of new products to decrease the likelihood of antimicrobial resistance to new drugs and treatment durations are generally short. At the same time, novel antibiotics face price pressure from generic competition and are often undervalued because existing HTA methodologies fail to capture their full value. The result is a lack of incentives to invest in antibiotic development under the traditional pharmaceutical innovation and reward model (O'Neill, 2014). Consequently, many large pharmaceutical companies left the antibiotics space while smaller players went bankrupt (Taylor, 2020; Bayer and Kansteiner, 2023)

Recognising the antibiotic market´s failure, both push and pull funding have been proposed to improve incentives. Push funding is given to companies by public research funds and philanthropy to support costs of R&D, whereas pull funding is promised to companies as a reward for a specified product if and when it reaches the market. Health economists have proposed a 'volume-delinked model' as a potential pull incentive to overcome the failures in the antibiotic market. The delinked model rewards successful antibiotic innovation to encourage companies to invest in antibiotic development in a way that is not linked to the volumes of antibiotics used (Clift et al., 2015; Rex and Outterson, 2016). A volume-delinked pull incentive gives companies guaranteed revenue on the market launch of a new antibiotic that would not be affected by low sales volumes. If aggregated global revenues, through pull incentives or traditional volume-linked reimbursement, are large enough, companies should be attracted to invest in antibiotic development.

Such a fully-delinked pull incentive has been coined the 'Netflix Model' as the manufacturers get paid based on a subscription fee, independently of how many antibiotics are used. For such a model to be successful, three major stages are necessary:

- It has to be established how much should be paid to reach a sufficient global pull, who should pay this (e.g., the G7 or G20) and how to determine each contributor's fair share.

- Clear eligibility criteria have to be defined for products to be selected for funding through the pull incentive.

[1] In this document we use antimicrobial resistance, or AMR, as a broad term encompassing resistance to drugs for infections caused by other microbes such as parasites (e.g. malaria), viruses (e.g. HIV), and fungi (e.g. Candida) (WHO, 2022). Although some papers referenced focus on antibiotic resistance and therefore bacteria, many of the themes are shared across the wider topic of AMR involving to antivirals and antifungals. For all technologies under the AMR-umbrella, traditional value assessments are outdated do not recognise their true value to society.

- The expected relative value of the selected antibiotics should be assessed considering their planned usage in a specific country to establish the corresponding payment level within the (range of) that country's fair share.

In 2020, England became the first country in the world to pilot a fully-delinked pull incentive for paying for antimicrobials. The National Institute for Health and Care Excellence (NICE)-NHS England AMR Pilot (the 'NICE-NHSE pilot') trialled a subscription-type model for two antibiotics for severe infections that are resistant to the last line of antibiotics (NICE, 2022). For the first time, the value assessment sought to account for the value of the antibiotics beyond the value to the individual patient to enable NICE and NHS England to tailor the subscription fee to the broader, population-level value of each antibiotic. The new methodology was an important step in recognising that the value of an antimicrobial should be considered at a population level rather than a patient level. However, there were a number of challenges to implementing the pilot, including the methodology to determine payment levels, the resources required for the value assessment process and the related high uncertainty within the value assessment process. The learnings from the NICE-NHSE pilot, however, will be helpful for future iterations in England as well as other countries looking to implement a pull incentive for antimicrobials (Leonard et al., 2023).

In this paper, we will describe the requirements for estimating a country´s fair share of the pull incentive, which antibiotics should be eligible for the pull mechanism and how to set a value-based reward. We also present key learnings from the NICE-NHSE pilot that policymakers and payers internationally should be aware of as they implement similar solutions to address the challenge of AMR. In addition, we will present our recommendations for best practices for pull incentive schemes for antimicrobials in the future based on literature research and insights from an expert workshop.

Throughout this paper, we will refer to antimicrobials to target bacteria and will not be discussing the specific requirements of antifungals and anti-virals, although the same considerations may apply in those contexts.

2 Methods

To develop this report, OHE undertook a pragmatic literature review and convened a workshop of experts to discuss principles of best practices for pull incentives for antimicrobials. Participants in the roundtable included policymakers, payers, health economists and experts in AMR from the UK and internationally. Chatham House Rules were used to encourage open discussion, and no names or affiliations will be disclosed in this report.

3 Requirements for a global pull incentive mechanism

Establishing agreed requirements for a global pull incentive is essential if the incentive is to be effective. There are, however, multiple areas of disagreement between experts on the key requirements of a successful pull incentive for antimicrobials. Some of these disagreements will require political judgement rather than evidence to solve, but they are important to articulate to increase the chance that pull incentives will achieve their stated goals.

Push and pull incentives

Push and pull incentives stimulate innovation in a particular field by changing how the innovation is funded and rewarded compared to how it would be under 'normal' market conditions. These incentives are used when there is a recognised market failure or weakness in the market and a high unmet need which together justifies intervention.

Push incentives comprise funding for development, reducing the costs of R&D for the development and include mechanisms like research funding grants and tax credits (Renwick, Brogan and Mossialos, 2014). Pull incentives instead increase future revenue by providing rewards for innovation outside of the normal market to motivate developers to invest at risk in R&D. They can be linked to explicit outcomes to increase the efficiency of the incentive. Examples include advanced market commitments, patent buyouts and prizes (Renwick, Brogan and Mossialos, 2014). There are also hybrid options that use both aspects of push and pull (Sciarretta et al., 2016).

The pull incentive model

Pull mechanisms differ in how much the reward is delinked from sales (Milken Institute, 2022). Volume-delinked options that allow for rewarding antimicrobials with low volumes include fully-delinked subscription models and partially-delinked transferable exclusivity extensions (TEEs). Subscription models function by guaranteeing the manufacturer an annual payment regardless of the actual number of doses used. Through a TEE, the antimicrobial developer is granted a right to extend the period of monopolistic patent protection on one of its other products, or it can sell the TEE to another company. The TEE, therefore, generates revenue in addition to the sales revenue of the antimicrobial (Seabury and Sood, 2017; Rome and Kesselheim, 2020; Årdal et al., 2020). Whereas the US and the UK have opted for a subscription model to pay for new antibiotics, and others have argued for this mechanism as well (Årdal, Lacotte and Ploy, 2020), the European Union (EU) is currently discussing a TEE model. However, significant pushback from member states to this model has been voiced (McDonnell, 2022; Årdal et al., 2023). As long as the aggregated rewards contribute to a large enough global incentive to stimulate investment, each country, or group of countries such as the EU, should choose their own preferred mechanism. That said, this may create additional challenges for implementation, with stakeholders needing to develop and negotiate a different approach in each country or group of countries.

The remainder of this paper will focus on a subscription mechanism and draws heavily from the specific learnings from the NICE-NHSE pilot. However, the overall insights are likely to be relevant across different types of pull incentive models.

The requirements for an effective pull incentive

In order to achieve the aim of stimulating innovation, the pull incentive has six main requirements that correspond to the three major stages mentioned above. Firstly, it needs a way to determine the minimum size of the global incentive that would be large enough to attract R&D investment.

Secondly, it needs a way to share this incentive across a reasonable group of contributor countries. Thirdly the pull incentive needs an *a priori*-defined description of what products will be rewarded, and fourthly a mechanism to assess product eligibility (i.e., whether or not it meets the *a priori* requirements). Fifth, the pull incentive needs an agreed mechanism to pay the reward defined through a contracting process, and finally, it should be able to distinguish higher from lower value products to incentive high-value innovation. The recommendations made in the rest of this report aim to contribute to the design of a pull incentive to meet these requirements.

4 Calculating the fair share of a global pull incentive for antibiotics

In general, a pull incentive is needed in cases where there is not a large enough expected market to attract private R&D investment (Kremer, 1998; Cernuschi et al., 2011; Kremer, Levin and Snyder, 2020; Towse et al., 2021). In the context of antimicrobials, estimates of the size of the incentive needed to attract private investment depend on several important assumptions.

4.1 Previous estimates of the size of a global pull incentive for an antibiotic

A number of studies have been published estimating how large a global pull incentive would need to be to support investment in new antimicrobial development. For example, Sharma and Towse (2011) attempted to estimate the reward needed from a Europe-only advanced market commitment (AMC) pull incentive for a new antibiotic to raise the net present value (NPV) of investing in a new antimicrobial from $100 million to $200 million[2]. Assuming global sales revenues are unaffected, they model that a 5 year European AMC would need to be €1.4 billion ($1.9 billion) to achieve an NPV of €150 million ($200 million) (Sharma and Towse, 2011).

The DRIVE-AB report (Ardal et al., 2018) estimated that $1 billion per novel agent would be needed globally to provide the return needed to drive innovation and would lead to an additional 18 antibacterial products over the course of three decades (when coupled with increasing push incentives, i.e., public research funding). The authors model the likelihood of an antibiotic reaching the market under various assumptions and policy interventions, assuming that expected NPV must be at least equal to a threshold which varies based on the developer. The model, however, assumes post-approval costs of only $10 million – a value considered to be a significant underestimate (Rex, 2020). By comparison, Towse et al. (2017) assume out-of-pocket costs of $354 million.

Sertkaya et al. (2014) calculated an estimate based on costs of development in which a reward of $1-1.4 billion is needed to produce an expected private NPV of $100 million on an antibiotic discovery project. They state that the $100 million used as a threshold in their analysis is the opportunity cost of engaging in R&D, although they admit the figure is arbitrary. Their results do not account for the investment needed to fund early stage discovery R&D and therefore understate the risk and cost of preclinical R&D (Outterson, 2021). They also potentially overestimate revenues as they assume the revenue of a novel antibiotic is equivalent to daptomycin, the most successful antibiotic in the past two decades (Outterson, 2021). A summary of these estimates is provided in Table 1.

TABLE 1 SUMMARY OF ESTIMATES OF THE GLOBAL PULL INCENTIVE NEEDED FOR AN ANTIBIOTIC

Cost-based estimates of the minimum pull needed to stimulate antibiotic development		
SOURCE	**NPV RETURN**	**INCENTIVE NEEDED**
Sharma and Towse, 2011	$200 million	$1.9 billion (Europe only)
DRIVE-AB report 2018	Positive	$1 billion
Sertkaya et al., 2014	$100 million	$1.0-1.2 billion
Outterson 2021	Positive	$1.5-8.9 billion

[2] They cite evidence that the NPV of investing in new antimicrobials ($100 million) is much lower than in other therapeutic areas, for example $300 million for oncology and $720 million for neuroscience.

4.2 Current best estimate of the size of a global antibiotic pull incentive

The Outterson (2021) estimates are regarded as the most up-to-date and appropriate for estimating the global pull incentive under a subscription model. Outterson conducted an exhaustive review of cost and success estimates for antibiotics (including cost estimates in Towse et al., 2017). Outterson then presents the best estimate of a cost-based pull incentive needed to generate a positive net present value for an antibiotic in a number of different scenarios. The pull incentive estimates were sensitive to assumptions of the level of development cost-sharing (i.e., push funding), expected peak year sales and the clinical and preclinical probability of success. The results are shown in Figure 1.

4.2.1 Fully delinked, phase 2-ready asset, subscription over 10 years

For a 10-year subscription payment, fully delinked from sales volumes, the appropriate pull incentive for a phase 2-ready asset is **$2.2-$4.8 billion (best estimate $3.1 billion)**. This scenario depends on the AMR Action Fund, a fund established by industry in collaboration with the World Health Organization (WHO), the European Investment Bank (EIB), and the Wellcome Trust to support assets through late-stage clinical development to market launch and aim to deliver 2-4 novel antibiotics by 2030 (AMR Action Fund, 2022). Assets at this stage have been through phase 1 but have not yet been through phase 2 or 3 studies; therefore, they are partially de-risked assets. The pull incentive in this scenario describes the return needed for the AMR Action Fund or other commercial acquirers to acquire a phase 2-ready asset for $500 million over the patent term. Over 75% of antibiotic developers are Small or Medium Sized Enterprises (SMEs), many of which have only one product (PEW, 2020). As a result, many antibiotic developers see the AMR Action Fund or another acquirer as part of their commercial pathway. Outterson judged it to be the best estimate for phase 2-ready assets.

4.2.2 Fully delinked, subscription over 10 years

For a 10-year subscription payment, fully delinked from sales volumes, for a full development process, the estimate for the appropriate pull incentive is **$3.3-$8.9 billion (best estimate $4.2 billion).** This estimate considers assets within earlier stages of development; therefore, the estimate is more representative of the whole antibiotic pipeline that a pull incentive aims to support.

4.2.3 Partially delinked, upfront payment

For a pull incentive that is based on a partially delinked market entry reward where the company will keep revenues generated by sales, Outterson's estimate is **$1.5-4.8 billion (best estimate $2.2 billion)**. In this scenario, the pull incentive will be paid on market entry, and revenues will be supplemented by sales. It is, therefore, similar to pull incentives based on market entry rewards like the Transferable Exclusivity Extensions (TEE) considered by the EU.

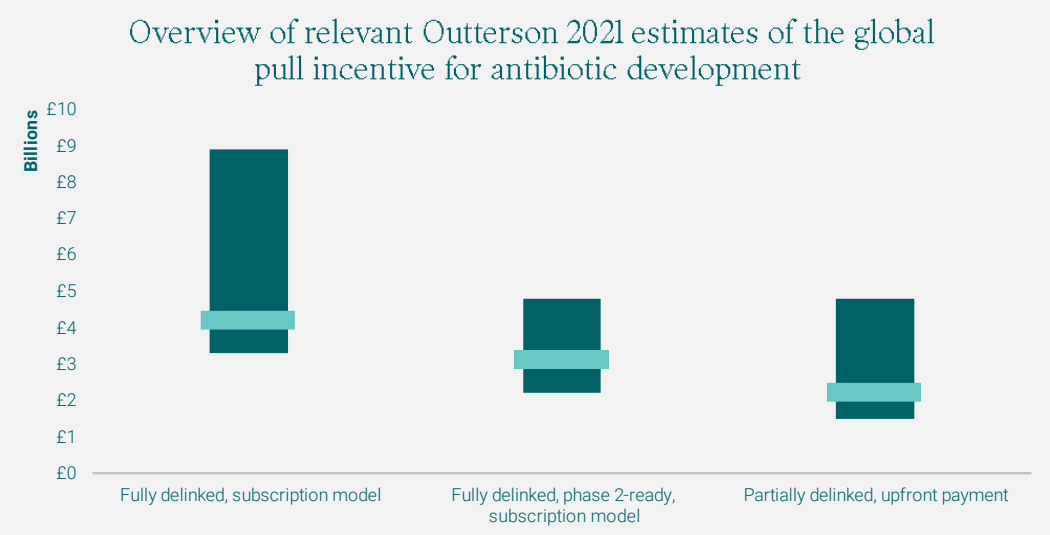


FIGURE 1 OVERVIEW OF OUTTERSON 2021 ESTIMATES OF GLOBAL PULL INCENTIVE FOR ANTIBIOTIC DEVELOPMENT.

4.2.4 Assumptions of estimates

The Outterson estimates are based on estimates of the costs of developing an antibiotic and the pull incentive needed to generate a positive NPV for companies. They are not intended to reflect the societal value of antibiotics, which previous work has shown is both highly variable across products and potentially significantly greater than the return needed to generate a positive NPV (Sertkaya et al., 2014). A cost-based estimate of a pull incentive needs to be complimented with some form of value assessment to support value-based rewards. However, the cost-based pull incentive from Outterson provides a global lower bound estimate of the size a pull incentive should be to bring a product to market. For a 10-year, fully delinked subscription model, the best estimate is $4.2 billion over 10 years globally.

4.3 Which countries should share the burden of paying the global pull?

Companies make investment decisions based on expectations of global revenues. Therefore, the size of a global pull incentive would be calculated by aggregating revenue from all countries where the product is sold.

Judgement is required to decide how the global pull incentive should be shared between individual countries, ensuring fairness and preventing free riding. The total global pull incentive could be divided between countries based on a number of metrics, including their relative need for antibiotics (i.e., resistance rates) or market share of the global antibiotics market. However, given pull incentives are targeting a global problem, the preferred method put forward in the literature for sharing the pull incentive is to use relative wealth (e.g., GDP or GDP per capita[3]). A country's ability to pay for the incentive would therefore be a key driver of its contribution to the global pull incentive rather than it

[3] *All GDP data for the estimates presented are taken from the 2021 GDP data published by the International Monetary Fund available from: World Economic Outlook Database April 2022*

being based on an estimate of current need. We follow others in proposing GDP as a reasonable metric for sharing the global pull incentive figures developed by the Outterson 2021 analysis.

4.4 Experience from NHS England estimates in the England AMR Pilot

According to NHS England and NHS Improvement (2021, p.2), the maximum payment threshold "took account of the available literature on the level of global sales that would be needed for antimicrobials to become attractive investment propositions and considered that £10,000,000 per annum per antimicrobial to be a reasonable "fair share" for England". In particular, they considered the Outterson 2021 model to estimate the fair share. However, the requirement for a contractual cap, due to the competitive selective element of the pilot, might be less needed in the future.

4.5 Scenarios for estimating a country's share of the global pull incentive

Below are two scenarios which aim to calculate the breakdown of the global pull incentive across countries by share of GDP. For the analysis, we use the best estimate ($4.2 billion over 10 years) from Outterson 2021 for the size of the global pull incentive to stimulate investment at any stage of the pipeline (i.e., including pre-phase 2-ready assets). We highlight what the UK, EU and the USA would have to pay to be covering their fair share, as these are the three countries/regions that have ongoing policy discussions on implementing a pull incentive.

The G7 share the pull incentive

The G7 has already committed to a joint agreement on AMR and made a political commitment to action (G7 Finance Ministers, 2021). In this scenario, the pull incentive would be shared between Canada, France, Germany, Italy, Japan, the UK and the United States. If all of the G7 countries committed to a pull incentive proportional to their share of the G7 GDP, the UK's share would be approximately 7.1%. Therefore, under this assumption, the UK's fair share of a pull incentive funded only by the G7 would be around £23M/year for 10 years, more than double the maximum subscription fee possible in the NICE-NHSE pilot (which was for England only). The US would need to pay $2.3 billion over 10 years, and Italy, Germany and France would have to pay a total of €940 million over 10 years. Figure 2 shows the full breakdown.

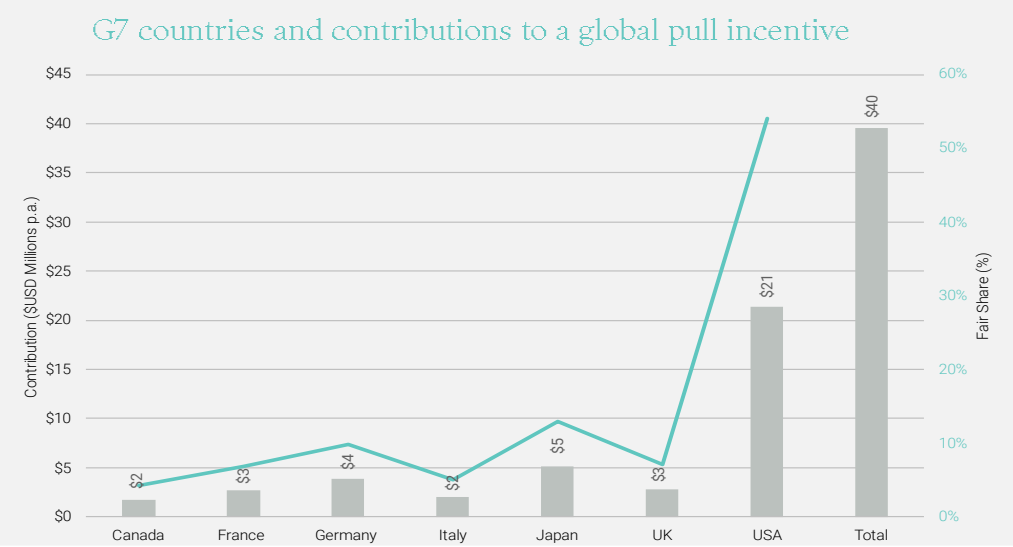


FIGURE 2 G7 COUNTRIES ANNUAL CONTRIBUTIONS TO A GLOBAL PULL INCENTIVE BASED ON THEIR SHARE OF GDP AND THE OUTTERSON (2021) ESTIMATE *SOURCE:* *WORLD ECONOMIC OUTLOOK DATABASE APRIL 2022* *NOTE:* VERTICAL BARS REPRESENT EACH COUNTRY'S INDIVIDUAL CONTRIBUTION; LINE REPRESENTS EACH COUNTRY'S SHARE IN PERCENTAGES.

G20 + EU share the pull incentive

Many assessments of the share of the global pull incentive, including that of the NICE-NHSE pilot, take the G20 as a reasonable group of countries to share the global pull incentive. Of the G20, nine are middle-income countries (including India as a lower middle-income country), two do not have national AMR action plans, and six have AMR action plans that have begun to be implemented (WHO, 2021). Given previous political commitments to fight AMR, it is very unlikely that all the G20 countries will support a global pull incentive. Assuming for now, however, that all the G20 countries and the remaining countries of the European Union would commit to a pull incentive that is proportional to their share of the total G20 GDP, the UK would be expected to pay almost 3.8% of the global total. Therefore, the UK's fair share of the global pull incentive would be £12.4M/year for 10 years. Accordingly, the US would have to pay $1.19 billion over 10 years, and the EU would have to pay €901 million over 10 years[4].

4.6 Recommendations for the subscription fee

To meet the requirements both of industry (to have a pull incentive that is large enough to stimulate investment in antibiotic development) and of payers (to reduce uncertainty regarding their budget planning), better information regarding the expected minimal annual subscription fee is required. The minimal required subscription fee per country is likely to fall into a range which depends on how many countries will contribute. The result should be that eligible products receive the minimum required pull incentive.

For the UK, in line with the best evidence, if all G20 countries contribute, the contribution should not be lower than 12 million/year over 10 years, as supported by the best estimates in the literature. If

[4] Precise figures will vary depending on the exchange rate used

fewer countries contribute to the global pull incentive, the UK's contribution might have to be more realistically around 23 million/year, as indicated by the estimate when only G7 countries participate.

The UK is leading the movement to fix the broken antibiotic market by example. However, it is now more urgent than ever for other countries to follow suit so that the UK's effort is worthwhile.

5 Which antimicrobials should be eligible for payment through a pull mechanism?

Another key part of a pull incentive is defining which products should be eligible for it. There are multiple reasons to target a pull incentive to a subset of antimicrobials. Firstly, clear eligibility criteria send a strong signal to the industry about what kind of innovation payers will reward, shaping the type of products the industry invests in. Secondly, payers have to decide which products are high priority, so the eligibility criteria allow payers to prioritise the highest value products and maximise value for money.

5.1 International experience

The NICE-NHSE pilot separated the eligibility screening of products from their actual value assessment. A scoring system was used to decide which products would be eligible for the pull incentive. The distribution of points between the six major categories of the scoring system is shown in Figure 3. Fifty-five per cent of the total points were awarded for unmet needs, with 21% of those allocated to the global need and 34% allocated to the local need. The remaining 45% of points were allocated towards the degree of novelty (17%) and other contractual factors like the surety of supply and processes for antimicrobial stewardship and surveillance (each 9% of the total points) (See Figure 3).

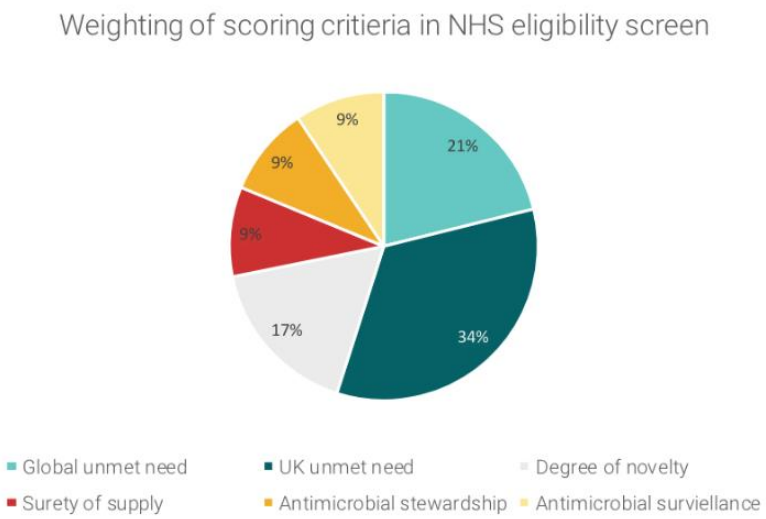


FIGURE 3 CHART SHOWING THE SHARE OF POINTS AVAILABLE TO DIFFERENT PRODUCT ATTRIBUTES USED WITHIN THE UK AMR PILOT ELIGIBILITY SCREENING PROCESS

The eligibility criteria within the PASTEUR Act in the US, as currently written, are the target pathogen, clinical outcomes achieved for patients with multi-drug-resistant infections, the severity of disease, route of administration, not being affected by cross-resistance and having a novel mechanism of

action. These mechanisms build on recommended criteria from Rex and Outterson (2016) and are also used to determine the product-specific reward level (see chapter 5).

5.2 Areas of agreement and debate

Balancing global vs local needs

The discussion on defining eligibility criteria highlights the balance that antimicrobial pull incentives need to strike between stimulating innovation to address global and local unmet needs. There should be alignment between countries regarding the signals sent to industry to 'pull' in the same direction. The global need is relatively well-defined, the most influential being the WHO priority pathogen list, and experts agree that the priority pathogen list is relevant for defining both existing and future threats. Unlike with viruses, it is unlikely that an entirely new bacterial species would emerge in the next 50-100 years that would pose a threat to human health. Experts, therefore, believe that the kinds of bacteria prioritised within the list (i.e., mainly gram-negative species and staphylococcus aureus) will remain the main bacterial threats in the long term.

Assuming we can define ´need´ at both a global and local level, there is a disagreement as to how to balance them. Some believe that globally unified criteria are advantageous as they send a consistent signal to industry, while others believe that the aggregate demand of more localised eligibility criteria would be sufficient while having the important benefit of reassuring local payers that they are getting value for money. In the short-term, local antibiotic priorities may not reflect the priorities within the WHO priority list. In high-income countries, like the UK, where the prevalence of untreatable drug-resistant infections is low, short-term priorities may differ. For example, there are calls within the UK for innovation within existing classes of antibiotics to improve safety profiles, for example, to develop broad-spectrum antibiotics with fewer side effects. Ultimately this tension needs to be balanced to ensure sufficient clarity of global signals to the industry.

Some argue, similarly to the debate around Covid-19 vaccines' allocation, that AMR is a global problem with the potential to arise anywhere at any time: countries cannot protect themselves, and infectious diseases do not respect national borders. While this is clearly true at some level, there are also significant differences in the prevalence of resistance to important antibiotics across different countries linked to the local use of broad-spectrum antibiotics (Murray et al., 2022; Tan et al., 2022; Boni et al., 2022). While the pull incentive amount per country should be based on the ability to pay, it makes political sense for countries like the UK to set eligibility criteria that at least in part reflect national priorities. Otherwise, part of the AMR pull incentive could arguably be more appropriately funded through the Official Development Assistance (ODA) budget along with other initiatives intended to support low- and middle-income countries' health systems.

Setting specific vs broad criteria for antibiotic innovation

There are implicit disagreements among experts about what kinds of product pull mechanisms should be used to incentivise. The debate often crystalises around which pathogens should be named within eligibility criteria, for example, whether all WHO priority pathogens should be incentivised or just level 1 (i.e., highest priority) pathogens. Some believe that pull incentives should mainly incentivise low-volume antibiotics for treating specific, low prevalence, untreatable resistant bacteria. Such new antibiotics would not be used day-to-day but would be available to prevent high-cost ward closures and save lives in the event of an outbreak. Others believe that pull incentives should be used to incentivise all antibiotics that address sufficient unmet needs defined in a broader sense, including higher prevalence and lower severity infections that place a burden on broad-spectrum antibiotics.

The benefit of broad eligibility criteria is that, in theory, the range of products developed is wide enough to give a portfolio of new antibiotics over the coming decades to address many different

infections. It also means that long-term investment signals can be sent without fear that over-specification may lead to a desire to 'move the goalposts' in the coming years, thereby changing the signal to the industry as short-term priorities are met. However, more specific criteria send a stronger signal to the industry and mean that, with a limited budget, the reward can go to products that would not generate enough return in the conventional volume-based reimbursement mechanism.

De-risking for companies via a precommitment

There is much debate resulting from different views on how the development risk should be shared between the developer and the payer. The two kinds of risk for developers are scientific risk resulting from uncertainty about the value of the product and commercial risk resulting from uncertainty about the returns the product is likely to generate. For the payer, there is also a risk associated with the value assessment during the second step of the scheme, whereby the points-based evaluation process is gamed by the industry to achieve higher value-based top-ups.

One mechanism for reducing scientific risk for developers is push funding, where public funders or private philanthropic organisations provide the investment needed for the early stages of antibiotic development. However, innovation still relies greatly on private investment for late-stage clinical development, which carries significant risks. Related risk reduction can be achieved in two ways: by reducing the absolute risk of bringing an antibiotic to market (e.g., through push funding) or by reducing the relative risk on the developer (e.g., by the payer assuming some of the risk). One way the payer can reduce the commercial risk is to offer precommitments of some of the contract value at an earlier stage of development, increasing the regulatory risk on payers. Although the context was exceptional in many ways, precommitments and advance commitments were shown to be powerful incentives in the context of Covid-19 vaccine development.

Within the PASTEUR Act, for example, the Department of Health and Human Services would give a guaranteed (minimum) reward based on comparing an early target product profile (TPP) to the pre-established valuation criteria. In this way, companies know at an earlier stage of innovation exactly what they need to deliver and exactly what they will receive if they deliver it, thereby reducing their commercial risk. Pull mechanisms proposed in other disease areas and country contexts have also suggested that linking the TPP to a set reward effectively strengthens the R&D incentive (Chalkidou et al., 2020; Towse et al., 2021). Some disagree with this approach, given the difficulty of judging value at the early stages of development and the question of what happens if the product does not meet its TPP. Experts also argue that scientific risk for antibiotics is already reduced substantially by push funding.

5.3 Recommendations for eligibility screening

The criteria for eligibility should be based on characteristics of the utility and efficacy of the product that are unlikely to change over time. The TPP is part of the eligibility criteria, and they should be clearly defined and designed to prevent regulatory risk-whereby the system can be gamed over time. For example, those criteria would cover global and local *unmet need*, *efficacy*, *novelty* and *safety*. Other important requirements, such as *surety of supply* and *processes for antimicrobial stewardship and surveillance*, may be better ensured through contractual arrangements and do not need to be included in the eligibility phase.

Unmet needs should incorporate global and local unmet needs with a weighting on global unmet need by using WHO's pathogen prioritisation. The usage strategy should be established at this stage of the process, for example deciding whether products are set to be used daily (albeit at low levels) or reserved for future outbreaks.

Following the eligibility screening process, the company and payer would enter into a contract guaranteeing the company a minimum subscription fee on the supply of the product matching the criteria, including the TPP. On a global level, the criteria will be refined in the medium to long run as global needs and, therefore, required products may change.

6 Setting the value-based subscription fee for a novel antibiotic

Value assessment of medicines used to set prices typically relies on a relatively narrow definition of value that considers only the costs and benefits associated with the immediate treated patient. This approach fails to capture the broader value of antibiotics (the "externalities") – such as reducing resistance, preventing transmission of pathogens, or enablement of other medical procedures (Karlsberg Schaffer et al., 2017; Morton et al., 2019). Evidence indicates that the value of these effects is likely to be many times the immediate health gain for the treated patients (Morton et al., 2019; Wilsdon, Robson and Lu, 2022). As a result, prices for antibiotics, and therefore the rewards for innovation, have historically not reflected their value (Colson et al., 2021).

For the pull incentive to shape an efficient market, there must be a strong link between the payment amount and the value of the product (Danzon, Towse and Mestre-Ferrandiz, 2015). Estimates of the value of an antibiotic suggest it varies substantially between products. Sertkaya et al. (2014) assessed the social value of new antibiotics over a product lifetime of 20 years as ranging from $0.5 billion (for acute bacterial otitis media) to $12.2 billion (for hospital- or ventilator-associated bacterial pneumonia). Megiddo et al. (2019) also estimated the value of a new oral antibiotic (for management of secondary S. aureus infections) following an influenza pandemic and found that if the new antibiotic was held completely in reserve until a pandemic, the value to the UK society would be $2-4 billion. These estimates are summarised in Table 2.

Source	Value Estimated	Value
Sertkaya et al. 2014	Value to society (US)	$0.5 billion-12.2 billion
Megiddo et al., 2019	Value to society (UK)	$2-4 billion

TABLE 2: ESTIMATES OF THE VALUE AN ANTIBIOTIC BRINGS TO SOCIETY

6.1 The broader value of antibiotics and the STEDI framework

Antibiotics deliver value beyond the treated individual. The STEDI framework is a conceptual framework to capture elements of the broader population value of an antibiotic, based on attributes of the value of antibiotics proposed by Karlsberg Schaffer et al. (2017), formalised by the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU) (Rothery et al., 2018), and used within the NICE-NHSE Pilot. It was first named ´STEDI´ by Outterson and Rex (2020) to refer to the five additional elements of value it incorporates[5].

In 2018 EEPRU (Rothery et al., 2018) published guidance for value assessment. EEPRU's proposal was to use an estimation of the total number of population-level QALYs an antibiotic can generate through each of the STEDI value elements, instead of an incremental cost-effectiveness ratio as common in HTA. NICE implemented this economic valuation method for the NICE-NHSE Pilot.

[5] *The additional elements of value beyond the traditional value elements are Spectrum value, Transmission value, Enablement value, Diversity value and Insurance value. More detail on the definitions of these value elements can be found in the EEPRU report (Rothery et al. 2018)*

Challenges with the STEDI-based value assessment experienced in the pilot

The application of the STEDI-based assessment within the pilot generated significant challenges. Despite the considerable effort and resources dedicated to the value assessment, the NICE committee agreed that the modelling had not fully captured many of the broader value elements. The NICE committee took the pragmatic action of adding a percentage uplift on the valuation (30% for one product and 50% for the other product) in proportion to the different population sizes across the products to correct for uncaptured STEDI (or population-level) value.

There are a number of other (i.e., apart from STEDI) reasons why there was uncertainty in the broader value assessment conducted by EEPRU. These include:

1. The valuations were sensitive to reasonable assumptions about core parameters such as patient population size, the proportion of the total value captured within the first ten years of the scheme, and which cost-effectiveness threshold should be applied to convert population QALYs into a monetary value total.
2. A lack of data (particularly around the rate at which resistance could be expected to develop for the products) and a lack of efficacy data from the clinical trials that were applicable to the patient population of interest as defined by NICE.
3. The methodologies of quantifying the STEDI framework are still in their infancy, and there is no consensus on how the STEDI elements should be quantified into QALYs or combined in a way that avoids double counting. In addition, the required expertise is siloed in different disciplines (notably infectious disease modellers, HTA experts, microbiologists, and infectious disease clinicians).

6.2 How a scoring system could set the subscription fee within the scheme

A process is needed to evaluate how much of a subscription fee any given antibiotic should receive. HTA has been used in England for over two decades to assess the value of medicines and guide NHS funding decisions. Given the challenges of the full QALY-based NICE approach (including STEDI-based economic evaluation methodology), and the limited experience to date of applying it, an alternative approach is needed for antibiotics in the short run until a fully QALY-based approach incorporating STEDI-based values can be developed and operationalised. Such an alternative approach should enable payment levels to be adjusted within a reasonable range above the minimum subscription fee without being methodologically too complex (at least in the short term).

A pragmatic decision-making process could divide the subscription fee range into a number of categories. Each category would correspond with a value of the subscription fee that a product would receive (e.g., 100-110% of the minimum, 110-120% of the minimum etc.), and placing a product into a ´value category´ would be based on pre-established decision rules. In particular, the categorisation would be informed by data on product characteristics, its specific target indication, and use strategy (line of treatment/hold back) available at the time of market launch or collected through post-launch surveillance mechanisms within the health system. Combining multiple criteria of value within the decision rules would allow both the clinical value and the broader STEDI value to inform the product´s value category.

Best practice for scoring systems

Scoring systems vary in the level of quantification and aggregation required and the total number of criteria considered (Devlin and Sussex, 2011; Marsh et al., 2016). The more criteria, the more quantification and aggregation are required, and the more complex the decision-making process. All scoring systems require a definition of the decision criteria and ex-ante judgements on how those

criteria will be combined (i.e., their weights). The process for the application of multi-criteria decision analysis (MCDA) is shown in Figure 4.

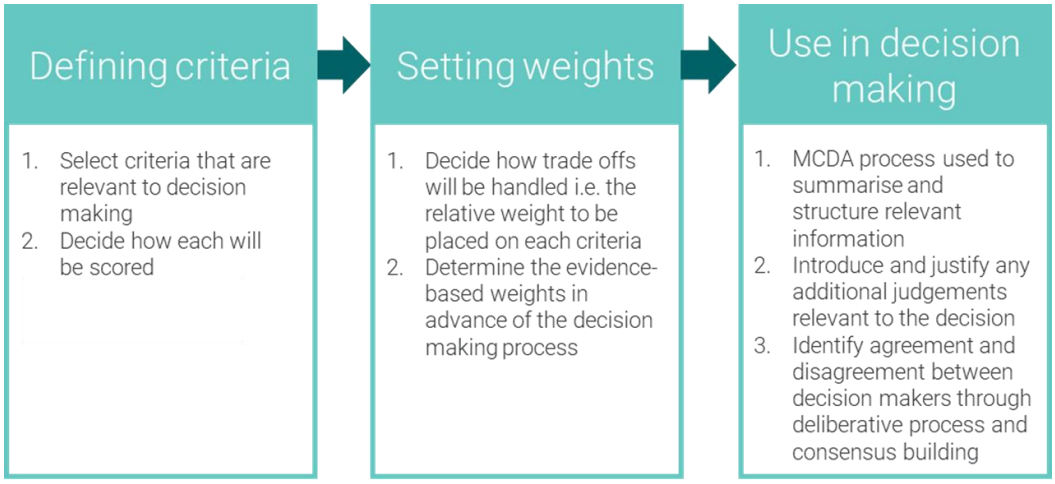


FIGURE 4: PROCESS FOR APPLICATION OF MULTI-CRITERIA DECISION ANALYSIS (MCDA) ADAPTED FROM DEVLIN AND SUSSEX 2011

When deciding on criteria to inform the ranking system, best practice states that those criteria should be: complete, nonredundant, nonoverlapping, and preference-independent (Marsh et al., 2016). This is a challenge for a scoring system whose criteria will include STEDI elements that likely have a degree of overlap and potential preference dependence (e.g., we care more about insurance value when spectrum value is low - i.e., when an antibiotic has broader application in a health crisis). Furthermore, the STEDI value profile will depend on the explicit usage strategy, which must be carefully chosen in order to maximise the expected overall value of the antibiotic. The scoring system should reflect this.

Once the criteria are established, the balance of quantitative methods and qualitative/deliberative methods for deciding on categories of value or aggregating across different value elements should be considered. Quantitative methods have the benefit of being more standardised and reducing the bias of human judgement; however, as shown with the pilot, they generate uncertainty when the assumptions and methods underpinning them are imprecise or variable. Qualitative and deliberative methods, which were ultimately used in the pilot to judge the population-level (STEDI) value for each antibiotic, require fewer resources than quantitative models but also add a level of subjectivity to judgements that can potentially undermine the decision-making process, particularly if methods of eliciting or combining qualitative information are unspecified.

Existing examples of scoring systems

A scoring system to set a value-based subscription fee within a subscription-based incentive system for antibiotics has been suggested in the literature by Rex and Outterson (2016). Their model suggested a baseline reward with additional value-based rewards according to binary scoring criteria (e.g., novel mode of action, oral formulation, CDC priority pathogen targeting and line of treatment) and population targeted (e.g., presence of paediatric data). The system could serve as a starting point but would have to incorporate a value assessment that includes STEDI value elements.

Limitations of scoring systems

Scoring systems for health technologies have been proposed, usually motivated by a need to simplify an assessment process, improve the interpretability of the results of an assessment, or improve the generalisability of results (Moore et al., 2021). The concern with a valuation based on scoring

systems is that, as the final subscription fee does not have to be linked to an objective measure of value, i.e., a QALY, there is likely to be depreciation of the value of a ´point´ over time. As long as there is no objective measure underpinning the analysis over time, all products may be scored at the higher end of the value range. Over time, as values regress to the maximum, the points system will stop being able to differentiate products based on value - a vital component of the scheme to incentivise high value innovation.

6.3 Areas of agreement and debate

One-step vs two-step process for setting the subscription fee

The NICE-NHSE pilot had a two-step process for setting the subscription fee. Firstly, NHS England assessed eligibility for the scheme, and then, NICE conducted a broader value assessment to model the broader, population-level QALYs of each product. The analysis used the cost per QALY threshold to estimate the total value of each of the products across the subscription period. In contrast, the PASTEUR Act proposes a one-step process for setting the subscription fee, which would be using the score at the eligibility screen based on the target product profile (TPP).

The structure of the health system in the country informs whether a one-step (just an eligibility screen) or two-step approach (eligibility screen and value assessment) is required. In England, the prices the NHS pays for therapies are informed by NICE's HTA process and ensure the value for money to the NHS; therefore, a QALY-based value assessment ensures cost-effective resource allocation decisions in a pull incentive for antimicrobials as it does with other medicines. Many health economists see no technical justification for why the reimbursement of products through a pull mechanism should not be tied to the quantification of their value to the health system, e.g., through QALYs. However, there is an important signalling role to an incentive, to pay a minimum that is independent of any value assessment. This requires some test of value to be applied by setting eligibility criteria in a two-stage process.

At the other end of the debate, even in the UK context, it has been argued that the resource allocation role that HTA plays could be done with a simpler methodology to manage the budget allocated to the pull incentive. If the total budget for the pull mechanism is set, the aim of the value assessment is to ensure the relative reward for each product reflects its relative value and that the final subscription payment fits within the fair share of the global pull incentive. Without the QALY-based value assessment, however, the budget for the pull incentive may be politically exposed as it does not allow the pull incentive scheme to objectively demonstrate its value compared to other uses of health funding, a crucial consideration for policymakers.

6.4 Recommendations for value assessment

Data gathering plan

After the eligibility screening phase, there should be a pre-agreed process between the HTA agency and the company to define how the antibiotic will be used in the health system to inform the local valuation. The population-level value of an antibiotic depends on the product itself, the indications chosen to be considered and how the new antibiotic will be used alongside existing antibiotics- the latter two factors being decided by the HTA agency using expert advice. Deciding how the antibiotic will be used within the health system should be supported by evidence and aim to maximise its value over time. By setting the ideal usage strategy following the eligibility screening, the company can develop appropriate evidence to support the broader valuation, e.g., in the appropriate target population.

After the eligibility screen, there can be a dialogue between the company and the HTA agency to define what evidence needs to be generated and in what patient groups to support the value assessment. This should include clinical data, modelling, observational and microbiological data that can support the subsequent value assessment. It may also be necessary to organise an expert elicitation process to estimate some parameters. This step would prevent a situation experienced in the NICE-NHSE pilot, whereby the highest value usage strategy was in a group of patients that were underrepresented within the clinical trial. The scope of the assessment should therefore be discussed between the company and the HTA agency as early as possible in the development process and ideally before the pivotal trial begins. In this way, the trial can be tailored, and specific data can be collected that supports the scope of the value assessment. Existing early-dialogue mechanisms, for example, the Innovative Licensing and Access Pathway (ILAP) in the UK, could be adapted to support this phase of the subscription model for antibiotics (MHRA, 2021).

A points-based value assessment

In the short term, the subscription fee should be adjusted using a categorical, points-based scoring system. The system should be designed to enable a value-based top-up from the minimum subscription fee given to eligible products. The system should consider the use of good practice MCDA and ensure decision rules are transparent to allow companies to anticipate the likely reward for their product during the product development process. Any value assessment should be reassessed in the medium term (3-5 years) following the initial assessment to take into account additional real-world evidence to ensure the correct valuation for the rest of the subscription period, reducing the risk of overpaying for the payer.

Transitioning to an economic evaluation

In the medium term (3-5 years), the methodology underlying the points-based system should be improved with the intent of moving the subscription fee to be informed by a population-level economic evaluation linked to QALYs. The STEDI framework-based Population Net Health Benefit estimation has the advantage of being linked to an objective measure of value (i.e., the QALY) and could continue to be developed as a methodology until it is practical and reliable to implement for antibiotics. This would have the benefit of aligning with HTA methods for other health technologies in the UK, allowing comparison of the value generated across them to inform resource allocation decision-making. It will also help to combat the inevitable drift we have highlighted of a points-based system to maximum scores, degrading the credibility of the scoring system and reducing the incentive properties needed to signal a willingness to pay more for higher value antibiotics. Research, industry-academic collaboration, and pilots running QALY-based approaches in parallel to the scoring approach will be needed to develop the discipline to a level where it can be used to support decision-making with a degree of credibility, quality and consistency, similar to traditional cost-effectiveness analysis.

In order to achieve methodological advances, there has to be an investment to ensure progress is made. The two most impactful activities to support are:

1. *Develop communities of practice*

In the short-term, investment is needed to develop communities of practice around economic modelling for antibiotics. The complexities in antibiotic modelling surpass even those of the population-based economic models built to support vaccine appraisals. In order to overcome these complexities, research is needed to validate the modelling approach. Interdisciplinary collaboration will be particularly crucial as many of the assumptions needed to quantify the STEDI elements depend on subtle clinical and microbiological phenomena that are likely to vary across products and indications. Over time a community of practice will develop standards and norms around the economic modelling of antibiotics that will allow good practice to be used to support decision-making by payers. These activities need to be supported with long-term targeted research funding

and the establishment of fora like academic interest groups and opportunities for work to be published, presented, and debated. The recent paper published by NICE sharing lessons learned from the process should be seen as a starting point for other countries to continue to develop the discipline (Leonard et al., 2023).

2. Investment in evidence gathering

Modelling expertise alone will not be enough to transition from a points-based system to an economic evaluation-based system. Evidence is needed to support some of the key assumptions of any population-based model. One crucial area of uncertainty is the link between antibiotic usage and the emergence of product-specific, class-specific and multi-class resistance. Understanding how the rate of resistance changes over time in relation to other factors, principally how much it is used and in which patients, is also vital. In addition, there is currently a lack of scientific understanding about how bacteria and resistance spread across a population and particularly the relationship between colonisation and the development of an infection. Without a better scientific understanding of the fundamental dynamics of bacterial infection, it will not be possible for health economic modellers to model the STEDI elements.

7 Conclusions

The NICE-NHSE pilot has been an important step forward in highlighting that (pull, delinked) incentives for antimicrobials can be implemented. Learning from the pilot process and the discussions it has initiated is important if we are to develop a sustainable model for implementing delinked pull incentives in the UK and globally. In this paper, we have presented recommendations for pull incentives for antimicrobials, focussing on subscription models, which health systems in the UK and around the world could consider. We have also highlighted areas of continued debate. Our recommendations have three key features:

1. The minimal reward within a pull incentive should fall into a range. This range should correspond to a realistic estimate of a country´s share of a global pull incentive, depending on how many other countries globally contribute.

2. Eligibility screening should be weighted towards global needs but should also consider local requirements. There should be a minimum precommitment at the eligibility screening stage between the payer and the developer to be paid on market launch based on an agreed TPP to strengthen the pull incentive mechanism. If the TPP is met, the minimum payment is guaranteed.

3. There should be a value-based top-up based on a points-based system in the short term and a full STEDI-based economic evaluation linked to an objective measure of health value in the long term, which reflects the population-level value of each antibiotic. The subscription fee should be reassessed after three years to assess real-world evidence and reduce the risk of overpayment from the payer.

Care should be taken by those implementing pull incentives to ensure that processes and decision criteria are defined and transparent. All experts consulted as part of this project agreed that transparency was a vital component of the pull incentive to increase the clarity for developers, reducing their commercial risk by ensuring they are able to accurately assess their likely rewards in a global market that includes pull incentives. The obligations of industry, particularly for data collection, should be clearly established early on in the process to ensure that investment in end-stage clinical development and post-launch evidence generation delivers data that is as helpful as possible to the value assessment process.

There are a number of limitations in our recommendations, which reflect trade-offs inherent in any pull incentive. The major trade-off is the balance of risk sharing between the developer and the payer. The recommendations presented above, particularly precommitments based on an early TPP and a points-based valuation system, may be vulnerable to gaming because the payer is required to make decisions based on less information than normal.

The NICE-NHSE pilot showed an example of what is possible, but in taking a theoretical model and seeking to make it real, it has highlighted many implementation challenges and also conflicting views about the precise function and requirements for pull incentives to combat AMR. We have highlighted some of those ongoing disagreements in this paper and hope to support future work to generate consensus.

Regardless of these disagreements, the UK has an important role in supporting other countries to adopt similar pull incentives (at a national level), particularly in the EU and the US. A successful pull incentive mechanism in the UK will not be enough on its own to stimulate antimicrobial development. More work needs to be done internationally to build on the NICE-NHSE pilot efforts through research and international political cooperation.

8 References

AMR Action Fund, 2022. *Antimicrobial Resistance Research & Development - AMR Action Fund*. [online] Available at: https://www.amractionfund.com [Accessed 6 Sep. 2022].

Antimicrobial Resistance Collaborators, 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325), pp.629–655. 10.1016/S0140-6736(21)02724-0.

Årdal, C., Findlay, D., Savic, M., Carmeli, Y., Gyssens, I., Laxminarayan, R., Outterson, K. and Rex, J., 2018. *Revitalising the antibiotic pipleine. Stimulating innovation while driving stustainable use and global access*.

Årdal, C., Lacotte, Y. and Ploy, M.-C., 2020. Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 71(8), pp.1994–1999. 10.1093/cid/ciaa153.

Årdal, C., Lacotte, Y., Ploy, M.-C., and on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), 2020. Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases*, 71(8), pp.1994–1999. 10.1093/cid/ciaa153.

Årdal C, Baraldi E, Busse R, Castro R, Ciabuschi F, Cisneros JM, Gyssens IC, Harbarth S, Kostyanev T, Lacotte Y, Magrini N, McDonnell A, Monnier AA, Moon S, Mossialos E, Peñalva G, Ploy MC, Radulović M, Ruiz AA, Røttingen JA, Sharland M, Tacconelli E, Theuretzbacher U, Vogler S, Sönksen UW, Åkerfeldt K, Cars O, O'Neill J. Transferable exclusivity voucher: a flawed incentive to stimulate antibiotic innovation. Lancet. 2023 Feb 9:S0140-6736(23)00282-9.

Bayer, M. and Kansteiner, F., 2023. *J&J's pharma group quietly works through global overhaul, with layoffs expected to reach multiple countries*. [online] Fierce Pharma. Available at: https://www.fiercepharma.com/pharma/johnson-johnson-quietly-works-through-global-overhaul-layoffs-spreading-multiple-countries [Accessed 7 Feb. 2023].

Boni, S., Marin, G.H., Campaña, L., Marin, L., Risso-Patrón, S., Marin, G., Gabriel, F., Corso, A., Garay, V. and Limeres, M., 2022. Association between Consumption of Fluoroquinolones and Carbapenems and Their Resistance Rates in Pseudomonas aeruginosa in Argentina. *Interdisciplinary Perspectives on Infectious Diseases*, 2022, p.3924212. 10.1155/2022/3924212.

Cernuschi, T., Furrer, E., Schwalbe, N., Jones, A., Berndt, E.R. and McAdams, S., 2011. Advance market commitment for pneumococcal vaccines: putting theory into practice. *Bulletin of the World Health Organization*, 89(12), pp.913–918. 10.2471/BLT.11.087700.

Chalkidou, K., Garau, M., Silverman, R. and Towse, A., 2020. *Blueprint for a Market-Driven Value-Based Advance Commitment For Tuberculosis*. [online] Centre for Global Development. Available at: https://www.cgdev.org/sites/default/files/MVAC-Blueprint-Final_2.pdf [Accessed 25 Apr. 2022].

Clift, C., Gopinathan, U., Morel, C., Outterson, K., Røttingen, J.-A. and So, A., 2015. *Towards a New Global Business Model for Antibiotics*. [online] Chatham House, p.46. Available at: https://www.chathamhouse.org/sites/default/files/field/field_document/20151009NewBusinessModelAntibioticsCliftGopinathanMorelOuttersonRottingenSo.pdf .

Colson, A.R., Morton, A., Årdal, C., Chalkidou, K., Davies, S.C., Garrison, L.P., Jit, M., Laxminarayan, R., Megiddo, I., Morel, C., Nonvignon, J., Outterson, K., Rex, J.H., Sarker, A.R., Sculpher, M., Woods, B. and Xiao, Y., 2021. Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem? *Value in Health*, 24(12), pp.1828–1834. 10.1016/j.jval.2021.06.002.

Danzon, P., Towse, A. and Mestre-Ferrandiz, J., 2015. Value-Based Differential Pricing: Efficient Prices for Drugs in a Global Context. *Health Economics*, 24(3), pp.294–301. 10.1002/hec.3021.

Devlin, N. and Sussex, J., 2011. *Incorporating Multiple Criteria in HTA: Methods and Processes*. [OHE Monograph] Available at: https://www.ohe.org/publications/incorporating-multiple-criteria-hta-methods-and-processes. .

G7 Finance Ministers, 2021. *G7 Finance Ministers' Statement on Actions to Support Antibiotic Development*. [online] Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040016/AMR_-

_G7_Finance_Ministers_statement_on_supporting_antibiotic_development_-_final_-_13_Dec_2021.pdf [Accessed 16 Aug. 2022].

Karlsberg Schaffer, S., West, P., Towse, A., Henshall, C., Mestre-Ferrandiz, J., Masterson, R. and Fischer, A., 2017. *Additional Elements of Value for Health Technology Assessment Decisions*. Briefings. [online] Office of Health Economics. Available at: https://ideas.repec.org/p/ohe/briefg/001851.html [Accessed 17 Jul. 2018].

Kremer, M., 1998. Patent Buyouts: A Mechanism for Encouraging Innovation. *The Quarterly Journal of Economics*, 113(4), pp.1137–1167. 10.1162/003355398555865.

Kremer, M., Levin, J. and Snyder, C.M., 2020. Advance Market Commitments: Insights from Theory and Experience. *AEA Papers and Proceedings*, 110, pp.269–273. 10.1257/pandp.20201017.

Leonard, C., Crabb, N., Glover, D., Cooper, S., Bouvy, J., Wobbe, M. and Perkins, M., 2023. Can the UK 'Netflix' Payment Model Boost the Antibacterial Pipeline? *Applied Health Economics and Health Policy*. [online] 10.1007/s40258-022-00786-1.

Marsh, K., IJzerman, M., Thokala, P., Baltussen, R., Boysen, M., Kaló, Z., Lönngren, T., Mussen, F., Peacock, S., Watkins, J., Devlin, N., and ISPOR Task Force, 2016. Multiple Criteria Decision Analysis for Health Care Decision Making--Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 19(2), pp.125–137. 10.1016/j.jval.2015.12.016.

McDonnell, A., 2022. The EU Wants to Transfer the Costs of New Antibiotics to its Member States—They Are Right To Revolt. *Center for Global Development | Ideas to Action*. Available at: https://www.cgdev.org/blog/transferring-costs-its-member-states-eus-proposed-voucher-scheme-incentivising-antibiotics [Accessed 17 Jan. 2023].

Megiddo, I., Drabik, D., Bedford, T., Morton, A., Wesseler, J. and Laxminarayan, R., 2019. Investing in antibiotics to alleviate future catastrophic outcomes: What is the value of having an effective antibiotic to mitigate pandemic influenza? *Health Economics*, 28(4), pp.556–571. 10.1002/hec.3867.

MHRA, 2021. *Innovative Licensing and Access Pathway*. [online] GOV.UK. Available at: https://www.gov.uk/guidance/innovative-licensing-and-access-pathway [Accessed 26 Sep. 2022].

Milken Institute, 2022. *Models for Financing Antibiotic Development to Address Antimicrobial Resistance*. [online] Available at: https://milkeninstitute.org/sites/default/files/2022-03/FIL-AMR%20v3.22.22.pdf [Accessed 19 May 2022].

Moore, F., Grunch, B.H., Miller, L.E. and Musacchio, M.J., 2021. Towards a More Simplified Approach for Evaluating Strength of Evidence in Health Technology Assessments. *Cureus*, 13(7), p.e16528. 10.7759/cureus.16528.

Morton, A., Colson, A., Leporowski, A., Trett, A., Bhatti, T. and Laxminarayan, R., 2019. How Should the Value Attributes of Novel Antibiotics Be Considered in Reimbursement Decision Making? *MDM Policy & Practice*, 4(2). 2381468319892237.

Murray, C.J., Ikuta, K.S., Sharara, F., Swetschinski, L., Aguilar, G.R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S.C., Browne, A.J., Chipeta, M.G., Fell, F., Hackett, S., Haines-Woodhouse, G., Hamadani, B.H.K., Kumaran, E.A.P., McManigal, B., Agarwal, R., Akech, S., Albertson, S., Amuasi, J., Andrews, J., Aravkin, A., Ashley, E., Bailey, F., Baker, S., Basnyat, B., Bekker, A., Bender, R., Bethou, A., Bielicki, J., Boonkasidecha, S., Bukosia, J., Carvalheiro, C., Castañeda-Orjuela, C., Chansamouth, V., Chaurasia, S., Chiurchiù, S., Chowdhury, F., Cook, A.J., Cooper, B., Cressey, T.R., Criollo-Mora, E., Cunningham, M., Darboe, S., Day, N.P.J., Luca, M.D., Dokova, K., Dramowski, A., Dunachie, S.J., Eckmanns, T., Eibach, D., Emami, A., Feasey, N., Fisher-Pearson, N., Forrest, K., Garrett, D., Gastmeier, P., Giref, A.Z., Greer, R.C., Gupta, V., Haller, S., Haselbeck, A., Hay, S.I., Holm, M., Hopkins, S., Iregbu, K.C., Jacobs, J., Jarovsky, D., Javanmardi, F., Khorana, M., Kissoon, N., Kobeissi, E., Kostyanev, T., Krapp, F., Krumkamp, R., Kumar, A., Kyu, H.H., Lim, C., Limmathurotsakul, D., Loftus, M.J., Lunn, M., Ma, J., Mturi, N., Munera-Huertas, T., Musicha, P., Mussi-Pinhata, M.M., Nakamura, T., Nanavati, R., Nangia, S., Newton, P., Ngoun, C., Novotney, A., Nwakanma, D., Obiero, C.W., Olivas-Martinez, A., Olliaro, P., Ooko, E., Ortiz-Brizuela, E., Peleg, A.Y., Perrone, C., Plakkal, N., Ponce-de-Leon, A., Raad, M., Ramdin, T., Riddell, A., Roberts, T., Robotham, J.V., Roca, A., Rudd, K.E., Russell, N., Schnall, J., Scott, J.A.G., Shivamallappa, M., Sifuentes-Osornio, J., Steenkeste, N., Stewardson, A.J., Stoeva, T., Tasak, N., Thaiprakong, A., Thwaites, G., Turner, C., Turner, P., Doorn, H.R. van, Velaphi, S., Vongpradith, A., Vu, H., Walsh, T., Waner, S., Wangrangsimakul, T., Wozniak, T., Zheng, P., Sartorius, B., Lopez, A.D., Stergachis, A., Moore, C., Dolecek, C. and Naghavi, M., 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325), pp.629–655. 10.1016/S0140-6736(21)02724-0.

NHS England and NHS Improvement, 2021. Annex 2 - Information for bidders.

NICE, 2022. *NICE reaches important milestone in the UK's efforts to tackle antimicrobial resistance. | News and features | News | NICE*. [online] Available at: https://www.nice.org.uk/news/article/nice-reaches-important-milestone-in-the-uk-s-efforts-to-tackle-antimicrobial-resistance [Accessed 30 Jun. 2022].

O'Neill, J., 2014. *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*. [online] Available at: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf [Accessed 23 Aug. 2022].

Outterson, K., 2021. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs*, 40(11), pp.1758–1765. 10.1377/hlthaff.2021.00688.

Outterson, K. and Rex, J.H., 2020. Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialisation. *Translational Research*, 220, pp.182–190. 10.1016/j.trsl.2020.02.006.

PEW, 2020. *Tracking the Global Pipeline of Antibiotics in Development, April 2020*. [online] Available at: https://pew.org/2UCFs46 [Accessed 24 Nov. 2022].

Prasad, N.K., Seiple, I.B., Cirz, R.T. and Rosenberg, O.S., 2022. Leaks in the Pipeline: a Failure Analysis of Gram-Negative Antibiotic Development from 2010 to 2020. *Antimicrobial Agents and Chemotherapy*, 66(5), pp.e00054-22. 10.1128/aac.00054-22.

Renwick, M., Brogan, D. and Mossialos, E., 2014. A Critical Assessment of Incentive Strategies for Development of Novel Antibiotics. p.37.

Rex, J., 2020. What does an antibiotic cost to develop? What is it worth? How to afford it? *AMR.Solutions*. Available at: https://amr.solutions/2020/03/06/what-does-an-antibiotic-cost-to-develop-what-is-it-worth-how-to-afford-it/ [Accessed 24 Nov. 2022].

Rex, J.H. and Outterson, K., 2016. Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *The Lancet. Infectious Diseases*, 16(4), pp.500–505. 10.1016/S1473-3099(15)00500-9.

Rome, B.N. and Kesselheim, A.S., 2020. Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 71(7), pp.1671–1675. 10.1093/cid/ciz1039.

Rothery, C., Woods, B., Schmitt, L., Claxton, K., Palmer, S. and Sculpher, M., 2018. FRAMEWORK FOR VALUE ASSESSMENT OF NEW ANTIMICROBIALS. p.178.

Sciarretta, K., Røttingen, J.-A., Opalska, A., Van Hengel, A.J. and Larsen, J., 2016. Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations From the Transatlantic Task Force on Antimicrobial Resistance: Table 1. *Clinical Infectious Diseases*, 63(11), pp.1470–1474. 10.1093/cid/ciw593.

Seabury, S. and Sood, N., 2017. *Toward A New Model For Promoting The Development Of Antimicrobial Drugs*. [online] Health Affairs Blog. Available at: https://www.healthaffairs.org/do/10.1377/forefront.20170518.060144/full/ [Accessed 6 Sep. 2022].

Sertkaya, A., Eyraud, J., Birkenbach, A., Franz, C., Ackerley, N. and Overton, V., 2014. Analytical Framework for Examining the Value of Antibacterial Products. *ERG*, p.107.

Sharma, P. and Towse, A., 2011. *New Drugs to Tackle Antimicrobial Resistance: Analysis of EU Policy Options*. [online] Office of Health Economics. Available at: https://ideas.repec.org/b/ohe/monogr/000184.html [Accessed 17 Jul. 2018].

Tan, S.Y., Khan, R.A., Khalid, K.E., Chong, C.W. and Bakhtiar, A., 2022. Correlation between antibiotic consumption and the occurrence of multidrug-resistant organisms in a Malaysian tertiary hospital: a 3-year observational study. *Scientific Reports*, 12(1), p.3106. 10.1038/s41598-022-07142-2.

Taylor, N., 2020. Melinta files for bankruptcy in another dark day for antibiotics. [Fierce Biotech] Available at: https://www.fiercebiotech.com/biotech/melinta-files-for-bankruptcy-another-dark-day-for-antibiotics [Accessed 11 Jul. 2022].

Towse, A., Chalkidou, K., Firth, I., Kettler, H. and Silverman, R., 2021. How Should the World Pay for a Coronavirus Disease (COVID-19) Vaccine? *Value in Health*, 24(5), pp.625–631. 10.1016/j.jval.2020.12.008.

Towse, A., Hoyle, C.K., Goodall, J., Hirsch, M., Mestre-Ferrandiz, J. and Rex, J.H., 2017. Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy*, 121(10), pp.1025–1030.

WHO, 2021. *Comprehensive review of the WHO Global Action Plan on Antimicrobial Resistance : Evaluation brief – September 2021*. Available at: https://www.who.int/publications/m/item/comprehensive-review-of-the-who-global-action-plan-on-antimicrobial-resistance-evaluation-brief-september-2021 [Accessed 16 Nov. 2022].

WHO, 2022. *2021 antibacterial agents in clinical and preclinical development: an overview and analysis*. [online] WHO. Available at: https://www.who.int/publications-detail-redirect/9789240047655 [Accessed 24 Nov. 2022].

WHO, 2022. *What is the difference between antibiotic and antimicrobial resistance?* [online] World Health Organization - Regional Office for the Eastern Mediterranean. Available at: http://www.emro.who.int/health-topics/drug-resistance/what-is-the-difference-between-antibiotic-and-antimicrobial-resistance.html [Accessed 28 Jul. 2022].

Wilsdon, T., Robson, A. and Lu, L., 2022. *A framework for assessing the potential net benefits realised through Transferable Exclusivity Extension (TEE) as an incentive for development of novel antimicrobials:* Charles River Associates.

World Bank, 2017. *Drug-Resistant Infections: A Threat to Our Economic Future*. [online] Washington, DC: World Bank. Available at: https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf [Accessed 26 Sep. 2022].

About us
Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

OHE. For better healthcare decisions.

Areas of expertise

- Evaluation of health care policy
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

CONTRACT RESEARCH REPORT
MARCH 2023

ohe.org

The Office of Health Economics A Company Limited by Guarantee of Registered No.09848965
OHE Consulting Ltd Registered Company No.09853113
OHE is a Charity Registration No.1170829
Registered Office 2nd Floor Goldings House, Hay's Galleria, 2 Hay's Lane, London, SE1 2HB