An assessment of EU Proposals for AMR Incentives against Europe's fair share

1. Introduction

Globally there is recognition that antimicrobial resistance (AMR) presents a significant threat to healthcare systems. In Europe, it contributed to ~40,000 deaths and over EUR 1.1bn in additional healthcare costs in 2019 alone, with this expected to increase as resistance continues to develop.[i] Despite a clear and urgent need for new antimicrobials, the number in clinical development is limited, with the World Health Organization (WHO) recently describing the pipeline as "insufficient".[ii] While this is partly due to the scientific challenges in developing antimicrobials, it is largely a result of the broken economic market that developers face in bringing new antimicrobials to market.[iii]

It is widely accepted that incentives are needed to address the market failures that antimicrobials face. However, there is considerable debate on various aspects including the overall size and type of incentive needed. In addition, there are also significant discussions on who is responsible for financing incentives and the respective share that they should be accountable for.

In 2023, the EU put forward several proposals for policy action on AMR incentives. The European Commission (EC) published its proposals for the revision of the General Pharmaceutical Legislation (GPL), which included introducing the transferable exclusivity voucher (TEV) as an incentive to encourage the development of antimicrobial drugs. [iv] This was followed by the EU Council adopting a recommendation aimed at stepping up EU action to combat AMR.[v] Furthermore, the European Health Emergency Authority (HERA) conducted a report evaluating various pull incentives' potential to stimulate innovation and support the availability and accessibility of AMR medical countermeasures.[vi]

Through a review of the existing literature and ongoing initiatives, this paper aims to contribute to the policy debate by considering if the current proposals are of sufficient size to sufficiently stimulate antimicrobial research and development and be aligned to the European fair share.

2. European Fair Share of the Required Global Incentive Size

In recent years, there has been substantial progress made in our understanding of the global incentive size that is needed to stimulate antimicrobial innovation, with various papers/reports published by leading academics, think tanks, and consultancies. However, this has resulted in a range of reward sizes which may lead to some confusion over the required incentive size. These differences have occurred for a variety of reasons including:

- **The region or country they relate to:** Some incentive sizes are focused on the global reward size whilst others can be specific to a region or country. For example, the incentive sizes range of $700m and $1.5bn put forward by the BEAM Alliance is for the EU only, whilst others refer to the global magnitude.[vii]
- **The type of pull incentive:** Some estimate the reward size for a market-entry reward incentive, whilst some estimates are for a subscription model, in some cases the estimate is for a partially de-linked incentive whilst others are fully de-linked.
- **The reward timeframe:** Whilst most estimates are for a 10-year period, others are done on an annual basis, such as in Outterson (2021) where the $3.1bn total for a

10-year subscription model for a Phase II-ready asset is reported as being paid out at $310m per year.[viii]

To provide consistency and comparability in the numbers being put forward, we have scaled the estimates to the global level over a 10-year time period. These have been set out in Table 1 below. $US has been used across all figures, with currency exchanges using current rates.

Table 1. Literature overview of required global incentive size (recent studies)

Source	Type of source	Size of global incentive per antimicrobial
Outterson *(2021)*[ix]	Academic	$4.2bn for a fully delinked end-to-end 10-year subscription model[1]
Center for Global Development *(2022)*[x]	Academic	$4.5bn
Boston Consulting Group (2022)[xi]	Academic	$2.3-3bn
BEAM Alliance[xii]	Industry association	$2.1-4.5bn

Many of the above studies were also considered by the EC in both the Impact Assessment for the revision of the GPL and the HERA study on bringing new medical countermeasures to market. [xiii] In the GPL documents, the EC stated that the "fair" EU contribution to a global pull incentive should be based on $2.5 billion per antimicrobial over 10 years.[xivxv] While the HERA study does not outline a specific size for a global pull incentive, it uses the literature to inform the minimum and maximum ranges used in its scenario analysis.

In his paper (2021) Outterson highlights that many earlier studies underestimate the size of the pull incentive needed and often set the size of a global pull incentive at ≅ $1bn. The paper set out the reasons for these differences, most notably that earlier estimates used revenue based on the most successful antimicrobial in the past two decades (daptomycin) rather than a representative antibiotic, and understated manufacturing and post-approval costs.[xvi] The Outterson approach builds on previous papers, correcting a number of methodological issues, and is largely seen as the most robust estimate to date and therefore is the estimate we use below.

We can also consider initiatives that have been launched by governments that aim to provide a pull incentive designed to stimulate antimicrobial R&D. In Table 2 below we summarize the scale of these incentives. While other initiatives exist such as the Swedish "Revenue Guarantee Model" or the Japanese "Antimicrobial Securement Support Program" these have been excluded from the review due to their current focus on securing access and availability vs. stimulating R&D. [xviixviii]

[1] In the study, Outterson provides best estimates for pull incentives across several scenarios. This includes a scenario for a fully delinked 10-year subscription model for a Phase II-ready asset ($3.1bn), which we refer to above, and an estimate based on a preclinical (end-to-end) asset ($4.2bn). From a methodological perspective the estimate from preclinical is preferred, although it is acknowledged there is greater uncertainty regarding the estimation.

Table 2. The scale of international policy initiatives

Source	Type of source	Size of global incentive per antimicrobial
US Pasteur Act *(proposed)*[xix]	Country incentive	$1.5bn – $6bn[2]
Canada Subscription Model *(proposed)*[xx]	Country incentive	$3.1bn[3]
UK Subscription Model *(ongoing)*[xxi]	Country incentive	$3.5bn[4]

Despite differences, there is also relative consistency between the recent (post-2021) literature and the international policy initiatives, with the reward size of the initiatives falling in between the estimated ranges. As such, it is expected that the ongoing and proposed policy initiatives are likely to be sufficient in stimulating the development of innovative antimicrobials.[5]

Similar to incentive size, there has been considerable discussion in the literature as to how the funding requirements should be proportioned or shared between countries, and which countries should be included. The figure that each country is required to pay is typically referred to as their "fair share".

When considering how to allocate the share of the global pull incentive that each country is required to contribute (i.e. their fair share), this is typically based on two economic measures gross domestic product (GDP) and gross national income (GNI).

Using the G7 + EU country split and the above economic measures, the required fair share per country can be seen in Table 3 below.

Table 3. Overview of each country's required fair share %[xxii]

Country	Fair share %
United States	46%
European Union	34%
Japan	10%
United Kingdom	6%
Canada	4%

It is worth noting that in the GPL proposals and HERA study a different % for the European fair share are used, with a range of 22-27% put forward on the assumption that China contributes its fair share. [xxiiixxiv] While this assumption lowers the fair share requirements of

[2] Calculation assumes a US share of 46%.
[3] Calculation assumes a Canada share of 4% and ~$12.5m annual funding per antimicrobial
[4] Calculation assumes a UK share of 6% and $21m annual funding per antimicrobial under new proposals (this funding amount is blended using the different payment bands in the model).
[5] Assuming that all countries contribute their fair share to a global incentive.

the EU (as well as all other countries) there is significant uncertainty around China's contribution. Historically, China has shown limited policy prioritisation in the field of AMR, both at the national and global levels. In addition, it has typically focused on AMR surveillance and monitoring, rather than the development of innovative antimicrobials.[xxv]

In this context, the fair share calculations set out in Box 1 below are based on the G7 + EU only. We have leveraged the Outterson best estimate of $4.2bn for a fully delinked 10-year subscription model as the required size of the global pull incentive.

Box 1: Calculating the EU fair share

Leveraging the identified global pull incentive size of $4.2bn and the EU fair share % of 34% we can calculate that:

- **The required EU contribution to a global pull incentive is $1.43bn per antimicrobial**

3. Assessing the Quantum of EU Policy Proposals

We can use the required EU fair share to assess the extent to which recent EU policy proposals on AMR incentives deliver the required amount. Below we assess:

1. The TEV proposed in the revision of the General Pharmaceutical Legislation
2. The policy actions proposed in HERA's study on bringing AMR medical countermeasures to market
3. The gaps that need to be filled

Assessing the EC's TEV

The EC proposed the TEV in recognition of the antimicrobial market failure and the need to develop new antimicrobials. As such, the introduction of the TEV is to provide an incentive for the R&D of novel products.

However, upon reviewing the EC's proposal and impact assessment on TEV, the estimated value is determined to be $440 million (EUR 413 million).[xxvi] This is notably lower than previous industry estimates which had outlined the required value of the EC TEV to be $650 million (EUR 614 million).[xxviixxviii]

The key reason why the value of the proposed EC TEV is significantly lower is due to its application to regulatory data protection-only (RDP) vs. RDP + supplementary patent certificate (SPC). The EC argues that the application of RDP increases the efficiency of the TEV as these products have lower average peak sales than those protected with a SPC.

Upon assessing this value in the context of the EU fair share for a global pull incentive, it is clear that the proposed EC TEV (in isolation) is substantially lower than what is required if applied alone.

Assessing HERA's proposed policy actions

In March 2023, HERA released a study focusing on bringing AMR Medical Countermeasures to the Market.[xxix] One of the key objectives was to explore "options for action" in order to stimulate innovation, alongside the aim to facilitate the availability and accessibility of AMR medical countermeasures across EU Member States. These were to be achieved through the implementation of pull incentives. The EC envisions that these incentives would be complementary to the TEV. The three types of pull incentives that were ultimately

considered for policy actions were: Revenue Guarantee model **(RG);** Small Market Entry Reward combined with revenue guarantee **(MERino)** and Milestone-Based Reward **(MBR).**

There appears to be wider stakeholder support for a RG.[xxx] This would provide antibiotic developers with a yearly revenue value over 10 years, with payments starting from the year of marketing approval.

Across these incentives, different monetary sizes were considered, with success determined by a mix of project profitability (at the start of Phase I) and optimal allocation of public funding. The proposed policy actions and their corresponding reward size can be seen in Table 4 below.[6]

Table 4. Overview of HERA proposed policy actions and reward size[xxxi]

Intervention	Total global reward	Implied EU Reward	Timeframe
RG at $150m/year	$1.5bn	$510 million	10 years
RG at $100m/year	$1bn	$340 million	10 years

Upon review of the proposed policy actions, the study findings show the importance of the incentive size to sufficiently stimulate antimicrobial research and development, with only interventions with total global rewards of at least $1.5bn being able to make 50% or more of projects profitable. None of the implied EU reward sizes in the HERA study deliver the required fair share.

The gap in delivering a European fair share

However, it is appropriate to look at the proposal in combination. The EC's communication upon publishing the HERA study states that the RG would be complementary to the TEV.[xxxii] As such it is reasonable to consider each combined with TEV to determine whether together they meet the EU fair share.

That being said, even with a TEV of $440 million and by taking the largest EU reward size proposed by HERA, this would total $950 million. This remains to be significantly lower than the required EU share of $1.43bn. The gap of $480 million in the required reward size is illustrated in Table 5 below.

Table 5. EU proposals and gap to European fair share

EU proposals	Size
Revenue guarantee at $150m/year	$510 million
Transferable exclusivity voucher	$440 million
Combined total	**$950 million**
European fair share	$1.43 billion
The gap between the combined total and European fair share	**$480 million**

[6] The interventions do not factor in discounting when determining the global reward and assume an equal contribution each year. This approach is consistent with Outterson's best estimate for a delinked subscription model.

The potential role of national incentives in delivering a European fair share

Across Member States, there have also been policy developments that could address the gap between the European fair share and existing EU incentive proposals. For example, Germany has recently introduced free pricing for reserve antimicrobials that are launched before 2031, whilst France has implemented new evaluation criteria for the assessment of antimicrobials.[xxxiiixxxiv] Both of these policy initiatives are aimed at addressing some of the pricing and reimbursement challenges that affect innovative antimicrobials. However, the extent they contribute to the required share is uncertain. For example, there is concern that the German model will result in higher unit prices that whilst reflective of the value of the innovative antimicrobial, will be perceived as too high relative to existing products and will not be purchased in enough volume to generate sufficient revenue.

Leveraging their relative share of EU GDP[7], (25% for Germany and 17% for France), this would see both countries needing to contribute $145 million and $100 million respectively through national incentives – in doing so, the remaining gap would be reduced to around $235 million.

Why public funding for early research should not be deducted from the EU fair share

Early antimicrobial research (also known as preclinical research) funded by public resources plays a key role in fostering scientific discovery and laying the foundation for future innovation. Public funding for early research often involves broader fundamental scientific inquiries rather than those tied to specific projects. For example, funding has been used to identify microbial genes that drug candidates could target, rather than developing specific drug candidates. This investment is made to provide the foundation for research into particular products and is usually described as a public good (a different purpose to that motivating the development of pull incentives). The costs of basic research enable innovation across the board. This is crucial as antimicrobial research is highly risky, evidenced by the extremely low probability of success rates from pre-clinical to marketing approval. It is estimated that for every 3 compounds that receive approval, ~200 have failed.[xxxv] This approach to the funding of basic research, supported through public subsidy, is consistent with other disease areas.

There are, however, different types of funding provided by public bodies that could be taken into consideration. For example, Outterson (2021) discussed public support for clinical research (that is attributable to a specific product but is a small proportion of public funding) that could be deducted when determining the size of the pull incentive, whereas funding for preclinical research (often focusing on broader scientific discovery) would not.[xxxvi]

The deduction of public funding for early research, from the existing EU proposals would further increase the gap with the EU Fair Share and risk not only disincentivizing innovation but discouraging investment in AMR compared to other areas.

4. Policy Implications

Across the analysis, it is clear that none of the proposed EU incentives, either in isolation or combination are expected to deliver the European fair share. Given the importance of a sufficient incentive size to stimulate antimicrobial research and development, serious consideration must be given to strengthening the EU proposals.

There are several ways in which this could be done:

- Broaden the application of TEV to include SPC as well as RDP. This would markedly increase the value of the TEV.

[7] EU GDP % taken from https://ec.europa.eu/eurostat/web/products-eurostat-news/-/ddn-20211220-1#:~:text=In%202020%2C%20slightly%20more%20than,and%20the%20Netherlands%20(6.0%25).

- Include a larger magnitude of revenue guarantee.
- Include national reimbursement incentives, such as those provided in Germany and France.

5. Conclusions

While there has been significant progress on the development of EU AMR incentives, the current proposals will not be sufficient in size to meet the European fair share. To ensure that new antimicrobials are developed, and the challenge of AMR is appropriately addressed, greater ambition needs to be shown in terms of the combined policy initiatives.

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