Estimating the Return on Investment of Pull Incentive Policies for New Antimicrobials - Insights for the EU and Beyond

Key Messages:

- Antimicrobial resistance is an increasing global threat and the world needs a reliable pipeline of new, effective antimicrobials as a crucial element of managing it.
- The antimicrobial market is characterised by a pervasive market failure where developers are unable to realise a sufficient return on investment once a new drug is approved, despite the high-societal value of new antimicrobials coming to market.
- Pull incentives policies, which offer alternative and/or additional methods of rewarding innovators for bringing high-value antimicrobials to market offer a well evidenced and widely supported mechanism to strengthen the antimicrobial pipeline through sufficiently awarding developers of new therapies.
- Building on previous analyses at the EU and G7 levels, we examined the expected return on investment for national governments investing in a new incentive scheme targeting the development of 18 new drugs over a 30-year time horizon.
- Our analysis show that for all countries considered, purchasing antimicrobials through a de-linked incentive program gives a robustly positive return on investment over both short- and long-term horizons, ranging from 1.3:1 to 4.6:1 over a 10-year horizon and from 6.1:1 to 21:1 over a 30-year horizon. This estimate conservatively only includes direct clinical benefits to patients and reduced healthcare costs, and should hence be considered as a lower bound.
- Based on this research, we created a dashboard which allows for the return on investment of a pull incentive scheme to be calculated under a wide range of assumptions.

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Background and Motivation

Antimicrobial resistance (AMR), the process by which microbes such as bacteria, viruses, fungi and parasites develop resistance to the medicines we use to treat them, is one of the greatest health challenges of the modern world. It threatens to claim millions of lives each year globally and undermine decades of medical advancement. The most comprehensive study to date on morbidity and mortality caused by AMR estimated that nearly 5 million deaths each year are associated with drug resistant bacterial infections and that of these deaths 1.27 million are directly caused by the drug resistant character of the bacteria.[1] AMR is therefore already a leading cause of death globally and unless rapid, decisive and coordinated action is taken, it is expected that these figures will grow significantly into the future. Low- and middle-income countries (LMICs) account for nearly 90% of the direct death toll and over 99.5% of AMR-related deaths among children under five, however antimicrobial resistance is a truly global issue. In 2015 the ECDC estimated 33,100 deaths in the EU/EEA alone[2] and the GRAM study estimated 58,300 fatalities directly attributed to AMR in 2019, with a further 196,600 deaths associated with resistance within the EU (figure 1).

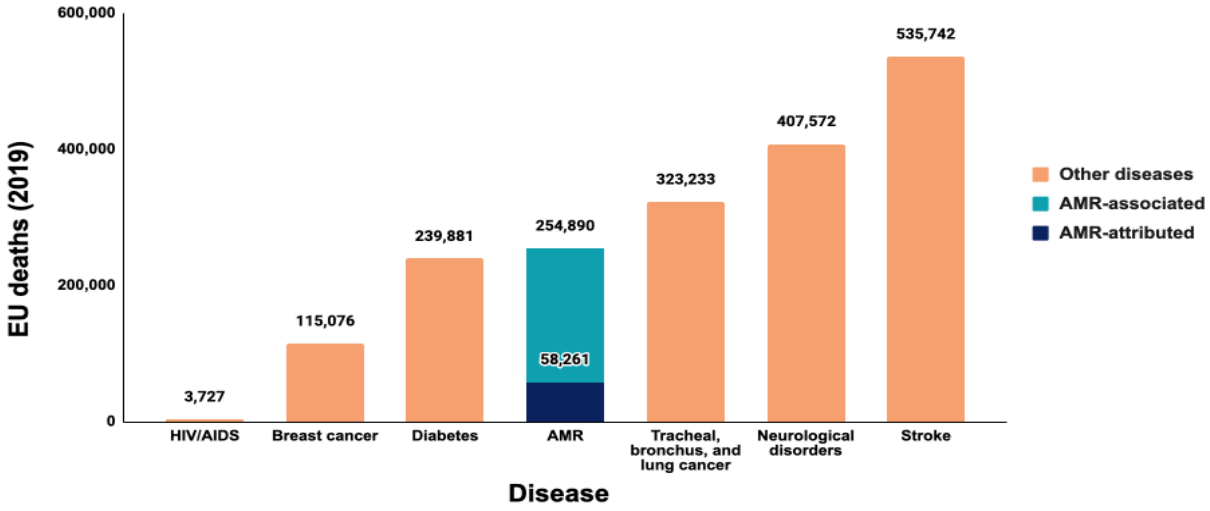

Figure 1. *AMR-associated deaths in the EU outnumbered deaths from HIV/AIDS, tuberculosis, diarrheal diseases, breast cancer, and diabetes in 2019*[3]

1 Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, *399*(10325), 629–655.

2 Cassini et. al., Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019 Jan;19(1):56-66. doi: 10.1016/S1473-3099(18)30605-4. Epub 2018 Nov 5.

3 Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019). Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2020.

In addition to its dire health impact, AMR already costs G7 countries an estimated US$30 billion annually[4] and the World Bank has estimated that by 2030 it could be responsible for a US$1 to US$3.4 trillion loss in global GDP per year and pushing 28 million people into poverty.[5]

Recent evidence from Boston University suggests a clear and significant increase of resistance to many key antibiotics over the last 20 years (figure 2).[6] These increased levels of resistance suggest that many of the antimicrobials that we currently rely on to treat common infections and safeguard medical procedures, such as invasive surgery and chemotherapy, may soon become increasingly unreliable or in a worst case scenario, be lost altogether.

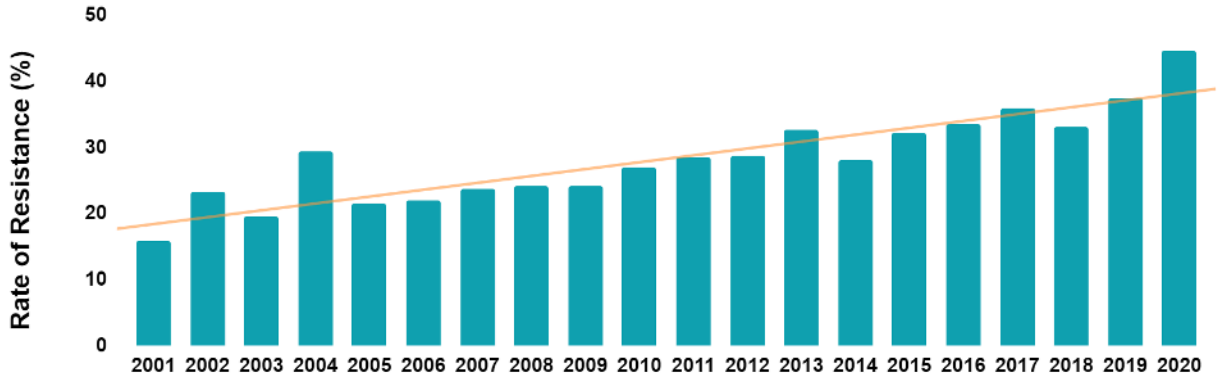

Figure 2. *Increasing rates of resistance to key antibiotics, 2001 - 2020*

We are also seeing an increasing body of evidence suggesting that drug resistance can be driven by other global crises. Conflict drives high injury rates, displacement, ineffective infection prevention and control, and environmental pollution which all contribute to AMR.[7] As an example, following the Great March of Return demonstrations on the Gaza/Israel border in 2018-19 there was a 300% increase in resistance to specific antibiotics among injured combatants.[8] Rising global temperatures linked to climate change have also hypothesised to exacerbate AMR through increased bacterial growth. A recent study in China found that a 1°C increase in air temperature has been associated with a 14% rise in carbapenem resistant

4 Data and references for the total G7 cost of AMR can be found linked here.

5 Jonas, Olga, B., Irwin, Alec, Berthe, Jean, F. C., Gall, L., Francois, G., Marquez, & Patricio, V. (n.d.). *Drug-resistant infections : a threat to our economic future (Vol. 2) : final report (English)*. Jonas,Olga B.,Irwin, Alec,Berthe,Franck Cesar Jean,Le Gall,Francois G.,Marquez,Patricio V.,. Retrieved May 11, 2024, from https://documents.worldbank.org/en/publication/documents-reports/documentdetail/323311493396993758/final-report

6 The drugs included were amoxicillin, amoxicillin-clavulanic acid, azithromycin, cefalexin, cefotaxime, ceftriaxone, ciprofloxacin, clarithromycin, cloxacillin, doxycycline, flucloxacillin, gentamicin, metronidazole, ofloxacin, and sulfamethoxazole-trimethoprim. The results are averaged across all drug-bug combinations and weighted by the sample size of the study. McDonnell, A., Klemperer, K., Pincombe, M., Bonnifield, R. S., Yadav, P., & Guzman, J. (n.d.). *A New Grand Bargain to Improve the Antimicrobial Market for Human Health*. Retrieved June 9, 2024, from https://pubs.cgdev.org/amr/

7 Pallett, S.J.C., Boyd, S.E., O'Shea, M.K. *et al.* The contribution of human conflict to the development of antimicrobial resistance. *Commun Med* 3, 153 (2023). https://doi.org/10.1038/s43856-023-00386-7

8 Moussally, K., Abu-Sittah, G., Gomez, F. G., Fayad, A. A., & Farra, A. (2023). Antimicrobial resistance in the ongoing Gaza war: a silent threat. *The Lancet*, *402*(10416), 1972–1973.

Klebsiella pneumoniae and a 6% increase in carbapenem resistant Pseudomonas aeruginosa[9], both pathogens on the WHO priority pathogen list. A lack of appropriate antimicrobial treatments can also be a significant driver of AMR, as physicians are forced to use suboptimal back-up options or treatment courses are cut shorter than required to fully clear the infection, leaving the remaining bacterial population with opportunities to develop resistance.

The Antimicrobial Pipeline Crisis

As increased resistance levels cause our existing treatments to lose their effectiveness, we need a robust and diverse pipeline of new antimicrobials coming to market to replace them. However, it is now well established that market dynamics are unsuitable for addressing this need as private firms struggle to achieve a satisfactory return on investment (ROI) to justify upfront costs. To preserve the effectiveness of new antimicrobials, they are often reserved for patients who have exhausted existing treatment options, thereby limiting initial sales volumes. In addition, treatment courses are often short which further limits sales revenue. Furthermore, new drugs are usually approved based on non-inferiority trials in non-resistant infections, this drives initial reluctance to pay a high price for them as their clinical benefit over existing, cheaper generics has not been demonstrated.[10] This has led to an unsustainable market for new antimicrobials, resulting in the majority of large R&D based pharmaceutical companies leaving this space and frequent bankruptcies among smaller companies, even when they do successfully bring a product to market (figure 3). Over 80% of the current antimicrobial pipeline is now in the hands of SMEs who often struggle to raise the funds needed to drive these vital projects forward, with 55% of the SMEs in the BEAM Alliance (the largest consortium of SMEs developing innovative products to tackle AMR in Europe) having less than €1M in funding available (figure 4).[11]

The lack of a robust ecosystem for antimicrobial R&D has led to a pipeline of new antimicrobials which the WHO has described as “insufficient to tackle the challenge of AMR”.[12] It is important to stress the time-sensitive nature of this problem. A robust pipeline of antimicrobial products not only requires aligned global incentives and financing structures, but experts trained on the various aspects of the R&D process. With large pharmaceutical companies leaving the space and SMEs struggling to attract funding, there has been a significant decrease in the number of people working in the AMR space, with the number of authors on AMR publications declining from 3,599 in 1995 to 1,827 in 2020. It is now estimated that there are 3,000 researchers active in the AMR R&D field, compared with 5,000 in HIV/AIDS and 46,000 in cancer.[13]

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9 Li, W., Liu, C., Ho, H. C., Shi, L., Zeng, Y., Yang, X., Huang, Q., Pei, Y., Huang, C., & Yang, L. (2023). Association between antibiotic resistance and increasing ambient temperature in China: An ecological study with nationwide panel data. *The Lancet Regional Health. Western Pacific*, *30*, 100628.

10 Outterson et al. Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality. PLoS Med. 2016 Jun 14;13(6):e1002043. doi: 10.1371/journal.pmed.1002043.

11 BEAMs SME Barometer, BEAM Alliance, Retrieved July 5, 2024 from https://beam-alliance.eu/wp-content/uploads/2023/05/2023-05-16-beams-barometer-2023-.pdf

12 WHO. 2021. 2020 antibacterial agents in clinical and preclinical development: An overview and analysis. https://www.who.int/publications/i/item/9789240021303

13 Leaving the Lab: Tracking the Decline in AMR R&D Professionals. AMR Industry Alliance. Retrieved July 5, 2024, from https://www.amrindustryalliance.org/mediaroom/leaving-the-lab-tracking-the-decline-in-amr-rd-professionals/

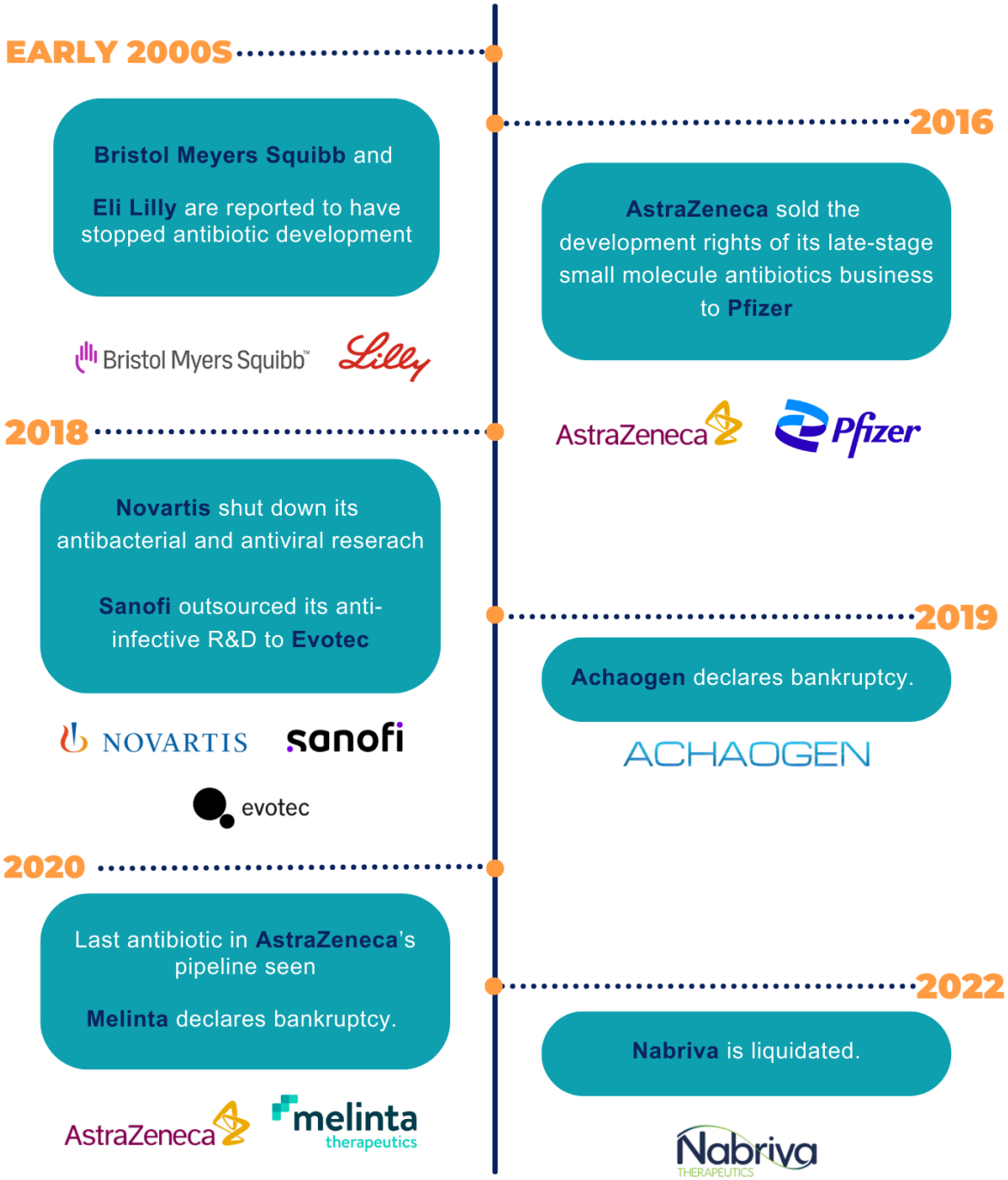

Figure 3. *Timeline of key exits and bankruptcies within antimicrobial R&D*[14]

14 *The crisis of antibiotic research and development*. (n.d.). Retrieved June 9, 2024, from https://www.cseindia.org/the-crisis-of-antibiotic-research-and-development-11960

Efforts to address this have been twofold. Push incentives, such as government grants, subsidies, or tax incentives, involve direct investments in R&D to spur innovation in antimicrobial development. These incentives aim to stimulate the initial stages of drug discovery and development by reducing financial barriers for developers. However, push incentives alone are not sufficient to address the AMR crisis. Even with funding support for R&D, many promising antimicrobial candidates fail to progress through clinical trials due to challenges such as high development costs, lengthy approval processes, and uncertain market demand.

Pull incentives, which offer financial rewards or market guarantees for successful developers, hold promise in addressing what push incentives alone cannot achieve, building a sustainable market for low volume antimicrobials. These mechanisms motivate developers to engage in antimicrobial R&D by guaranteeing a viable return on investment and aligning financial incentives with broader societal goals. Pull incentives can also offer the ability to 'de-link' revenue from sales volume, which removes the incentive to oversell the drug in order to make larger returns and facilitates responsible stewardship by prescribers, helping reduce the growth of resistance to the new drug. Given a lack of certainty in early stage development, pull incentives also have the benefit that they are not required to "choose" a winner, as you have to do with traditional grants for R&D, and can benefit from market competition allowing the best products to emerge and receive the incentive reward.

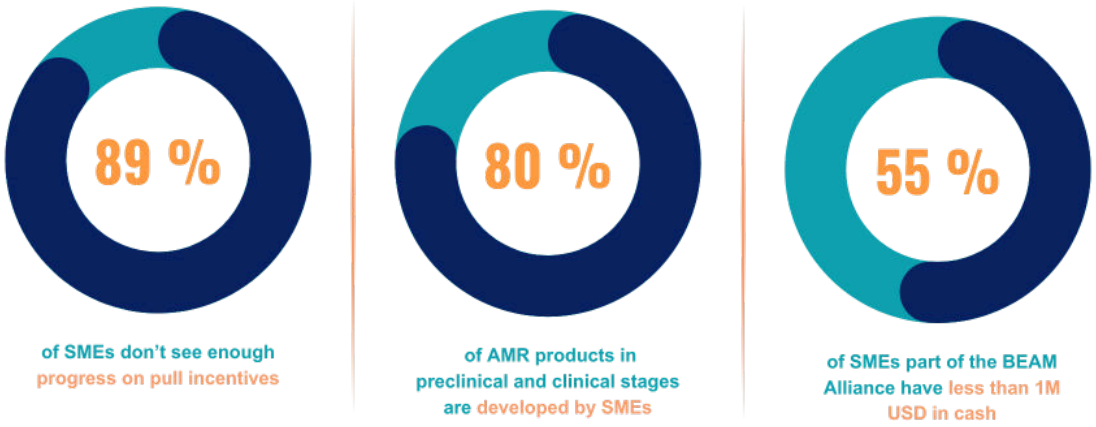

Figure 4. *The antimicrobial development pipeline is dependent on SMEs who struggle to attract investment to develop their products*

Various pull incentive models have been developed and discussed extensively within literature and different options may be appropriate for varying country contexts[15]. Despite persistent commitments to implement pull incentives, including within the G7 and G20 leaders communique, we are yet to see significant action, particularly around long term predictable financing being put in place to stimulate antimicrobial R&D.[16]

15 Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy. 2021 Mar;125(3):296-306. doi: 10.1016/j.healthpol.2020.11.015.

16 Apulia G7 Leaders' Communique https://www.g7italy.it/wp-content/uploads/Apulia-G7-Leaders-Communique.pdf

Estimating Return on Investment for Pull Incentives

The Centre for Global Development (CGD) and Office of Health Economics (OHE) have previously conducted a cost-benefit analysis to estimate the ROI for G7 members and the EU investing in pull incentive policies targeting the development of 18 new antimicrobials over three decades.[17] They estimate a 3.9:1 ROI for the EU and a 26.5:1 ROI globally over a 10-year time horizon. Additionally, Anderson *et. al.* have recently extended this model to include an estimate of ROI over a 30 year period for individual EU countries.[18] Our analysis seeks to build on their work and uses more specific figures for each country's willingness to pay to avert a disability adjusted life year (DALY) and for cost impacts on healthcare systems to better capture differences between national healthcare systems. Additionally, we have developed an interactive model which can easily be used by policymakers to vary assumptions to best reflect varying estimates and to perform sensitivity analysis. This is available as a dashboard here.

We have also expanded our analysis beyond the original CGD/OHE study to also include Switzerland, Norway, Australia and New Zealand as other high-income countries who could be reasonably expected to contribute to a global pull incentive scheme.

Table 2 below summarises the results of our analysis for the European countries with the most deaths attributable to AMR using the following base case assumptions. The assumptions are elaborated in more detail in the technical appendix and summarised below:

- Pulling one new antimicrobial to market with full delinkage would require a $3.1 billion (€2.9 billion) global revenue guarantee (using the EUR:USD 2023 avg. of 1.08). This matches the estimate provided by Outterson for a total global pull incentive for a phase II ready asset and assumes public finance has also supported the product through early stage push funding.[19] This matches the cost used by *Anderson et. al.*
- The model is based on a 10 year long revenue guarantee where payments for the new drugs are made evenly each year (e.g. $310/€290 million per year).
- Country contribution to the total above (each country's "fair share") is based on its GDP share within the G7 and EU, spread out over the 10 year period.
- Program targets the 6 priority pathogens as per the GRAM study, totaling 73% of deaths from to AMR globally in 2019: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa*

17 Silverman Bonnifield and Towse, (2022) Estimating the European Union's Return on Investment from an Ambitious Program to Incentivize New Antibiotics, available at: https://www.cgdev.org/sites/default/files/estimating-eus-return-investment-ambitious-program-incentivize-new-antibiotics.pdf

18 Anderson et. al .,Implementing an EU pull incentive for antimicrobial innovation and access: blueprint for action Lancet Microbe. 2024 June;. doi: https://doi.org/10.1016/S2666-5247(24)00109-5

19 Outterson K. Estimating the appropriate size of global pull incentives for antibacterial medicines. Health Aff (Millwood) 2021; 40: 1758–65.

- Program seeks to incentivise the development of 18 new drugs over the 30-year period to treat the 6 priority pathogens. This ensures multiple treatment options are available and defrays the design risk from a pull mechanism that selects only one winner
- Each new drug is held in reserve for 4 years and then reduces deaths from the 6 priority pathogens by 5% per year
- 2% per year decrease in drug effectiveness due to evolved resistance
- 2% per year increase in counterfactual AMR deaths without new drugs
- Discount rate of 3.5% for costs and a lower 1.5% for health benefits, reflecting the increasing value attached to health as living standards grow

Country / region	Time Horizon	Benefit : cost ratio	Total cost (discounted)	Lives saved	DALYs averted	DALY benefits (discounted)	Healthcare savings (discounted)
Germany	**10 years**	**4.6**	$636 m	3,040	48,900	$2,870 m	$38 m
	30 years	**21.5**	$2,114 m	58,170	938,000	$44,900 m	$463 m
Italy	**10 years**	**3.9**	$320 m	2,900	44,500	$1,140 m	$97 m
	30 years	**18.0**	$1,062 m	55,500	853,000	$17,900 m	$1,180 m
Poland	**10 years**	**2.6**	$107 m	1,780	35,600	$264 m	$16 m
	30 years	**12.2**	$356 m	34,100	682,000	$4,140 m	$190 m
France	**10 years**	**3.2**	$434 m	2,420	36,500	$1,291 m	$91 m
	30 years	**14.8**	$1,440 m	46,400	699,000	$20,300 m	$1,110 m
Spain	**10 years**	**3.4**	$221 m	2,050	30,300	$740 m	$23 m
	30 years	**16.2**	$736 m	39,400	580,000	$11,600 m	$276 m

***Table 2**. Costs and benefits for the 5 countries with the highest number of AMR related deaths*

Taking Germany to illustrate, the key takeaways are:

- After 10 years of the program, 6 new antimicrobials will have been developed saving over 3,040 lives, averting 48,900 DALYs and saving $38 million in healthcare costs. This gives a total benefit of over $2.9 billion for a cost of $636 million, for a ROI of 4.6.
- Over the program's full 30-year horizon we see significant increases in these returns. The program averts over 58,000 deaths, 938,000 DALYs, and $460 million in healthcare costs; the time-discounted value of the direct health benefits is over $45 billion as compared to $2.1 billion in costs, for an ROI of >21. This is expected since the costs are spread evenly throughout the program whereas the benefits are cumulative as we see an increasing number of antimicrobials reach the market and become widely available.

It is important to note that the ROI that we have demonstrated in this analysis only charts the direct clinical benefits to patients and the effects of reduced costs on the healthcare system. In reality, the benefits of such a scheme extend considerably beyond this and include reducing the overall AMR burden and treating infections which aren't fully resistant. The so-called STEDI benefits are an attempt to quantify this and we discuss this in the technical appendix. Therefore, the ROI figures that we have given could be considered as a lower bound for the benefits of these programs, with the benefits likely far higher than we have accounted for.

Sensitivity Analysis

Due to significant uncertainty in some of the assumptions used in our model, we follow *Towse & Bonnifield (2022)* and model a range of scenarios to test the robustness of the results.[20] Table 3 below summarises this scenario analysis, again using Germany to illustrate.

Scenarios - Germany	ROI horizon	
	10-year	30-year
Base case	4.6	21.5
No growth in AMR deaths (0% per year)	3.9 (-15%)	14.2 (-34%)
Fast growth in AMR deaths (5% per year)	5.8 (+27%)	40.7 (+89%)
Slow resistance growth to new antimicrobials (1% per year)	4.6 (+2%)	23.3 (+8%)
Fast resistance growth to new antimicrobials (5% per year)	4.3 (-5%)	17.2 (-20%)
Lower Antimicrobial efficacy (2% per AM)	1.8 (-60%)	8.6 (-60%)
Using GRAM data	8.1 (+77%)	38.1 (+77%)
Higher Antimicrobial incentive required ($4.5bn)	3.1 (-31%)	14.8 (-31%)
AM efficacy needs to be < 1.1% for 10-year ROI to drop below 1		

Table 3*. Scenario analysis demonstrating the robustness of the ROI*

Based on our sensitivity analysis, it can be robustly concluded that:

- The benefits of funding this pull incentive initiative far exceed costs over a wide range of scenarios for both short- and long-term horizons.
- The biggest sensitivity that can plausibly affect the conclusion above pertains to antimicrobial efficacy at reducing AMR burden: assuming a lower 2% efficacy, the ROI for Germany drops by -60% to 1.8, and ROI would drop below 1 if the new antimicrobials reduced AMR burden by less than 1.1% (i.e. funding the initiative would be more costly than value-of-life benefits and healthcare savings gained)

[20] Bonnifield, R. S., & Towse, A. (n.d.). *Estimating the European union's return on investment from an ambitious program to incentivize new antibiotics.* Center for Global Development. Retrieved May 11, 2024, from https://www.cgdev.org/sites/default/files/estimating-eus-return-investment-ambitious-program-incentivize-new-antibiotics.pdf

- While the ROI is also sensitive to the uncertainty in AMR burden growth rate, it is nevertheless still high if we assume no increase in AMR burden.

- We also investigate the case where the amount required for a global incentive is taken as $4.5 billion rather than $3.1 billion. The $4.5 billion figure from Outterson[21] represents the pull incentive required where no push funding is available to support the asset through pre-clinical and clinical development. It is also inflation adjusted from an initial figure of $4.2 billion. The 31% reduction in ROI in this case is directly proportional to the increase in the amount of funding required.

- Uncertainties in other inputs do not affect the ROI as much as antimicrobial efficacy, AMR growth rate and the overall cost of the incentive.

Conclusion and Policy Recommendations

Previous commitments by the G7[22], G20[23] and EU[24] have emphasised the urgent need to implement pull incentives as a key component of managing the burden of AMR, however, only the UK has thus far taken action which matches the ambitions of these commitments.[25] Our analysis shows that investment in pull incentive policies yields a strong ROI across various scenarios for all countries considered. This echoes the growing call from industry, academia, and civil society for the swift and efficient implementation of policies to support antimicrobial development and improve access to these drugs through innovative financing mechanisms. Without fast and decisive action, we will continue to see antimicrobial developers struggling to attract necessary investment to advance their assets, a lack of availability of both new and existing antimicrobials and the continued exodus of experienced researchers from the field.

Alongside the existing UK antimicrobial subscription model, efforts to develop and scale-up complementory pull incentive schemes, such as those under discussion within the US (PASTEUR act), Canada (proposed subscription model), Japan (Antimicrobial securement project and cooperative fund) and the EU, should be expedited. It is also crucial that these schemes are appropriately sized to act as an incentive for innovation and not just to secure access to existing drugs. These schemes should also be seen as working alongside push funding initiatives such as CARB-X and GARDP which should continue to receive funding as key elements of the antimicrobial R&D and access ecosystem.

It must be recognised that AMR is a truly global problem and therefore any pull incentive scheme must also include structures designed to ensure equitable global access and strong stewardship provisions. This could include requirements or incentives for developers to partner

21 Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Aff (Millwood). 2021 Nov;40(11):1758-1765. doi: 10.1377/hlthaff.2021.00688. PMID: 34724432.

22 Apulia G7 Leaders' Communique, Retrieved 5 July, 2024, accessible at: https://www.g7italy.it/wp-content/uploads/Apulia-G7-Leaders-Communique.pdf

23 G20 Leaders Osaka Declaration, Retrieved 5 July, 2024, accessible at: https://www.consilium.europa.eu/media/40124/final_g20_osaka_leaders_declaration.pdf

24 Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach, Retrieved 4 July 2024, Accessible at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023H0622(01)

25 Outterson, K., Rex, J.H. Global Pull Incentives for Better Antibacterials: The UK Leads the Way. *Appl Health Econ Health Policy* **21**, 361–364 (2023). https://doi.org/10.1007/s40258-023-00793-w

with groups such as GARDP or the MPP to register their products widely, provide them at affordable prices in resource scarce settings, conduct clinical trials in LMICs and paediatric populations, and support product adaptations.

Pull incentives are not a silver bullet which will resolve the AMR crisis by themselves and they must be placed in a portfolio of solutions which include improved stewardship and prescribing practices, better surveillance of changing resistance patterns, improved use of vaccinations and diagnostics and improved sanitation and hygiene standards, particularly in LMICs. However, we cannot fully address AMR without the discovery and development of new antimicrobial therapeutics and creating pathways for responsible access to them, and here the consensus is clear, pull incentive policies are a necessary part of the solution.

Technical Appendix

Methodology & Cost-Benefit Calculations

The methodology is based on the model used by the CGD/OHE to calculate ROIs. It can be illustrated by using Germany as an example, looking at costs and benefits in the short term (10-year horizon), and setting scenario parameters to our baseline assumptions; the same methodology applies to all other countries. Following the CGD/OHE, we only consider the cost to finance the pull incentive and conservatively only look at health benefits/reductions in healthcare costs associated with reduced AMR deaths; we do not include STEDI values, which plausibly increase benefits by an order of magnitude (more discussion here).

- **ROI = 4.6 = $2,904M total benefits / $636M total cost over 10 years**
- **Cost: $636 million over 10 years**
    - Outterson[26] estimated that it would require $3.1 billion to pull one phase II ready asset onto market, which assumes public finance has supported the product through early stage push funding. We assume that will be paid for by the G7 and EU27 proportional to their corresponding GDP (The additional cost for Australia, New Zealand, Norway, Switzerland and Iceland are included in addition to this $3.1 billion and again prorated to their GDP).
    - We therefore assume the share-of-GDP proportion for Germany to be ~$244 million per antimicrobial (based on a 7.9% share of GDP). Since the subscription model payment duration is 10 years, Germany would be expected to pay $24.4 million per year per antimicrobial.
    - The subscription model program aims to incentivise production of 3 antimicrobials for each of the 6 priority pathogens, hence 3 x 6 = 18 new antimicrobials over its 30-year program duration, which works out to 18 / 30 = 0.6

[26]Outterson, K. (2021). Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs* , *40*(11), 1758–1765.

new antimicrobials per year in expectation. Over the 10-year horizon under consideration, 0.6 x 10 = 6 new antimicrobials are expected to be produced.

- *Towse & Bonnifield (2022)* model payment amount 'in (statistical) expectation' as follows: 0.6 new AMs need to be paid for in year 1, 2 x 0.6 = 1.2 new AMs in year 2, 1.8 new AMs in year 3, … plateauing in year 10 where 6 new AMs need to be paid for every year, since in year 11 the first AM will have been fully paid for. This means model payment amount as starting at 0.6 x $24.4M = $14.7M in year 1, growing linearly to $147M per year in year 10 and then plateauing until end of program in year 30.
- The total amount paid by Germany over 10 years is hence $807 million, which after the 3.5% time-discounting per year for costs yields $636 million.

- **Health benefit: 3,035 lives saved and 48,917 AMR DALYs averted over 10 years, valued at $2,866 million**
  - Some high-level remarks:
    - Benefits are estimated counterfactually; the default scenario is AMR deaths growing 2% p.a., so that by the end of the 10-year horizon, it would have increased from 4,223 to 5,147 deaths
    - Benefits grow faster than costs: the longer the program runs, the more antimicrobials collectively go to market, increasing the fraction of total AMR burden averted per year. This is why e.g. the ROI for Germany grows from 4.6 over a 10-year horizon to 21.5 over a 30-year horizon.
    - DALYs averted is converted from lives saved, using the GRAM study's AMR DALYs / deaths ratio for each individual country (in Germany it is 16.12 DALYs / death). The number of DALYs averted is therefore calculated by initially calculating the lives saved and then using this ratio to convert to DALYs. This differs from the CGD/OHE analysis which uses a fixed DALYs / death ratio for all EU countries of 16.8.
    - For simplicity, *Towse & Bonnifield (2022)* ignored these factors which would reduce benefits:
      - R&D duration - they assume the start of the program would immediately yield new AMs.
      - AM 'diffusion speed' to region-wide coverage - they assume instantaneity. They do however assume a 4 year reserve period for each antibiotic between when it starts being paid for and when it becomes available, so this could be a way of capturing the slow ramp to perfect coverage.
  - Analogously to the payment amount logic above, *Towse & Bonnifield (2022)* model lives saved 'in (statistical) expectation':

- From year 1 - 4, no AMR deaths are averted, since the new antimicrobials are held in reserve
- In year 5, the 'first 0.6 new antimicrobial' goes to market; since the default scenario assumes 5% antimicrobial efficacy, '0.6 of an antimicrobial' would then avert 0.6 x 5% = 3% of the total AMR burden. Since in year 5 we estimate 4,662 AMR deaths, the '0.6 new antimicrobial' then averts 0.6 x 5% x 4,662 = 140 AMR deaths
- In year 6, the 'second 0.6 new AM' goes to market. Now there are '1.2 new AMs'. The 'first 0.6 new AM' has already declined in efficacy by -2% due to evolved resistance, so it only averts 0.6 x 5% x (1 - 2%) of total AMR deaths in year 6. The 'second 0.6 new AM' is still in its own 'year 1', so it averts 0.6 x 5% of total AMR deaths. The total benefit in year 6 is the sum, which works out to 282 AMR deaths averted in expectation
- Following this logic, by year 10 there will be 0.6 x 10 = 6 new AMs on the market in expectation, collectively averting 0.6 x 28.5% = 17.1% of the 5,147 AMR deaths from the 6 priority pathogens in the counterfactual scenario after accounting for evolved resistance, which works out to 881 lives saved in year 10
- Over 10 years, this adds up to 3,035 lives saved

- Doing a similar calculation for AMR-attributable DALYs averted in expectation yields 48,917 DALYs averted
- Using Germany's cost-effectiveness threshold from Gandjour, 2023[27] and using the geometric mean of their low and high estimates as the midpoint, Germany's healthcare system is willing to pay $66,339 to preserve a year of healthy life. Applying this value to the 48,917 DALYs averted at a 1.5% time discount per year for health benefits yields a $2,866 million health benefits valuation

- **Healthcare savings benefit: $38 million over 10 years**
  - The OECD[28] estimate that AMR costs Germany's healthcare system $191,207 per 100,000 population, which – using Germany's national population of 83,797,985 and 9,648 AMR-attributable deaths – works out to $16,607 per AMR death. Note that the healthcare cost is due to all AMR pathogens, so the cost per death should be calculated by reference to all AMR pathogens.[29]

27 Afschin Gandjour 2023, "A Model-Based Estimate of the Cost-Effectiveness Threshold in Germany" https://link.springer.com/article/10.1007/s40258-023-00803-x

28 OECD (2018), Stemming the Superbug Tide: Just A Few Dollars More, OECD Publishing, Paris. https://doi.org/10.1787/9789264307599-en

29 Driss Ait Ouakrim, Tiago Cravo Oliveira, Mario Jendrossek. (n.d.). *Health and economic burden of antimicrobial resistance*. Retrieved January 25, 2024, from https://www.oecd-ilibrary.org/sites/9789264307599-en/1/2/4/index.html?itemId=/content/publication/9789264307599-en&_csp_=33f7c05cefd0845031c4db9085aa0f90&itemIGO=oecd&itemContentType=book

- We assume that every AMR death averted saves Germany's healthcare system $16,607 on average, so averting 3,035 deaths hence saves $38 million over 10 years after time-discounting

- **Cost-effectiveness: $13,000 per AMR DALY averted and $209,700 per life saved from dying of AMR-attributed infections**
  - $636M cost over 10 years / 48,917 AMR DALYs = $13,000 per DALY averted
  - $636M cost over 10 years / 3,035 lives saved = $209,700 per life saved

Assumptions discussion

The assumptions that go into estimating the outputs in the baseline scenario above are as follows:

- The AMR burden figures for both deaths and DALYs used in the analysis, informed by data gathered in 2015 by the ECDC, are those solely attributable to antimicrobial resistance.[30] Deaths and DALYs associated with AMR were omitted to focus on direct costs and avoid overestimation, so the results should be interpreted as conservative.

- In addition, the AMR burden figures are conservatively limited to the 6 WHO priority pathogens (*Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii,* and *Pseudomonas aeruginosa*), instead of including all pathogens, following the methodology in *Towse & Bonnifield (2022)*. That said, we depart from *Towse & Bonnifield (2022)* in using the specific burden estimates for the 6 pathogens named above, whereas *Towse & Bonnifield (2022)* took the 6 highest pathogen burdens in each EU country rather than fixing the 6 priority pathogens globally; they mention their numbers being an overestimate as a result of this so we've corrected it.

- Finally, we have conservatively set year 1 figures (corresponding to the program starting in 2025) to the 2015 estimates by *Cassini et. al (2018)*, instead of applying the 2% per year growth rate assumption to the period between 2015 and 2025. This penalises all our estimated return on investment figures by -18%

- We use an opportunity-based approach to consider the country-specific value of averting a DALY. Whenever available, we determine each country's DALY value by obtaining the monetary value it is willing to invest in preserving a year of healthy life from the existing literature, using conservative estimates; while this method does not directly represent AMR values, it offers insight into what is feasible for a country to spend on therapeutic interventions. For many countries, we were unable to find these figures in the literature, in which case we used the cost-effectiveness threshold estimation tool developed to

30 European Antimicrobial Resistance Collaborators. (2022). The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *The Lancet. Public Health*, *7*(11), e897–e913.

accompany; the tool's estimates are generally in line with or less than the CGD figures and were vetted via expert interview, so we think they are reasonable.[31]

- The cost to national healthcare systems due to AMR were based on figures from the OECD[32]. These figures are likely to now be an underestimate given the increase in both AMR burden and inflation since 2018.

- Introducing a new antimicrobial to the market, fully delinked, would necessitate a 10-year global revenue guarantee valued at $3.1 billion, which in this analysis is implemented in the form of a subscription model. This figure is in line with Anderson *et. al.* and reflects the estimated value required for a pull incentive for a phase II ready asset, falling within the range previously modelled by *Outterson (2021)* of $2.2 to $4.8 billion. This differs from the original value of $4.5 billion used by *Towse & Bonnifield (2022*) which represented the total required pull incentive for a pre-clinical asset adjusted for inflation. We have used $3.1 billion to account for the current levels of expected public push funding which is available to support an asset to the end of phase II.

- There are several methods that can be used to ascertain the equitable contribution of each country to ensure a proportional distribution of the financial burden. We default to the GDP share method, but include other methods to enable users to explore the impact of choosing other ways to apportion country contribution:

    - The GDP share method, employed by *Towse and Bonnifield (2022)* and also adopted in our study, calculates contributions based on the GDP share of each country within the G7 and EU, specifically including the EU, US, UK, Japan, and Canada. In addition, in our modelling we have included contributions from Switzerland, Norway, Australia and New Zealand. *Outterson (2021)* similarly uses this approach, though our GDP data are more current.[10] This method presumes uniform health priorities among the analysed nations and that countries with larger GDPs should bear a proportional share of the financial burden associated with antimicrobial resistance (AMR).

    - The AMR burden method, which we did not utilise, would allocate financial responsibilities based on each country's share of the AMR burden within the EU and G7, in particular the EU, US, UK, Japan, and Canada*)*. This approach is impractical due to the constrained health budgets of countries with higher AMR burdens, which typically have lower GDP per capita, and would necessitate an additional contribution of $501 million from the EU collectively.

    - The antibiotic consumption-based method would allocate financial responsibility in proportion to the country's antibiotic consumption within the EU, US, UK, Japan, and Canada, following *Towse and Bonnifield (2022)*. We use consumption

31 Pichon-Riviere, A., Drummond, M., Palacios, A., Garcia-Marti, S., & Augustovski, F. (2023). Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. *The Lancet. Global Health*, *11*(6), e833–e842.

32 OECD (2018), Stemming the Superbug Tide: Just A Few Dollars More, OECD Publishing, Paris. https://doi.org/10.1787/9789264307599-en

figures from WHO GLASS whenever available, since it represents actual data. For countries without WHO GLASS data, we use the modelled estimates from *AJ Browne et al (2021)*, whose country coverage is more comprehensive.[33] Since these modelled estimates are consistently higher than the actual figures from WHO GLASS, we adjust them downwards by the average ratio of the figures (which incidentally is 1.286x for both mean and median)

    - We also include fair share methods based on member state GNI-based contributions to the EU budget (following *Anderson et. al. (2024)*), GNI PPP, and population, all calculated using the same logic as that of the GDP share method. Data for the first method is from Annex I of the special report *Verification of Gross National Income for financing the EU budget* by the European Court of Auditors, and data for the second and third methods are from the World Bank

- A total of 18 new drugs were proposed to guarantee multiple treatment options for 6 priority pathogens, launched at an average of 6 new drugs per decade over a 30-year period
- The drugs are held in reserve for 4 years, and the cost of incentivizing the development and introduction of each new drug to the market is paid in full within the first 10 years. After the 10 year revenue guarantee the EU member state will be able to procure the drug for marginal cost
- Each new drug reduces deaths by 5% annually, with a 2% decrease in effectiveness yearly due to resistance, and an assumed 2% annual increase in deaths without new drugs
- Discount rates of 1.5% for health effects and 3.5% for costs were applied, reflecting the increasing importance of health as living standards improve

33 Browne, A. J., Chipeta, M. G., Haines-Woodhouse, G., Kumaran, E. P. A., Hamadani, B. H. K., Zaraa, S., Henry, N. J., Deshpande, A., Reiner, R. C., Jr, Day, N. P. J., Lopez, A. D., Dunachie, S., Moore, C. E., Stergachis, A., Hay, S. I., & Dolecek, C. (2021). Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. *The Lancet. Planetary Health*, *5*(12), e893–e904.

Sensitivity Table

Table 3 shows the same scenario analysis as earlier, with additional outputs:

Scenarios - Germany	Time Horizon	Benefit : cost ratio	Lives saved	DALYs averted	DALY benefits (discounted)	Healthcare savings (discounted)	Change vs. base case
Base case	10 year	**4.6**	3,035	48,917	$2,866 m	$37.9 m	-
	30 year	**21.5**	58,170	937,527	$44,974 m	$463 m	-
No AMR burden growth (0% per year)	10 year	**3.9**	2,573	41,475	$2,432 m	$32.2 m	**-15%**
	30 year	**14.2**	37,868	610,313	$29,623 m	$310 m	**-34%**
Fast AMR burden growth (5% per year)	10 year	**5.8**	3,870	62,379	$3,652 m	$48.2 m	**27%**
	30 year	**40.7**	111,933	1,804,031	$85,193 m	$858 m	**89%**
Slow resistance growth (1% per year)	10 year	**4.6**	3,087	49,745	$2,914 m	$38.5 m	**2%**
	30 year	**23.3**	63,164	1,018,014	$48,706 m	$499 m	**8%**
Fast resistance growth (5% per year)	10 year	**4.3**	2,887	46,529	$2,728 m	$36.1 m	**-5%**
	30 year	**17.2**	46,267	745,685	$36,039 m	$375 m	**-20%**
Lower AM efficacy (2% per AM)	10 year	**1.8**	1,214	19,567	$1,146 m	$15.1 m	**-60%**
	30 year	**8.6**	23,268	375,011	$17,990 m	$185 m	**-60%**
Using GRAM data	10 year	**8.1**	5,381	86,719	$5,081 m	$67.1 m	**77%**
	30 year	**38.1**	103,123	1,662,035	$79,730 m	$821 m	**77%**
Higher Antimicrobial incentive required ($4.5bn)	10 year	**1.8**	3,035	48,917	$2,866 m	$37.9 m	**-31%**
	30 year	**8.6**	58,170	937,527	$44,974 m	$463 m	**-31%**

***Table 3**. Same scenario analysis as in Table 2, with additional outputs*

STEDI Benefits of Antimicrobials

As mentioned in the methodology section, much of the benefit of new antibiotics lie outside of the set of benefits that traditional reimbursement policy mechanisms like Health Technology Assessment (HTA) focus on, which are limited to direct benefit to the immediate patient and cost savings to the healthcare system. Outterson and Rex (2020) summarise these benefits using the STEDI acronym: [34]

- **Spectrum value** arises from preventing 'collateral damage' to the microbiome and reducing AMR buildup
- **Transmission value** arises from preventing infection spread among the wider population
- **Enablement value** arises from protecting the safety of surgical procedures relying on prophylactic or post-operation antibiotics, or of using drugs that suppress the immune system hence risking infection
- **Diversity value** arises from preserving efficacy of existing antibiotics against resistant pathogens
- **Insurance value** arises from having access to an effective treatment available in case of a pandemic

An EFPIA-commissioned report by Charles River Associates estimates STEDI benefits to be roughly an order of magnitude higher than direct benefits and healthcare cost savings.[35]

Differences between our work and the original CGD/OHE model

There are a few reasons our estimated figures differ from those of Anderson *et. al. (2024)* and the CGD/OHE whose methodological approach we have otherwise faithfully replicated. That said, our dashboard enables exploration of both sets of inputs, and the bottomline is unchanged: return on investment in this program remains robustly positive over both short- and long-term horizons.

- For AMR burden estimates, Anderson *et. al. (2024)* took the 6 highest pathogens in each EU country, while we fix the 6 priority pathogens globally following the highest global burden based on the *GRAM study (2022)*. Our reasoning is that pathogen selection should be fixed to guide drug development.
- For converting lives saved into DALYs averted, Adrian et al used the weighted average of deaths in Western Europe EU countries (15.5 DALYs per death) and of Central

34 Outterson, K., & Rex, J. H. (2020). Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization. *Translational Research: The Journal of Laboratory and Clinical Medicine*, *220*, 182–190.

35 By:, P. (n.d.). *A framework for assessing the potential net benefits realised through Transferable Exclusivity Extension (TEE) as an incentive for development of novel antimicrobials: FINAL REPORT*. https://www.efpia.eu/media/676634/cra-efpia-a-framework-for-assessing-the-costs-and-benefits-of-tee-final-report.pdf

European deaths (20.3 DALYs per death) calculated using data from the *Gram study (2022).* We also used the *GRAM study (2022)*, but instead took country-specific figures which are more accurate (e.g. Germany has a DALY/death value of 16.12 based on 68,058 DALYs and 4,223 deaths).

- For healthcare cost savings, *Anderson et. al. (2024)* used an average based on *Cassini et. al. (2018)* of €33,000 per death totalled and then prorated across member states according to shares of deaths, while we used member state-specific health cost estimates based on the OECD SPHeP-AMR model as tabulated by *Ouakrim et. al. (2018*). This allows for more specific country figures to be used, based on the most granular data available.

- For country-specific cost-effectiveness thresholds, *Anderson et. al. (2024)* divided EU member states into "high" or "low" income according to whether they were above or below the GDP median and applied the Swedish cost-effectiveness threshold number to above average and the Polish threshold to below average, while we reference country-specific estimates from the health economics literature whenever possible and otherwise reference the outputs of the threshold estimation tool whose data and methodology is elaborated in *Pichon-Riviere et. al. (2023).*[36]

- For calculating "fair share" of costs borne by member states, *Anderson et. al. (2024)* used the relative size of the GNI-based contributions of each member state to the 2021 EU budget based on figures in Annex I of the special report *Verification of Gross National Income for financing the EU budget* by the European Court of Auditors. We have instead aimed to provide a variety of fair share options including the GNI-based approach as an adjustable parameter in our model so stakeholders can see how they affect costs and ROI; we discuss these options at length in the assumptions section

- For calculating "fair share" of costs borne by the EU as a whole, both *Anderson et. al. (2024)* and we use GDP figures from the World Bank and both of us define the denominator to be G7 + EU[37]. The slight difference of 34% EU share of global in *Anderson et. al. (2024)* vs 32.4% in our model arises from us using more recent World Bank data we have used.

36 Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. Lancet Glob Health. 2023 Jun;11(6):e833-e842. doi: 10.1016/S2214-109X(23)00162-6.

37 More specifically: EU27, US, UK, JP, CA

Future work

This is a preliminary analysis. Future work may include:

1. Determining the willingness to pay for a year of healthy life (or of averting a DALY) for all the countries in the EU and G7 from the literature: lower and upper bounds.
    - Currently we have only done this for a few countries (see below); other figures have been estimated using the cost-effectiveness threshold estimation tool (*Threshold Estimation Tool*, n.d.) developed to accompany *Pichon-Riviere et. al. (2023). List of countries: the Netherlands, Denmark, Italy, Switzerland, Australia, the UK, the US, Japan, and Canada. Those last 3 countries are also missing low and high estimates*
    - Currently we use an opportunity cost-based approach following *Towse & Bonnifield (2022*); it might be good to consider if other approaches are appropriate.
2. Including STEDI benefits and productivity benefits, not just direct clinical benefits and healthcare cost savings.
3. Turning the dashboard into an app, like the threshold estimation tool above.
4. Modelling other kinds of pull incentives, not just subscription models: market entry rewards, revenue guarantees, various kinds of exclusivity extensions, accelerated approval & priority review.
5. Analysis considering what happens if not all countries participate in pull incentive.

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About ARMoR

ARMoR is an evidence-led, non-profit combating Antimicrobial Resistance (AMR) through advocacy and research. We support policies designed to reinvigorate antimicrobial R&D and ensure wide, equitable access to these vital medicines. We are a philanthropically funded global health organisation with no financial stake in the policies we advocate for and full autonomy over our decision-making process.