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Estimating the European Union's Return on Investment from an Ambitious Program to Incentivize New Antibiotics

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KEY MESSAGES

- We estimate the benefits to the European Union (EU) of a new antibiotic incentive program, which would seek to generate a total of 18 new antibiotics over three decades to treat six priority pathogens.
- We assume that every country in the G7 + EU pays its "fair share" toward the total cost of $4.5 billion per drug; the EU contribution is 34.0%, or $1.5 billion per new drug.
- The incentive payments would be spread over 10 years and following fulfilment the EU will be able to procure the new antibiotic for close to marginal cost.
- Over 10 years, such a program would save 20,000 lives and generate $15.5 billion in total benefits for the EU, for an ROI of 4:1.
- Over 30 years, such a program would save 385,000 lives and generate $541 billion in total benefits for the EU, for an ROI of 11:1.
- The global return on investment is much larger, at 27:1 over 10 years (with 518,000 lives saved); and 125:1 over 30 years (with 9.9 million lives saved).

Background and Motivation

Anti-microbial drugs form the backbone of modern medicine. Yet their lifespan is naturally limited; over time, use of these drugs selects for mutations that survive exposure those same drugs, driving "anti-microbial resistance," or AMR. Already, drug-resistant infections kill an estimated 33,000 citizens of the European Union (EU) every year.[1] In the absence of sufficient research and development (R&D) investment for new antimicrobials, deaths from drug-resistant infections could increase dramatically in the coming decade.

To address this growing crisis and solve market failures that prevent the development of new antibiotics, the EU is considering incentive programs that would help provide predictable and value-based compensation to the successful developers of new antibiotics. In this note, we present the results of a modelling exercise to estimate the likely return on investment (ROI) from such a program, assuming it is paired with complementary and proportionate efforts from the EU's G7 partners. The results are necessarily imprecise due to several uncertain parameters, but nevertheless provide evidence of a very high expected ROI that is robust to different inputs and assumptions.

Assumptions and Methods

We construct a country-specific Excel models for each member of the G7 + EU, which we will make publicly available. We make the following assumptions across all our G7 modelling, which are explained in further detail in a companion Policy Paper:[2]

- The European Union would commit to a new antibiotic incentive program, which seeks to generate a total of 18 new antibiotics over three decades to treat six priority pathogens.
- Each new drug is held in reserve for 4 years and then reduces deaths from the six priority pathogens by 5% each year; starting from year 5 onwards, effectiveness falls by 2% year on year, due to the build-up of resistance.
- Pulling one new antimicrobial to market (with full delinkage) would require global revenue guarantees of $4.5 billion USD. (For consistency, we use USD across our estimates; we assume a EUR to USD conversion rate of 1.05:1, which is average YTD for 2022 as of end-November).
- Following fulfilment of its revenue guarantee, the EU will be able to procure new antibiotics for close to marginal cost.
- We use a discount rate of 1.5% for health effects, and 3.5% for costs; and
- We assume the rate of growth of resistance is 2%. Absent new drugs, annual deaths increase by 2% each year.
- We consider only direct health gains and averted health system costs; we do not consider the broader "STEDI" benefits of new antibiotics.[3]

For the EU specifically, we make the following key assumptions:

- We assume that the EU's share of this financing will be proportionate to its current GDP share in the G7 plus EU (34.0%) with the remainder paid by other countries, which means that the EU would pay $1.5 billion per new drug. We amortize the costs over a ten-year period following market entry.
- Current annual EU deaths from the six priority pathogens are 27,942; each death is associated with 17 DALYs.[4]
- Each DALY is valued at $58,000 USD, which reflects heterogeneity across the EU.[5] This implies a total DALY value per AMR death of $972,000, and $27.2 billion in annual health losses from the six priority pathogens.
- Each death is associated with health system costs of $35,000 USD; total (current) health system costs are $1.16 billion.[6]

Estimated Return on Investment

Headline results of the modelling, from the EU's perspective, are presented in Table 1. The returns are very large over 30 years, with 385,000 lives saved and benefits exceeding the costs by a factor of 18. Over 10 years, the program saves 20,000 lives; benefits exceed costs by a multiplier of around 4. This reflects the fact that costs are incurred throughout the program, whereas the benefits are cumulative, with many occurring decades into the future as a sustainable program is put in place.

TABLE 1 Domestic EU costs and benefits, over 10 years and over 30 years

	TOTAL COST (DISCOUNTED)	LIVES SAVED	DALYs SAVED	DALY VALUE (DISCOUNTED)	HEALTHCARE SAVINGS (DISCOUNTED)	DALY + HEALTHCARE SAVINGS (DISCOUNTED)	BENEFIT: COST RATIO
10-Year	$3.99 bn	20,000	337,000	$14.98 bn	$530 m	$15.50 bn	4:1
30-Year	$13.25 bn	385,000	6,461,000	$234.98 bn	$6.5 bn	$241.45 bn	18:1

Global benefits are presented in Table 2, assuming that the full $4.5 billion pull incentive per antibiotic is covered in full by G7 members based on proportionate GDP. Over its full 30-year time horizon, the program averts 9.9 million deaths and 374.5 million DALYs, generating an ROI of 125 to 1. Over the shorter 10-year period, the program averts 518,000 deaths and 19.5 million DALYs, generating an ROI of 27 to 1.

Results of a sensitivity analysis are shown in Table 3, demonstrating robustness of the high ROI to many different assumptions and scenarios. From both the EU and global perspectives, the biggest sensitivity is related to the efficacy of drugs that result from this initiative against AMR-related deaths. Another significant sensitivity is number of deaths at baseline; our base case uses numbers derived from Cassini

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

	TOTAL COST (DISCOUNTED)	LIVES SAVED	DALYS SAVED	VALUE OF DALYS SAVED	BENEFIT: COST RATIO
10-Year	$11.7 bn	518,000	19.5 m	310.6 bn	27:1
30-Year	$38.9 bn	9,933,000	374.5 m	4,874.2 bn	125:1

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

SCENARIO	10-YEAR, EU[a]	30-YEAR, EU[a]	10-YEAR, GLOBAL[b]	30-YEAR, GLOBAL[b]
Base Case	4:1	18:1	27:1	125:1
GRAM #s on EU Baseline Deaths (49,182/ year)	7:1	32:1	27:1	125:1
No Growth in AMR Deaths (0 % Per Year)	3:1	12:1	23:1	82:1
Fast Growth in AMR Deaths (5% Per Year)	5:1	35:1	34:1	237:1
Slower Resistance Growth to New Antimicrobi-als (1% Per Year)	4:1	20:1	27:1	136:1
Faster Resistance Growth to New Antimicrobials (5% Per Year)	4:1	15:1	25:1	100:1
Lower Drug Efficacy Scenario (2% Death Reduc-tion Per Drug at Peak Efficacy)	2:1	7:1	11:1	50:1

a. Includes health benefits and averted healthcare costs
b. Includes health benefits only

et al (2018); as these figures are substantially lower than the estimates presented in the GRAM study (2019), use of the latter estimates would increase the expected ROI. The program remains highly beneficial even if there is no counterfactual growth in AMR deaths over the next 30 years.

Technical Appendix

This technical appendix details the construction for EU-specific parameters that are input into the modelling. The rationale for all other input parameters, and complete model design, are detailed in a companion working paper (Towse and Silverman Bonnifield, 2022).

GDP fair share calculation

Each country's "fair share" was calculated as proportionate to their respective GDPs within the G7 + EU using World Bank data for 2021 (Appendix Table 1).

Exchange rates

All figures were converted into USD for consistency, using the year-to-date average exchange rate for 2022 as of November 30, 2022. For the EU, the exchange rate used was 1.05 USD to 1 EUR.

Deaths and DALYs at baseline

Across all G7 members, we consider six priority pathogens. For the EU, we used the figure presented in Cassini et al. (2018) on total number of deaths per year at baseline (33,100).

We used data associated with the GRAM study, available via this data portal, to derive estimates on (1) proportion of deaths attributable to the six priority pathogens (84%); and the number of DALYs associated with each AMR death (17).

1. **Proportion of deaths attributable to the six priority pathogens:** For each country in the EU, we extract data on total estimated number of AMR deaths and AMR deaths from the six leading pathogens in each country; dividing the latter by the former, we estimate that 84% of EU deaths are from the six leading pathogens. We use this figure as a rough estimate of the proportion of total EU deaths from our six priority pathogens, though we note this is likely to be a slight over-estimate, as some countries within the EU may have different top-six pathogen lists than those that we select as our priority pathogens (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*).

APPENDIX TABLE 1 GDP fair share calculation

	GDP (TRILLION)	PERCENT	CONTRIBUTION PER NEW DRUG
USA	23,00	45,8%	2.061.342.362
Japan	4,94	9,8%	442.740.490
United Kingdom	3,19	6,4%	285.899.223
Canada	1,99	4,0%	178.350.926
European Union	17,09	34,0%	1.531.666.999
Total	50,21	100,0%	4.500.000.000

2. **Number of DALYs associated with each AMR death:** We extract region-wide data from Western Europe and Central Europe on (1) total deaths attributable to AMR (70,000); and (2) total DALYs attributable to AMR (1.18 million). Dividing the latter by the former, we estimate that each AMR death in the European region, and by extension in the EU (though the country groupings differ slightly), is associated with 17 DALYs.

Health system costs

We calculate total national health system costs associated with each death – that is, total health system costs for AMR divided by the number of deaths, not the direct costs incurred by each patient who dies of AMR.

For the EU, health system costs are derived from OECD (2019), which cites another OECD (2018) estimate of $1.1 billion in annual healthcare costs attributable to AMR between 2015 and 2040, which implies in EUR 33,000 healthcare spending associated with each of the 33,000 deaths. This converts to $35,000 USD given the YTD exchange rate.

Value per DALY

Given the heterogeneity across the EU, we use a weighted average of cost-effectiveness thresholds used by Poland (a lower-income country within the EU) and Sweden (a higher-income country within the EU). These thresholds are $39,500 (PLN 175,926) and $67,500 (SEK 700,000), respectively. For Sweden, we use the lower end of their threshold range.

We extracted nominal GDP per capita for each country of the EU from World Bank databank. We average Poland ($17,800) and Sweden ($60,200) to get a categorization threshold for EU countries ($39,000). We categorize EU countries by whether their GDP per capita is above or below this threshold. We then construct a weighted average of the two categories based on number of deaths attributable to the six leading pathogens in the GRAM study.

This approach yields an EU weighted average threshold of $50,300 per DALY.

Endnotes

1 Cassini et al. 2018. 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 Inf Disease 19(1):56-56.

2 Towse and Silverman Bonnifield, 2022. "An Ambitious USG Advanced Commitment for Subscription-Based Purchasing of Novel Antimicrobials and Its Expected Return on Investment." CGD Policy Paper 277. Washington, DC: Center for Global Development. https://www.cgdev.org/publication/ ambitious-usg-advanced-commitment-subscription-based-purchasing-novel-antimicrobials

3 See Outterson and Rex (2020) and broader discussion in the Towse and Silverman Bonnifield (2022).

4 Figures derived from Cassini et al. (2018) and GRAM data; see technical appendix for full details .

5 Figure is derived as a weighted average of opportunity cost-based thresholds used in Sweden ($67,500) and Poland ($39,500); see technical appendix for full details of the construction.

6 Figure is derived from figures presented in OECD (2019). Antimicrobial Resistance Tackling the Burden in the European Union. See technical appendix for full details.

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