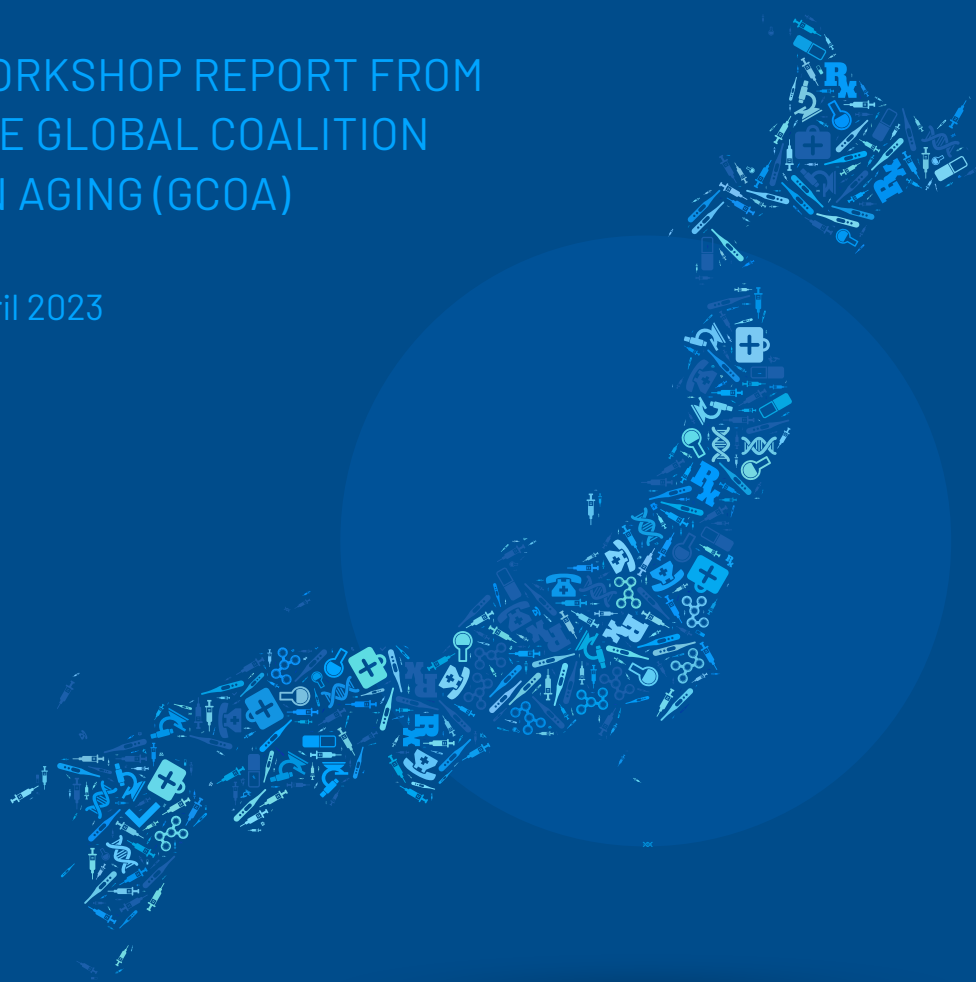


The Value of Pull Incentives in Japan to Encourage Investment in Antibiotic Innovation to Solve the AMR Crisis

WORKSHOP REPORT FROM
THE GLOBAL COALITION
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Introduction

Antimicrobials are the foundation of modern healthcare systems. In addition to curing infectious diseases, they make medical care safe—surgeries, pregnancies, and chemotherapy are all supported by the protection from infections provided by antimicrobials. Antimicrobials have enabled the miracle of longevity over the 20th century, adding an estimated average of 23 years to lifespans across the world, and they continue to make healthy aging possible.¹

The effectiveness of these life-saving drugs is now in crisis and under threat. The rise of antimicrobial resistance (AMR) is weakening the ability of antimicrobials to treat infections. New drugs are needed as back-up options when existing antimicrobials fail. However, new antimicrobial research and development is stagnating. It is crucial that the world develop policy action to help address antimicrobial market issues that are preventing novel drugs from reaching patients.

On April 13, 2023, the Global Coalition on Aging (GCOA) convened a small, private workshop of experts and officials from Japan, Sweden, the United Kingdom, Italy and the United States to discuss how pull incentives within Japan and around the G7 could reinvigorate antimicrobial innovation.

Experts discussed the importance of AMR, the value that antimicrobials bring to society, and the need for further leadership on antimicrobial research and development by the countries of the G7.

Key Takeaways

1. AMR is a major health threat in G7 countries, disproportionately impacting people with weakened immune systems such as aging populations
2. It is estimated that the world needs at least six new antimicrobial innovations per decade to make serious progress to solve the AMR crisis. This will only be possible through further funding for “pull incentives”
3. The antimicrobials market can be revitalized by pull incentives worth between US\$2.2 and US\$4.5 billion per drug, paid over 10 years.² This can be achieved if G7 countries contribute their fair share of funding to new incentives
4. Antimicrobial incentives produce tremendous returns on investment for the societies that create them. Pull incentives will help countries around the world avoid serious economic and fiscal problems in the future due to AMR
5. The world is looking to Japan and other G7 economies to show leadership on AMR

The following report summarizes the discussion at the workshop on these points.

AMR is a major health threat in G7 countries, disproportionately impacting people with weakened immune systems such as aging populations

AMR is the next infectious disease crisis. It threatens to undo gains in longevity seen around the world since the 20th century and hinders our ability to realize healthy longevity right now. AMR is currently estimated to be claiming the lives of 1.27 million people worldwide every year—more than the annual number of deaths from malaria or HIV/AIDS.³ If strong action is not taken to address this problem, it is predicted that the death toll from AMR could outclass cancer, killing 10 million yearly by 2050.⁴ As the world saw with COVID-19, immunocompromised and older populations are particularly vulnerable to infectious diseases. G7 societies are getting older, with an average one-fifth of their populations currently over the age of 65.⁵ Delayed action on AMR threatens the ability of G7 countries to protect the health of their aging populations and will hamper their ability to achieve healthy longevity. Modern healthcare is entirely dependent on antimicrobials, and so work to develop novel drugs is of vital importance, with health, economic and ethical consequences.



It is estimated that the world needs at least six new antimicrobial innovations per decade to make serious progress to solve the AMR crisis. This will only be possible through further funding for “pull incentives”

The pace of AMR innovation has slowed down over the past 40 years. Every FDA-approved antibiotic in use today for the treatment of Gram-negative bacterial infections is based on a scientific discovery made prior to 1962.⁶ In countries like Japan, new antimicrobial approvals are declining as research pipelines slow.

Japanese patients gained access to 27 new antimicrobials in the 1990s.

In the 2010s, only 11 new drugs were introduced.¹⁴

Since it can take 10 to 15 years to develop an antimicrobial,⁷ the lack of development now poses a serious threat to public health in the future and has a consequent impact on fiscal sustainability. It is estimated that the world needs to produce at least six new antimicrobials every ten years covering the top six priority pathogens on the World Health Organization Priority Pathogens List (PPL) for the R&D of new antimicrobials⁸ in order to ensure protection against AMR. That is going to necessitate intensive effort—achieving six new antimicrobials every decade is going to require approximately 4,000 basic research projects, leading to 200 pre-clinical projects, leading to 30 first-in-human studies.⁹ Both push and pull incentives are needed to shepherd new antimicrobials from the pre-clinical stage to the market. Organizations like CARB-X and GARDP are essential to ensuring that projects can be successfully pushed forward. These organizations should be funded further to ensure that development is happening. However, push funding will be wasted if there are no pull incentives to support new drugs after they hit the market. Without pull incentives, the problem of AMR cannot be solved.

**PUSH
INCENTIVES**

‘Push’ incentives refer to funding initiatives that support antimicrobial development from the stage of basic research through clinical trials. This includes funding for research from Government agencies like the Japan Agency for Medical Research and Development, product development and phase 1 support from CARB-X, or clinical development support from GARDP or the AMR Action Fund.

**PULL
INCENTIVES**

‘Pull’ incentives refer to funding that helps support antimicrobials after they have been commercialized. Post-market funding for antimicrobials can help to delink revenue from sales volume, making it possible for manufacturers to support continued antimicrobial production and new R&D without needing to actively sell new antimicrobials. This helps to ensure that new antimicrobials are not over-used, which helps to maintain their effectiveness for the times they are needed as a last resort.

The antimicrobials market can be revitalized by pull incentives worth between US\$2.2 and US\$4.5 billion per drug, paid over 10 years.² This can be achieved if G7 countries contribute their fair share of funding to new incentives

The risk that resistance might develop among new drugs means that when a novel antimicrobial is created, it is important to hold off on using it whenever possible. This can result in limited revenue for new drugs, making it difficult to recoup R&D and manufacturing costs and limiting the funding available for investment into new R&D moving forward. Looking at investments versus market capitalization and returns realized by investors in antimicrobial R&D companies over the past decade, investors have already lost over US\$3.5 billion on their investments.¹⁰ Every company is struggling to succeed with antimicrobials—the market is in crisis.

The cost of inaction on antimicrobial innovation is far higher than the cost of action. In Japan, it is estimated that 19,600 deaths occur annually from just six priority pathogens with growing resistance to antimicrobials, at a cost to the health system of US\$69,000 per death.¹¹ Movement toward pilot antimicrobial R&D incentives is tremendously important. It will be crucial to increase the size of incentive programs moving forward in line with the growing size of the threat posed by AMR.

No single country need be responsible for fixing the crisis of the antimicrobials market if every country in the G7 steps up and contributes its fair share. Being responsible for 9.8% of the GDP of the G7, Japan's fair share of a US\$4.5 billion incentive would be US\$443 million.¹² Table 1 shows fair share calculations across the G7, assuming that incentives are sized in proportion to each region's share of total G7 GDP.

TABLE 1.

TABLE 1.				CONTRIBUTION PER NEW DRUG (MILLION USD)
		GDP (TRILLION)	PERCENT	
Fair Share per Country/ Region in the G7 Assuming an Incentive of US\$4.5 Billion per Year over 10 Years ¹²	US	\$23.00	45.80%	\$2,061
	Japan	\$4.94	9.80%	\$443
	UK	\$3.19	6.40%	\$286
	Canada	\$1.99	4.00%	\$178
	European Union	\$17.09	34.00%	\$1,532
	Total	\$50.21	100.00%	\$4,500

Antimicrobial incentives produce tremendous returns on investment for the societies that create them. Pull incentives will help countries around the world avoid serious economic and fiscal problems in the future due to AMR

Returns on investment from antimicrobial R&D incentives will be significant from both a public health and economic perspective. Table 2 shows estimates of the annual number of deaths across the G7 from *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, as well as the estimated cost to each health system per death.

TABLE 2.

Mortality and cost per death estimates for six priority pathogen¹¹

	ANNUAL DEATHS FROM SIX PRIORITY PATHOGENS	HEALTH SYSTEM COST/DEATH
US	27,800	\$131,000
Japan	19,600	\$69,000
UK	6,400	\$29,500
Canada	3,500	\$200,000
European Union	28,000	\$35,100
Total	85,200	\$464,600

Based on the cost of lost lives and costs to health systems of treatment, if Japan supported 18 new antimicrobials over a 30-year program with a fair share incentive of US\$443 million per drug, the economic impact of that program would be US\$8.92 billion and it would save 270,000 lives in Japan alone—a 28:1 return on investment.¹² Table 3 shows estimates of the returns on investment of antimicrobial incentives in Japan and other countries and regions of the G7.

TABLE 3.

TABLE 3.		10-YEAR LIVES SAVED	30-YEAR LIVES SAVED	10-YEAR ROI (BENEFITS PER USD)	30-YEAR ROI (BENEFITS PER USD)
Return on Investment by Country ¹¹	Canada	2,500	48,100	4.5	20.4
	European Union	20,000	384,900	3.9	18.2
	Japan	14,100	269,700	6.0	27.7
	UK	4,600	88,400	2.5	11.4
	US	20,000	383,00	5.9	27.6
	G7 Total	61,300	1,174,100	5.0	23.1

Antimicrobial R&D failures are already costing societies around the G7 billions of dollars. The World Bank estimates that treatment for AMR-related issues rise to as much as US\$1 trillion per year worldwide by 2050.¹³ The analysis is clear—the cost of antimicrobial incentives pales in comparison to the much more expensive choice of doing nothing.

The world is looking to Japan and other G7 economies to show leadership on AMR

Antimicrobials have low profitability and high development costs. This challenge has been discussed at the G7, with the G7 Health and Finance Ministers' Meeting in 2021 strongly urging countries to develop market incentives to fix the world's novel antimicrobials R&D problem. Countries around the world are rising to this challenge. Meeting participants discussed several actions across the G7.

UK



The UK has led the way on pull incentives, launching a joint National Institute for Health and Care Excellence and the UK Department of Health and Social Care pilot project in 2019 for a subscription

model based on the value of medicines rather than sales volume. The UK will launch a consultation in the summer of 2023 on further expanding this system.

US



In the United States, the Pioneering Antimicrobial Subscriptions to End Up surging Resistance (PASTEUR) Act has been reintroduced to Congress. Cost has previously been a challenge with pull incentives, but

following on from the COVID-19 pandemic, momentum is building in the United States for action on hazard and pandemic preparedness, and AMR is an important part of those topics.

Sweden



Sweden is leading debate in Europe on AMR and antimicrobial incentives as President of the Council of the European Union in 2023. Sweden has held a high-level meeting on AMR as part of its presidency, furthering discussion in Europe on how

to further encourage drug development. Sweden has a reimbursement model that guarantees a minimum income for pharmaceutical companies in return for providing the product on the market. Evaluations have shown that this system has

helped Sweden gain access to novel antimicrobials sooner than other countries in Europe. This is an access system that works for a smaller market like Sweden.

It depends on a functioning R&D ecosystem in larger markets such as G7 countries that can make new drugs available.

Japan



Japan has set aside 1.1 billion yen to start a pilot pull incentive that will offer revenue guarantees for new pharmaceuticals. Although the amount set aside for the pilot is small, this budget allocation represents a major step forward for Japan. The plan is to calculate a minimum revenue target for drugs in the system by considering the amount of antimicrobials needed to treat select pathogens, minus 20% as an antimicrobial stewardship target. If companies do not sell enough of the antimicrobial they have in the system to hit the minimum revenue target, the Government will subsidize the company. If companies sell more than the minimum revenue amount, they will be required to

invest any extra revenue in future R&D. Companies will be prohibited from seeking additional indications for drugs that are a part of this system aside from their initial indication.

The pharmaceutical industry can address AMR through drug discovery. The AMR Action Fund is working to push forward new antimicrobials, but it requires more support. If pull incentives fail, the investment made through push incentives like the AMR Action Fund will have been a waste. The situation in the market is desperate. There are multiple projects for the creation of novel antimicrobials that could benefit from the support of Japan's new system.

Policy action by each of these countries represents progress in the fight against AMR. There is also ongoing debate in Europe on the implementation of a Transferable Exclusivity Extension (TEE) as an antimicrobial R&D incentive. Taken together, the actions currently being implemented are not enough to revitalize the antimicrobials market to the point that it can support six new antimicrobials per decade. It is important that the G7 come together on incentives that are large enough to fully revitalize antimicrobial R&D.

Conclusion

The 2023 G7 will be critical for global efforts to revitalize the global antimicrobials market and halt the progress of AMR. Global experts agree that pull incentives are needed, that they are valuable, and that they offer societies excellent returns on investment. Organizations like CARB-X and the AMR Action Fund are stepping up to push new antimicrobial projects forward. Their efforts will be wasted if novel antimicrobials fail due to market conditions post-commercialization. Japan has shown tremendous leadership in starting a pilot pull incentive for new antimicrobials. It is vital that countries like Japan think about the future health of their populations and the future of antimicrobial innovation and act now to prepare against the possibility that the AMR crisis grow even worse. AMR is the next pandemic that will threaten the health of the world. If G7 countries come together and put forth their fair share for pull incentives, they could effectively revitalize the antimicrobials market and address AMR before the health and financial costs of this problem become unsurmountable.

Expert Participants

The Global Coalition on Aging (GCOA) would like to thank the following experts for their participation in our workshop, and for their invaluable contributions that made the creation of this report possible. The content of this report was developed based on the discussion content at the April 13, 2023 workshop, and should not be taken to represent the exact views of any single workshop participant or be endorsed by them.

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GCOA represents a cross-section of global business including technology, pharmaceuticals, healthcare, home care, financial, transportation, and consumer sectors. We engage global institutions, policymakers, and the public to drive debate on, create, and promote innovative policies and actions to transform challenges associated with the aging of the global population into opportunities for social engagement, productivity and fiscal sustainability.

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