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Estimating Japan's Return on Investment from an Ambitious Program to Incentivize New Antibiotics

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KEY MESSAGES

- We estimate the benefits to Japan 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 Japanese contribution is 9.8%, or $443 million per new drug.
- The incentive payments would be spread over 10 years and following fulfilment Japan will be able to procure the new antibiotic for close to marginal cost.
- Over 10 years, such a program would save 14,000 lives and generate $6.9 billion in total benefits for Japan, for an ROI of 6:1.
- Over 30 years, such a program would save 270,000 lives and generate $106.2 billion in total benefits for Japan, for an ROI of 28:1.
- 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 23,210 Japanese citizens 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 Government of Japan is considering a new antibacterial pull incentive (such as a minimum revenue guarantee or a subscription) for successful developers of qualifying antibacterials. 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 Japan'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, 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]

- Japan 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 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 USD to JPY conversion rate of 1:131, which is average YTD for 2022 as of end-November).
- Following fulfilment of its revenue guarantee, Japan 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 Japan specifically, we make the following key assumptions:

- We assume that Japan's share of this financing will be proportionate to its current GDP share in the G7 plus EU (9.8%) with the remainder paid by other countries, which means Japan would pay $443 million per new drug. We amortize the costs over a ten-year period following market entry.
- Current annual Japanese deaths from the six priority pathogens are 19,575; each death is associated with 13.1 DALYs.[4]
- We use an opportunity-cost based approach to conservatively value a DALY at ¥5 million,[5] which translates to $38,170 USD. This implies a total DALY value per AMR death of $499,000, and $9.8 billion in annual health losses from the six priority pathogens.
- Each death is associated with hospital costs of $69,100 USD.[6]

Estimated Return on Investment

Headline results of the modelling, from Japan's perspective, are presented in Table 1. The returns are very large over 30 years, with 270,000 lives saved and benefits exceeding the costs by a factor of 28. Over 10 years, the program saves 14,000 lives; benefits exceed costs by a multiplier of around six. This reflects the fact that costs are incurred throughout the program, whereas the benefits are cumulative, with many occurring decades into the future as a sustainable program is put in place.

TABLE 1 Domestic Japanese 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	$1.15 bn	14,000	184,000	$6.20 bn	$730 m	$6.93 bn	6:1
30-Year	$3.83 bn	270,000	3,523,000	$97.25 bn	$8.92 bn	$106.2 bn	28:1

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 518,262 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 Japanese and global perspectives, the biggest sensitivity is related to the efficacy of drugs that result from this initiative against AMR-related deaths. The program remains highly beneficial even if there is no counterfactual growth in AMR deaths over the next 30 years.

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, JAPAN[a]	30-YEAR, JAPAN[a]	10-YEAR, GLOBAL[b]	30-YEAR, GLOBAL[b]
Base Case	6:1	28:1	27:1	125:1
No Growth in AMR Deaths (0 % Per Year)	5:1	18:1	23:1	82:1
Fast Growth in AMR Deaths (5% Per Year)	8:1	52:1	34:1	237:1
Slower Resistance Growth to New Antimicrobials (1% Per Year)	6:1	30:1	27:1	136:1
Faster Resistance Growth to New Antimicrobials (5% Per Year)	6:1	22:1	25:1	100:1
Lower Drug Efficacy Scenario (2% Death Reduction Per Drug at Peak Efficacy)	2:1	11:1	11:1	50:1

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

Technical Appendix

This technical appendix details the construction for Japan-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 Japan, the exchange rate used was 131 JPY to 1 USD.

Deaths and DALYs at baseline

Across all G7 members, we consider six priority pathogens, which are detailed in Appendix Table 2. For Japan, numbers on baseline deaths and DALYs attributable to each of the six priority pathogens are drawn from data associated with the GRAM study, available here (Appendix Table 2). Dividing attributable deaths by attributable DALYs implies an average loss of 13.1 DALYs associated with each AMR death from the six priority pathogens.

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

APPENDIX TABLE 2 Deaths and DALYs at baseline (Japan)

SIX PRIORITY PATHOGENS	DEATHS	DALYs
Escherichia coli	4.194	56.170
Staphylococcus aureus	9.351	119.609
Klebsiella pneumoniae	993	13.161
Streptococcus pneumoniae	1.983	23.759
Acinetobacter baumannii	1.716	25.617
Pseudomonas aeruginosa	1.338	17.457
Total	19.575	255.773

We are also aware of a paper by Tsuzuki et al. (2021) which estimates 9,587 deaths per year in Japan (as of 2018) from bloodstream infections due to all pathogens. As this estimate is larger than the corresponding value suggested in the GRAM study (6,588 annual deaths)—and as the paper does not include data for other syndromes—we opt to use the GRAM study for a conservative estimate.

Hospital costs

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

For Japan, hospital costs are derived from Table 5 of Matsumoto et al. (2021). Total hospital costs presented are ¥329.4 billion; the paper suggests that these costs are amortized over 804,542 life years lost, and the footnotes clarify that they estimate 22.1 years of life are lost per death. This implies that the paper's costs are estimated based on 804,542 YLL/22.1 = 36,404 deaths per year. Amortizing the total hospital costs over the number of deaths presented, we estimate of ¥9.1 million in total costs per death, which translates to $69,100 in total hospital costs associated with each AMR death from the six priority pathogens.

Endnotes

1 See data for G7 countries associated with the GRAM study here.

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 Figure is derived from GRAM-study data, available here.

5 This is the lower end of the threshold range used by Japan's agency; see here, for example.

6 Figure is derived from the total costs of ¥329 billion from Matsumoto et al. (2021), Table 5, amortized over 23,210 total deaths (GRAM study) and converted into USD at the current exchange rate.

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