



Asia-Pacific
Economic Cooperation

Gap Analysis of Economic Incentives for Antimicrobials in APEC Economies

Addressing barriers to market
entry and new drug development

March 2024

APEC Health Working Group





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Executive Summary

The purpose of this gap analysis is to identify current challenges and compile strategies to address antimicrobial market failure and incentivize the development of novel antimicrobials to meet public health needs.

A survey titled "New Antimicrobial Market Incentives Questionnaire for Interested APEC Member Economies" was distributed among all APEC economies on a voluntary basis as part of the "Incentives to Bring New Antimicrobials to APEC Markets" project.

Based on the survey findings, this analysis highlights several key gaps and opportunities in addressing antimicrobial resistance (AMR) and promoting access to novel antimicrobials. Insufficient targeted reimbursement processes and pull-incentives pose challenges to research and development (R&D), manufacturing, and sustaining access to antimicrobials in APEC.

To address these challenges and capitalize on opportunities, it is essential to strengthen financing mechanisms and resources for sustainable antimicrobial R&D. This includes supporting public-private partnerships like CARB-X and GARDP, evaluating the effectiveness of pull incentive pilot approaches, and exploring international collaborative mechanisms. Furthermore, integration of AMR into international development cooperation initiatives and provisions within push funding agreements can enhance equitable and global access to essential health products, including diagnostics and vaccines.

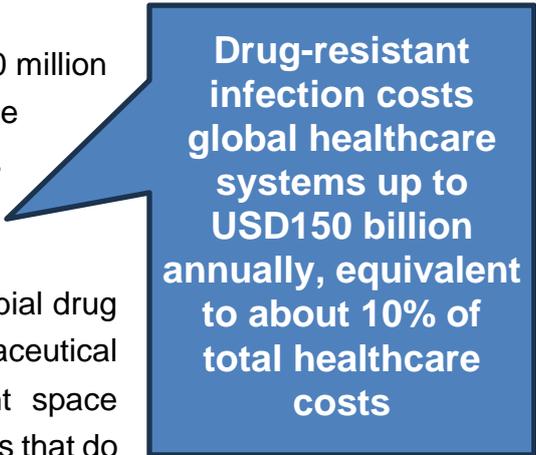
In light of these findings, economies are encouraged to evaluate their current support for antimicrobial R&D financing, establish sustainable mechanisms, and demonstrate commitments to public-private partnerships. It is crucial to foster evaluation, adaptability, accountability, transparency, flexibility, and continuous improvement within AMR action plans. By addressing these areas, economies can make substantial progress in combating AMR and promoting equitable access to antimicrobials.

Introduction

Antimicrobial resistance (AMR) is a global health crisis that poses a serious threat to modern medicine and public health. As bacteria evolve and become resistant to the drugs designed to combat them, once easily treatable infections can become lethal. According to recent publications from the World Bank, in the optimistic case of low AMR impacts, simulations found that by 2050, annual global gross domestic product (GDP) would likely fall by 1.1 percent, relative to a base-case scenario with no AMR effects; the GDP shortfall would exceed USD1 trillion annually after 2030. In the high AMR-impact scenario, the world will lose 3.8 percent of its annual GDP by 2050, with an annual shortfall of USD3.4 trillion by 2030. It is critical that global economies and partners work to stabilize and incentivize market entry so these much-needed antimicrobials are available on a sustainable scale.

The current pipeline for new antimicrobials is weak, with over 80% of new antimicrobials belonging to existing classes where resistance is already high (WHO, 2022), and no new classes of antimicrobials (which target bacteria) has secured regulatory approval since the 1980s.

According to the AMR Alliance Japan, despite GBP520 million in global public spending for antimicrobial R&D since 2016, the antimicrobial market continues to shrink. Between 2016 and 2019, Sanofi, Novartis and AstraZeneca have shuttered their antimicrobial-development divisions. Economic barriers to antimicrobial drug development has caused many large biopharmaceutical companies to withdraw from the R&D development space leaving much of antimicrobial R&D to smaller companies that do not have the resources to ensure global access and are more susceptible to failure (Taylor, 2020) (Bayer, 2023). This greater risk, however, is not rewarded: expected sales volumes are likely to be low as antimicrobial stewardship practices to ensure appropriate use limits the use of new products to prolong their effectiveness and treatment durations are generally short. Various reasons, including the struggle to achieve the capital needed to commercialize, cause small companies to struggle to remain commercially sustainable after regulatory approval and before the drugs can reach the patients that need them. Collectively the market challenges of antimicrobials disincentivizes investment into an R&D pipeline capable of adequately addressing current or future resistant threats.



Drug-resistant infection costs global healthcare systems up to USD150 billion annually, equivalent to about 10% of total healthcare costs

AMR poses significant challenges across APEC economies. Diseases with drug resistance do not respect borders, and severely strain hospital systems and economies. The Global

Health Security Agenda notes that resistant pathogens and genes continue to spread globally, and new resistance mechanisms are emerging, which threaten our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. According to a study by the Institute of Health Metrics and Evaluation (IHME), in 2019, 1.27 million deaths were directly attributed to bacterial resistance, higher than the incidence of death due to HIV/AIDS or malaria, with a total of 4.95 million deaths associated with bacterial resistance (Antimicrobial Resistance Collaborators, 2022).

The IHME also reported “in Southeast Asia [(APEC economies in bold) **Cambodia; Indonesia, Laos; Malaysia; Maldives; Mauritius; Myanmar; the Philippines; Seychelles; Sri Lanka; Thailand; Timor-Leste; Viet Nam**] between 96,981 and 369,343 people died because of bacterial antimicrobial resistance (Figure 1). According to the same source, “in East Asia [(APEC economies in bold) **China; North Korea; Chinese Taipei**], between 154,474 and 637,631 people died because of bacterial antimicrobial resistance (Figure 2); Of those, 17,821 deaths occurred among children under 5”, and “In High-income Asia Pacific [(APEC economies in bold) **Brunei Darussalam; Japan; Korea; Singapore**], between 30,903 and 132,492 people died because of bacterial antimicrobial resistance.” Additionally, a recent report by the WHO anticipated that AMR will incur a cost of USD148 billion in the WHO Western Pacific Region over the next 10 years (citation figure 3). The report also projects more than 5 million AMR-related deaths will occur in the Western Pacific Region over the next decade (Figure 4).

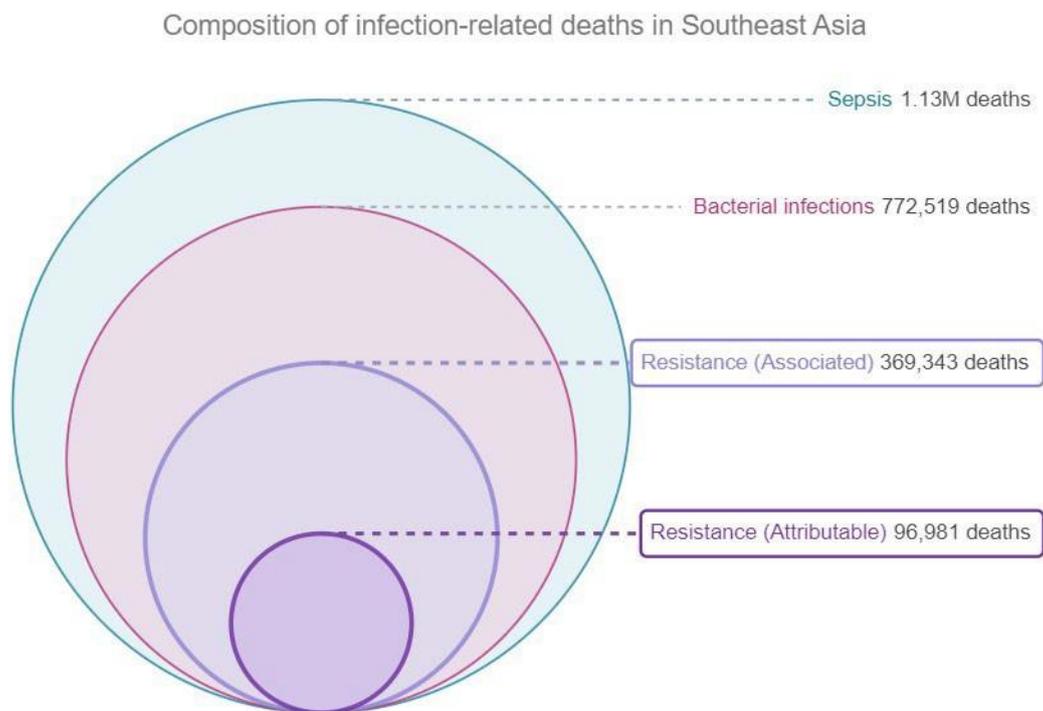


Figure 1: from IHME and University of Oxford MICROBE Tool

Southeast Asia: Cambodia; **Indonesia;** Laos; **Malaysia;** Maldives; Mauritius; Myanmar; **the Philippines;** Seychelles; Sri Lanka; **Thailand;** Timor-Leste; and **Viet Nam**

Composition of infection-related deaths in East Asia

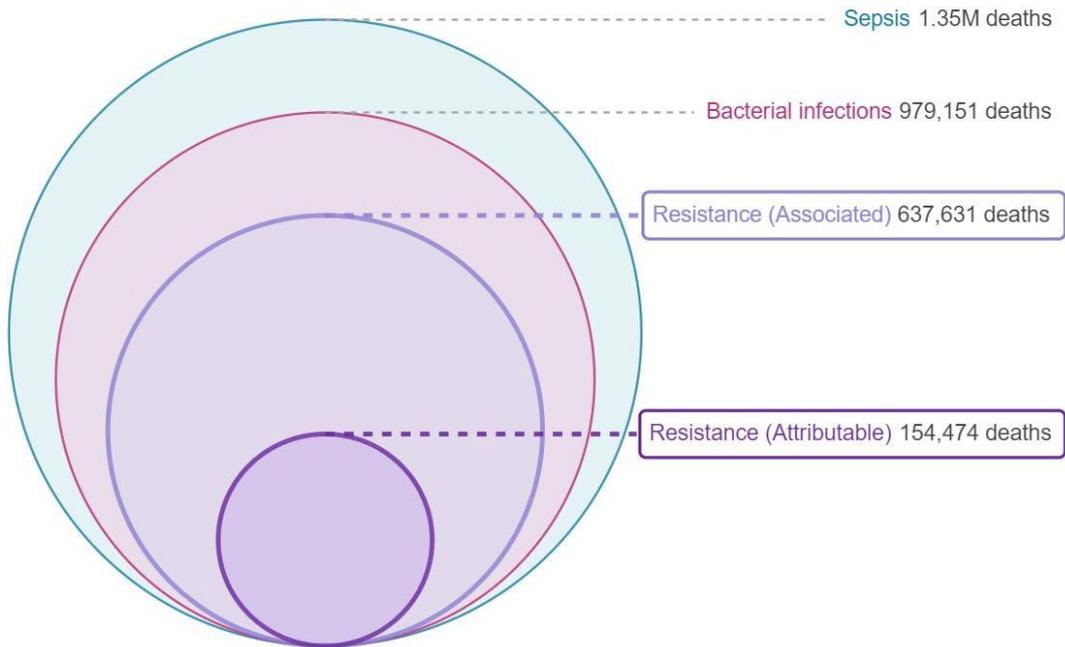
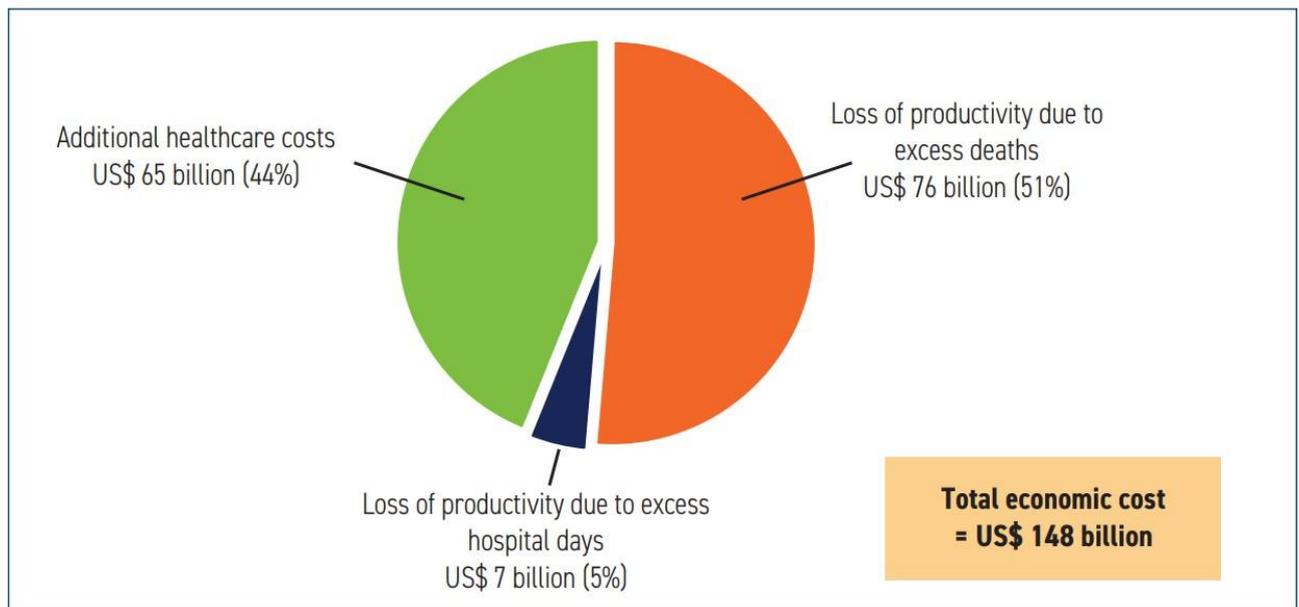


Figure 2: from IHME and University of Oxford MICROBE Tool

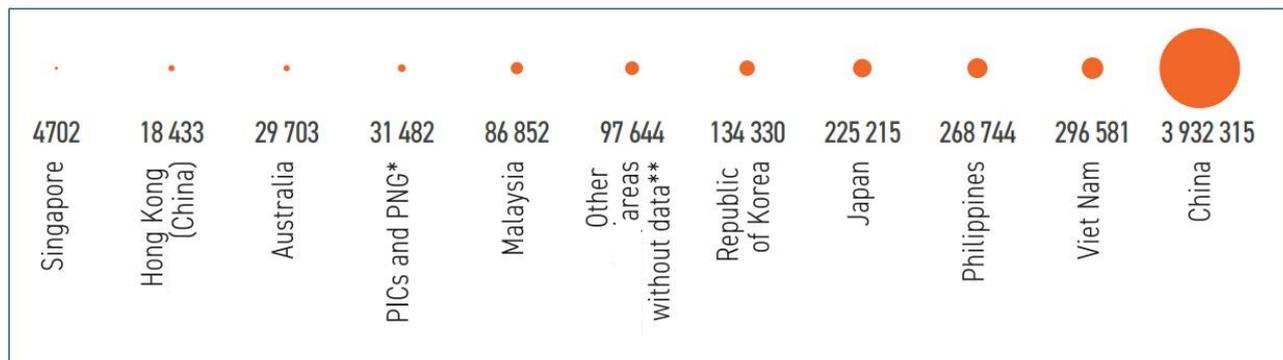
East Asia: China; North Korea; Chinese Taipei

Fig. 3. AMR-related economic impact in the Western Pacific Region by cost component, 2020–2030 (US\$ billions)



Source: Health and Economic Impacts of Antimicrobial Resistance in the Western Pacific Region, 2020–2030.

Fig. 4. AMR-related deaths in the Western Pacific Region by country/area, 2020–2030



* Pacific island countries and areas and Papua New Guinea

** Brunei Darussalam, Cambodia, the Lao People's Democratic Republic, Macao SAR (China), Mongolia and New Zealand

Source: Health and Economic Impacts of Antimicrobial Resistance in the Western Pacific Region, 2020–2030.

Challenges in Bringing New Antimicrobials to Market

There are multiple barriers to developing new antimicrobials which contribute to the slow progress in advancing these medicines to market. Some of the key barriers include:

Scientific challenges: The discovery and development of new antimicrobials is becoming increasingly difficult as many of the 'low-hanging fruits' have already been discovered. Novel targets and mechanisms of action are harder to identify, and the development of new drug classes faces significant scientific hurdles.

High development costs and risks: The R&D process for new antimicrobials is expensive and time-consuming, often taking more than a decade and costing hundreds of millions of dollars. This high investment cost can deter companies from pursuing antimicrobial development, especially when considering the uncertain financial returns.

Regulatory challenges: The regulatory approval process for new antimicrobials can be complex and lengthy, adding to the time and cost of development. Additionally, clinical trial requirements may be challenging to meet, especially for antimicrobial drugs targeting multi-drug resistant pathogens, where patient populations may be small and geographically dispersed. While some economies work to align and strengthen regulatory systems to prioritize quality and safety, others exhibit a lack of capacity to ensure the same standards, for numerous reasons; therefore, the application of pharmaceutical regulations is profoundly heterogeneous across the globe.

Market uncertainties: The market for new antimicrobials can be unpredictable, with shifting patterns of resistance, competition from existing drugs, and the implementation of stewardship programs to ensure appropriate use will often result in limited demand. These uncertainties can

make it difficult for companies to forecast sales and justify investments in antimicrobial development.

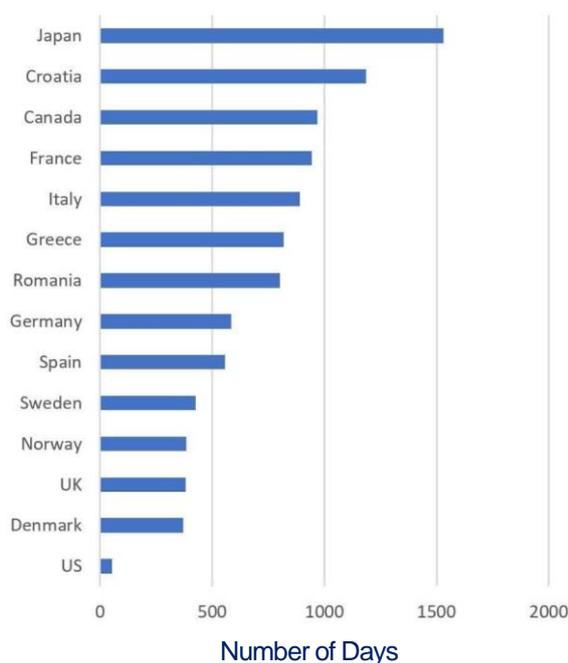
Reimbursement and pricing challenges: Securing favorable reimbursement and pricing for new antimicrobials can be a challenge, as healthcare systems often prioritize cost containment and frequently do not have capabilities to adequately assess the broader societal value of antimicrobials. This can further limit the financial attractiveness of developing new antimicrobials. While not specifically addressed in the scope of this report, when considering external reference pricing (i.e. pricing for the same product across multiple economies), it is important to note that this practice requires engagement in price negotiations.

Market access and adoption: Even after regulatory approval, new antimicrobials may face challenges in gaining market access as well as uptake by healthcare providers. This can be due to factors such as outdated or entrenched prescribing habits, lack of awareness, the need for updated clinical guidelines that reflect new antimicrobials, or the need for additional screening and diagnostic tools to also be deployed to identify appropriate patient populations for treatment.

Unsustainable financial return: Unlike drugs for chronic conditions, antimicrobials are typically used only for short durations, and their use is limited to minimize the development of resistance. Last line antimicrobials are generally reserved for a small population and face pricing barriers that create an unsustainable investment climate for R&D.

One example of a cumulative impact is the "Lag to launch"; this refers to the time it takes for a new antimicrobial drug to be developed and brought to market (Figure 5). There will be more mention of health technology assessments (HTA) below. The process of discovering, developing, and launching antimicrobials can be lengthy and complex. The lag to launch for antimicrobials is often longer compared to other types of drugs due to various reasons.

Figure 5: Median Launch Lag in Days for New Antimicrobials
adapted from Antimicrobial Resistance Solutions



For the handful of drugs that ultimately are launched, the median lag to launch is in the range of several years ([AMR Solutions](#))

Current Policies to Support Sustainable Investment and Access to Antimicrobials

There are several existing policies to encourage antimicrobial development, which can be broadly categorized as push incentives, pull incentives, and reimbursement and HTA reform (see Figure 6 for pull-incentive models). These policies are not mutually exclusive, however. Additionally, public-private collaboration is imperative when working to create an ecosystem that incorporates both push and pull incentives. A study from Boston Consulting Group (BCG) highlights that the private sector’s capabilities will come into play only if a sustainable ecosystem—involving both push and pull incentives—is in place to appropriately reward success (Group, 2022).

Rating of Pull-Incentive Models Against Six Success Factors

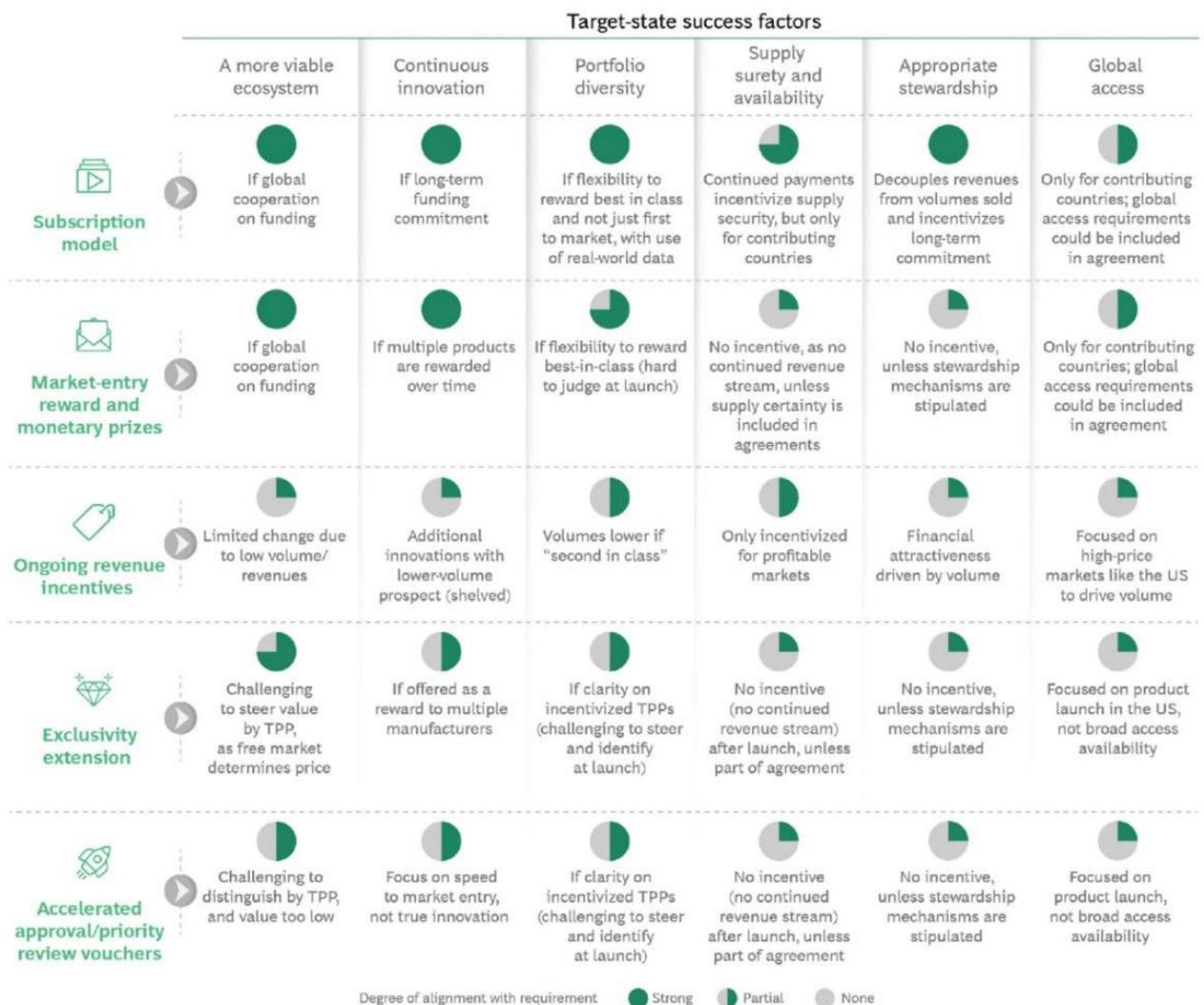


Figure 6 from Boston Consulting Group

Note: AMR = antimicrobial resistance; TPP = target product profile.

Push Incentives: These incentives aim to reduce the cost and risk of R&D for new antimicrobials by providing funding and resources upfront.

Public-Private Partnerships and Research and Development Funding: Collaborative initiatives between public and private entities can pool resources, share knowledge, and jointly invest in antimicrobial R&D projects. These can include grants, subsidies, and other funding mechanisms that are provided by government agencies, non-profit organizations, and partnerships (e.g., CARB-X, the Innovative Medicines Initiative) to support early-stage antimicrobial R&D.

- Policy examples:
 - JPIAMR: Joint Programming Initiative on Antimicrobial Resistance
 - CARB-X: Combating Antimicrobial-Resistant Bacteria Biopharmaceutical Accelerator
 - ND4BB: New Drugs for Bad Bugs
 - BARDA: Biomedical Advanced Research and Development Authority
 - NIH: National Institutes of Health
 - MRC: Medical Research Council
- Advantages:
 - Lowers cost for R&D which will promote antimicrobial innovation
 - Funds projects which researchers or developers may lack the capital reserve to otherwise pursue
- Disadvantages:
 - Potentially support projects that will fail so it is not as efficient a use of public funds as rewarding success
 - Does not address market challenges that occur once products are launched
- Tax Incentives: Governments may offer tax credits, deductions, or exemptions to companies involved in antimicrobial research to offset R&D costs and encourage investment in this area.

Pull Incentives: These incentives aim to increase the potential financial returns for successful antimicrobial development by rewarding companies once their products reach the market.

- Subscription Models: this model involves the payment of a fixed fee or subscription by a government or healthcare system to pharmaceutical companies or other stakeholders in the pharmaceutical supply chain. It generally operates on the principle of leveraging the subscription payment to ensure payment of the pull incentive is “decoupled” from the volume antimicrobials used. Depending on the size of the subscription payments, these models can support antimicrobial access, or if larger in size, can serve as pull incentives that incentivize early-stage investment into new antimicrobials.

Examples of Subscription Models

Sweden

Under Sweden's subscription model, pharmaceutical companies would be paid a fixed fee by the government on an annual basis. In return, these companies would provide access to a predetermined portfolio of antimicrobials. The payment structure is based on the "pay-for-access" principle rather than the traditional "pay-per-use" model and guarantees an annual revenue of SEK4 million (~USD372,000) for participating antimicrobials. Given its primary objective is to support access of antimicrobials approved by the EMA, the model does not incentivize R&D. The subscription fee covers the manufacturing expenses associated with producing the antimicrobials.

United Kingdom

The National Institute for Health and Care Excellence (NICE)-NHS England Antimicrobial Resistance (AMR) Pilot is a project aimed at encouraging the development of new antimicrobials and addressing the issue of antimicrobial resistance. Launched in 2019, this pilot project introduced a novel reimbursement model in the UK, known as the "subscription model," which delinks the payments made to pharmaceutical companies from the volume of antimicrobials sold. Under this model, NICE assesses the value of a new antimicrobial based on factors such as its effectiveness, the number of patients who would benefit, and the overall public health impact. NHS England then agrees to make fixed annual payments no greater than GBP10 million (~USD12.6 million) per annum to the drug manufacturer for a predefined period, regardless of the actual usage of the antimicrobial. This approach ensures that companies receive a predictable revenue stream while discouraging overuse of antimicrobials. The UK is actively pursuing the launch of a full-scale program in 2024 which incorporates learnings from the pilot program.

United States

Proposed:

The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act is a bipartisan bill that has been proposed to the United States government, seeking USD6 billion to fund a ten-year program that establishes a delinked subscription program to encourage innovative antimicrobial drug development targeting the most threatening infections, improve the appropriate use of antimicrobials, and ensure domestic availability when needed. The program proposes subscription payments of between USD750 million to USD3 billion based on a defined set of characteristics to inform contract value.

Below are additional pull incentive models, while sometimes also considered subscription models, depending on the configuration, and elements of both mentioned below are woven into the above models:

-
- Market Entry Rewards: Companies that successfully bring a novel antimicrobial to market may receive a one-time, lump-sum payment to offset development costs and provide a financial incentive for further R&D. If payments are made over a period of years, these can be considered a subscription model.
 - Advanced Market Commitments: Governments or other entities may guarantee the purchase of a certain volume, or revenue level like the Swedish access program, of a new antimicrobial, providing a predictable revenue stream for companies and encouraging investment in antimicrobial development.

Reimbursement and Health Technology Assessment (HTA) Reform refers to the process of compensating healthcare providers or individuals for the costs incurred in providing or receiving healthcare services. It involves the repayment or payment of medical expenses, which can include fees for consultations, diagnostic tests, treatments, medications, hospital stays, and other related services. An HTA (Health Technology Assessment) is a systematic process that evaluates the medical, clinical, economic, ethical, and social aspects of healthcare technologies. It is used to inform healthcare decision-making by assessing the value, safety, effectiveness, and cost-effectiveness of various healthcare interventions, such as drugs, medical devices, diagnostic tests, and healthcare procedures. While these are not necessarily considered incentives, they can significantly support antimicrobial access within an economy.

- Alternative HTA approaches that do not require demonstration of superiority over generic antibiotics: Not requiring new antimicrobials be superior to generics to support a payment level is important for several reasons:
 - Ethical considerations: Antimicrobials are used to treat infections, some of which can be life-threatening. Conducting a superiority trial could potentially involve withholding the best-known treatment from a group of patients, which raises ethical issues.
 - Clinical trial limitations: Proving superiority requires large and expensive clinical trials. For rare antimicrobial-resistant infections, it may be difficult or even impossible to enroll enough patients to statistically demonstrate superiority.
 - Resistance considerations: Even if a new antimicrobial is not superior to existing treatments, it can still play a vital role in the medical armamentarium. Antimicrobial resistance is an ever-present threat, and maintaining a diverse range of effective antimicrobials helps ensure that clinicians can select the most appropriate antimicrobial based on the specifics of each case, including

the resistance profile of the infecting bacteria.

- Encouraging R&D: If only superior antimicrobials are rewarded with higher payment, it could disincentivize pharmaceutical companies from investing in antimicrobials R&D. Given the increasing prevalence of antimicrobial-resistant bacteria, new antimicrobials are needed even if they are not more effective than current generics.
- Stewardship and the "last-resort" drugs: New antimicrobials, particularly those effective against multi-drug resistant organisms, are often held in reserve and used as "last resort" treatments. This means they're used sparingly to slow the development of resistance. Requiring these new drugs to demonstrate superiority in widespread use before they can receive adequate reimbursement is inconsistent with good stewardship practices.
- Better incorporate societal value: A significant issue with the current HTA models is that they typically focus on individual patient benefits rather than the broader societal impact. In the context of antimicrobials, the societal value is immense because they're critical in preventing the spread of infectious diseases and can enable many medical procedures from cancer chemotherapy to complex surgeries. By including this societal value into the HTA evaluation, it could lead to higher valuation for new antimicrobial drugs, thus incentivizing pharmaceutical companies to invest in R&D. The NHS England Subscription Pilot was one of the first attempts to implement new assessments of antimicrobial value via "STEDI" principles (Spectrum, Transmission, Enablement, Diversity, and Insurance value) (Schaffer et al., 2017).
- Separate payment of antimicrobials from bundled payments: Bundled payments aim to control healthcare costs by capping the payment for a defined episode of care. While this may encourage efficiency, it can also discourage the use of novel, potentially more expensive antimicrobials, even when they may be the best option for the patient. This may reduce the projected market for new antimicrobials, thus making their development less appealing. Additionally, the benefits of using a novel antimicrobial (for example, preventing the development of antimicrobial resistance) often accrue over a longer period and beyond the individual patient. These long-term benefits might not be recognized in a bundled payment model, thus reducing the perceived value of new antimicrobials. This also highlights the importance of understanding the cost of value-based pricing which aligns antimicrobial prices to their clinical benefits. However, there are concerns that this practice could potentially result in a downstream increase in the market price of antibiotics.

To address these issues and incentivize antimicrobial development, modifications to payment models can be considered, such as creating carve-outs for novel antimicrobials in bundled payments, or using value-based pricing which would reward the long-term societal benefits of effective new antimicrobials.

Examples of HTA and Reimbursement Solutions:

German Act on the Reform of the Market for Medicinal Products (AMNOG)

Aspects of HTA assessments also have relevance to some pull incentive models, such as the UK's pilot. Under the AMNOG, all newly approved prescription drugs must undergo a benefit assessment to determine their additional benefit compared to existing standard therapies. The assessment is conducted by the Institute for Quality and Efficiency in Health Care (IQWiG) and considers the therapeutic benefit, patient-relevant outcomes, and cost-effectiveness of the new drug.

Germany

According to Dzintars et al., the reimbursement authority assesses the therapeutic value of new medicines, and those with no added benefit are subject to internal reference pricing. Medicines with added therapeutic value are not subject to reference pricing, and pricing negotiations are influenced by the level of benefit assessed. Legislation in 2020 exempts Reserve-group antimicrobials from standard HTA processes, providing exemptions from price controls and faster market access.

The impact of bundled diagnostic-related groups (DRG)-based payment reimbursement is still relevant in the Germany system. Kevin Outterson and John Rex commented on this model stating, "the DRG hurdle was made worse in Germany by a 2018 revamp of their Health Technology Assessment (HTA) processes for hospital products. In the revamped model, antibiotics automatically faced generic pricing unless they could prove 'added benefit' compared to existing therapies in the HTA process. Essentially, new antibiotics needed to demonstrate superiority, which any careful observer knows is nearly impossible for new antibiotics." However, Outterson and Rex commend Germany for listening to stakeholders and pivoting on their approach.

Korea

The Health Insurance Review and Assessment Service (HIRA) is the primary agency responsible for conducting HTA in Korea. HIRA evaluates the clinical efficacy, safety, and cost-effectiveness of healthcare technologies. In the early 2000s, HIRA implemented cost-control measures through the Drug Expenditure Rationalization Plan (DERP). This plan included a positive list system (PLS). Under a positive list system, healthcare technologies must meet certain criteria and be included on the list to be covered and reimbursed. These criteria typically involve considerations such as the clinical effectiveness, safety, cost-effectiveness, and overall value of the technology. The

technologies that meet these criteria are included in the positive list, and their use is covered and reimbursed by the healthcare system or insurance provider. In 2020, Korea expanded its exemption pathway for economic valuation for drugs with no alternatives to include antimicrobials (Health Insurance Review & Assessment Service, 2022; Kfoury, J. et al., 2022).

France

France has enacted a mechanism to support a more sustainable price for antibiotic drugs that meet certain HTA criteria (ASMR IV “minor improvement”). According to Dzintars et al, France has implemented measures to support sustainable pricing for antibiotic drugs that meet certain HTA criteria. The economy has a strategic contract focused on combating AMR and creating favorable economic conditions for AMR solutions. In the French DRG system, high-cost medicines, including recently approved antimicrobials, are reimbursed separately through a list called '*liste en sus*'. The HTA system in France guarantees a minimum price for medicines with added therapeutic value, except for antimicrobials with minor improvement. Pharmaceutical companies selling antimicrobials used in AMR are exempted from the clawback scheme for social security contributions.

The extension of minimum price guarantees to antimicrobials with 'minor' therapeutic benefit serves as a protection mechanism in cases where the reimbursement evaluation process might undervalue such antimicrobials based on non-inferiority trials.

Excluding antimicrobials and other AMR tools from the calculation of pharmaceutical turnover clawbacks eliminates a potential disincentive for manufacturers to sell antimicrobials. However, this exemption is likely only relevant when manufacturers are nearing a percentage threshold for the next tier of clawbacks.

United States

The DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms) Act was a proposed legislation in the United States aimed at addressing the growing problem of AMR.

The act proposed to create a separate payment mechanism for hospital bundle payments that can remove disincentives for hospitals prescribing last line antimicrobials, even when they are appropriate. It also included improved mechanisms to track antimicrobial prescribing to encourage appropriate use.

New Technology Add-on Payments (NTAPs) are a payment mechanism used in the United States by the Centers for Medicare and Medicaid Services (CMS) to provide additional reimbursement for certain qualifying new medical technologies that demonstrate substantial clinical improvement and meet

specific criteria. This provided supplemental payments on top of the DRG payment to support utilization – in general, due to a variety of factors, this has been of limited impact.

Changes in Medicare's payment methodology serve as an important regulatory tool to ensure patient access to new antibiotics. The Inpatient Prospective Payment System (IPPS) Rule for FY 2020 provided an opportunity to restructure payment for new antibiotics, particularly those used in inpatient settings for treating drug-resistant patients. CMS has implemented specific policy changes to promote antibiotic innovation and access for beneficiaries, including an alternative pathway for NTAPs and adjusting severity levels for AMR within relevant DRGs ("Aligning Payment And Prevention To Drive Antibiotic Innovation For Medicare Beneficiaries", 2019).

According to Dzintars et al., the impact and implications of the IPPS rule changes regarding NTAP reimbursement for new antimicrobials are multifaceted. While it can provide an additional reimbursement route for hospitals using recently approved antimicrobials and encourage earlier adoption of these drugs, there are still economic disincentives for hospitals due to reimbursement caps. The effectiveness of the rule changes in incentivizing drug developers will depend on whether they result in increased spending on high-cost antimicrobials. However, previous experiences with NTAP reimbursements for antimicrobials have shown limited uptake and unclear effects on revenues. The administrative burden and limited duration of NTAP inclusion can further hinder uptake. The use of new 'Z' codes for drug-resistant cases may be less burdensome but lacks a formal cost-effectiveness mechanism.

APEC economies are diverse in size, health system structures, and boast different procurement frameworks. According to a recent BCG study by Boluarte and Schulze, "local HTA assessment frameworks impede sufficient value attribution to novel antimicrobials, since they focus primarily on cost effectiveness; application would create underfunding and hence maintain an unviable ecosystem." The current structure of HTAs would not be sufficient to capture the full scope of health benefits that novel antimicrobials provide.

Stewardship is also key to the discussion, and by ensuring novel antimicrobials are prescribed only when necessary through recommended diagnostics, with coordination between manufacturers, practitioners, policymakers, and payers, this can ensure antimicrobials are used as a last resort (Group, 2022). Additionally, Boluarte and Sculze believe, "Manufacturers, contributing countries, and international organizations must commit to developing and implementing robust domestic stewardship programs that evidence clear political will and commitment, funding support, community awareness raising, diagnostic infrastructure development, and establishment of suitable medical education programs for health care practitioners and pharmacists."

Survey Results Summary

A survey, *New Antimicrobial Market Incentives Questionnaire for Interested APEC Member Economies*, was distributed to all APEC economies to be completed on a voluntary basis. The survey is part of the **Incentives to Bring New Antimicrobials to APEC Markets** project. Key to combatting AMR is addressing economic incentives to developing new antimicrobials and preserving the efficacy of currently available products. Global efforts incentivizing the antimicrobial R&D pipeline have somewhat succeeded, with new drugs gaining approval and proving that revitalizing the development of antimicrobials works. However, maintaining responsible stewardship continues to be a challenge.

We have received a total of eight (8) completed surveys, along with one (1) "null response." The completed surveys were provided by the economies of Canada; Indonesia; Malaysia; the Philippines; Russia; Chinese Taipei; Thailand; and the United States. Based on the survey results, we have identified several gaps and opportunities.

Identified Gaps and Opportunities

Insufficient targeted reimbursement processes exist to support R&D, manufacturing, and the creation of a reserve of novel antimicrobials. Our survey reinforces this concern, revealing that only one economy has implemented a specific reimbursement process for antimicrobials.

Insufficient pull-incentives currently exist to motivate and reward innovative R&D initiatives. Our survey reports that **only two responding economies responded that they have pull-incentives in place (Russia and United States)**. WHO contends that an augmentation of pull incentives, along with other innovative financing mechanisms, would effectively bolster the development of a sustainable pipeline for novel antimicrobials. Such measures would also reinvigorate innovation within the broader life sciences ecosystem, yielding positive outcomes for health and the economy.

Most reporting economies do not provide sufficient cost offsets for antimicrobial production and maintenance through push incentives. According to WHO, government or regulatory interventions that directly reduce the costs of development have helped alleviate certain challenges associated with antimicrobial development. However, these interventions, in their current scale and isolation, are inadequate to meet R&D objectives and bring a satisfactory number of products to the market.

The majority of reporting economies stated that data is analyzed and used by the AMR multisector coordination mechanism for decision making. The Philippines

highlighted their Antimicrobial Resistance Surveillance Program (ARSP) which monitors the current levels and developing trends of antimicrobial resistance.

All economies reported having an AMR National Action Plan (NAP), all < 5 years old. While certainly a positive development that all reporting economies indicated that they had a NAP in place, these should be reviewed and updated with a particular focus on accountability and transparency, flexibility and responsiveness, and continuous improvement. According to the Global Database for Tracking Antimicrobial Resistance (AMR) Country Self- Assessment Survey (TrACSS), financial provision for the AMR NAP implementation is included in the domestic plans and budget in Malaysia; the Philippines; Russia; Thailand; and the United States.

Japan Plans New Incentives As it Tackles Antimicrobial Resistance Issues

The Japanese government is launching a JPY1.1 bn (USD8.3 million) incentive project (specific to antibiotics) to support the research and development (R&D) and continued sales of safe and effective antimicrobials, as part of broader measures to counter antimicrobial resistance (AMR) and ensure adequate supplies. The program will select certain marketed antimicrobials for financial support, ensuring sales are maintained at an appropriate level. The Ministry of Health, Labour and Welfare (MHLW) acknowledges the need for both push and pull incentives to create a favorable environment for continuous R&D and the launch of new antimicrobials. However, business challenges exist due to limitations on antimicrobial use and low profits under the current domestic health reimbursement pricing system. Japan plans to open applications for the pilot project before July and start offering incentives by April 2024, with the pilot phase running until 31 March 2026. (Takagi, 2023)

Australia Renews its Commitment to AMR Eradication through Various Projects

As of 2 June 2023, according to the Australian Government's AMR website, as part of the 2020–21 Budget, the Australian Government provided funding for several AMR projects including:

- Pricing and Reimbursement Scoping Study: Australia is looking at ways to promote research into new types of antimicrobials through the Pricing and Reimbursement Scoping Study. This scoping study will look at funding models and other incentives that could be used in Australia to support innovative research for novel antimicrobials to improve market access.
- Enhancement of AURA Surveillance System: This collects and reports on antimicrobial use and resistance in human health.
- National One Health Surveillance System: Australia plans to use the data collected through this surveillance system to guide research, appropriate antimicrobial use activities, and the public health response to this issue.

Questions for Discussion

Financing Mechanisms:

1. How does your economy currently support the financing of antimicrobial research and development (R&D) initiatives?
2. Are there existing sustainable and predictable financing mechanisms in place to address the antimicrobial R&D and access crisis?
3. What commitments has your economy made towards public-private partnerships such as CARB-X and GARDP?
4. Can you provide examples of economy-level experiences with pull incentive pilot approaches in antibacterial R&D?
5. What measures has your economy taken to evaluate the effectiveness of these pull incentive pilot approaches?

Equity and Access:

1. In what ways is the economy actively integrating antimicrobial resistance (AMR) into international development cooperation initiatives?
2. Are there provisions in place within relevant push funding agreements to prioritize access to essential health products for AMR, including diagnostics and vaccines?
3. Can you provide examples of specific measures or programs implemented by the economy to improve access to antimicrobials and other essential health products?
4. How does the economy engage with stakeholders, including low- and middle-income economies, to address access challenges and improve global equity in antimicrobial availability?
5. Does the economy have strategies in place to monitor and evaluate the impact of its initiatives on improving global and equitable access to antimicrobials?

How Large Should a Global Incentive Be?

The best estimate for a 10-year 'subscription' type payment covering the entire development process and generating a large enough global incentive fully delinked from sales volumes is USD4.2 billion (Outterson, 2021).

Annex: Full Survey Results

Table of survey questions and responses follow on Pages 22-23, with selected graphs and comments included on the subsequent pages.

Measure	Canada	Indonesia	Malaysia	The Philippines	Russia	Chinese Taipei	Thailand	US
Research and Development:								
Provide incentives for antimicrobial R&D?	Yes	No	No	Yes	Yes	No, but such incentives have been proposed	No	Yes
Class of antimicrobials incentivized?	Bacterial, Fungal, Viral, Parasitic	ND	ND	Bacterial, Fungal, Viral, Parasitic	Bacterial, Fungal, Viral, Parasitic	ND	ND	Bacterial, Fungal, Viral, Parasitic
Incentives economic?	Yes	ND	ND	Yes	Yes	ND	ND	Yes
Certificate format(s) issued?	No	ND	ND	ND	ND	EU DCC; Smart Health Card	ND	ND
Production and Maintenance:								
Offset cost for production and/or maintenance of antibiotics?	No	No	No	Yes, production	Yes, both	No	No	Yes, both
Antimicrobial manufacturers SME or large organizations?	SME	Large organization	"Not applicable"	Large organization	SME and Large organization	Large organization	SME	ND
Data								
Fund data collection on antimicrobial use?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data gathered by stewardship or domestic regulatory requirements?	Domestic regulatory requirements; IQVIA	Stewardship programs; domestic regulatory requirements	Stewardship programs	Stewardship programs	Other (National programs)	Stewardship programs; domestic regulatory requirements	Stewardship programs; domestic regulatory requirements; other	Stewardship programs; domestic regulatory requirements
Does data help identify populations at increased risk of resistant infection?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Have an AMR Action plan?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

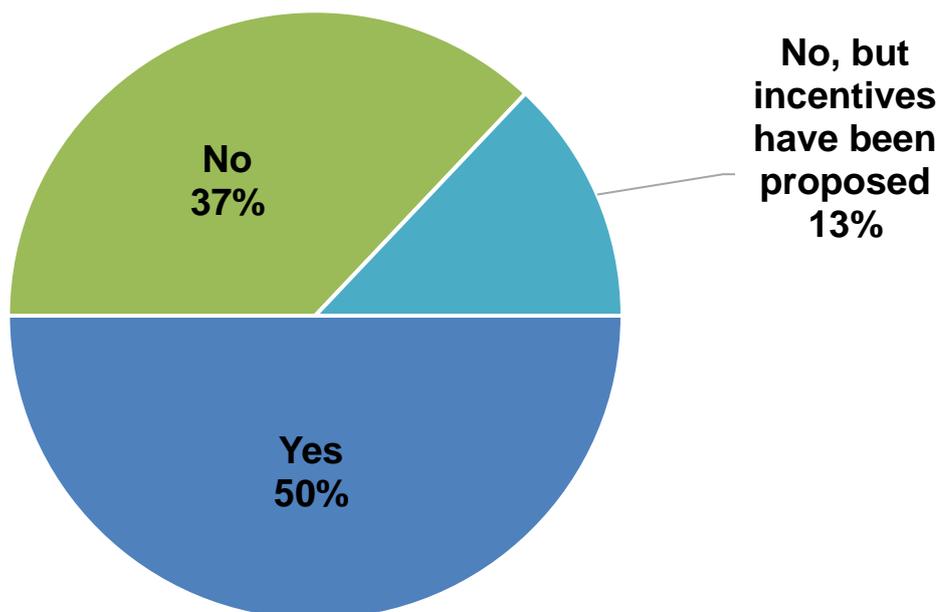
Last AMR Action Plan Update/Publication?	2023	2021	2023	2019	2019	2020	2022	2020
Antimicrobial supply chains diversified?	No	Yes	No	Yes	Yes	Other	Yes	Yes
Pull Incentives:								
Offer pull-incentives?	No	No	No	No	Yes	No	No	Yes
Is the pull payment in one installment or staggered over a multi-year implementation plan?	ND	ND	ND	ND	Multi-year implantation	ND	ND	Multi-year implantation
How is the payment processed?	ND	ND	ND	ND	Transferable IP Rights; Priority Review Voucher	ND	ND	Other
Are there contractual conditions?	ND	ND	ND	ND	Yes	ND	ND	Yes
What is the intention of the pull incentive?	ND	ND	ND	ND	To support local access / launches of antimicrobials (outcome-based)	ND	ND	To support local access / launches of antimicrobials (outcome-based); lego-regulatory based; other
Barriers to market access?	Regulatory and licensing requirements ; lack of antimicrobial industry presence, other (see survey for more)	Other	Lack of antimicrobial industry presence, small market size	Regulatory and licensing requirements	Regulatory and licensing requirements	ND	ND	ND
Reimbursement								
Have a targeted reimbursement process for antimicrobials?	No	No	No ¹	No	No	No	No	No

¹ On 15 June 2023, Malaysia enacted the Madani Medical Scheme which establishes reimbursement prices for **all listed medicines, including antibiotics**, and implements price capping.

Research and Development (R&D)

Q1: Does your economy provide incentives for antimicrobial research and development?

Incentives Provided for Antimicrobial R&D



50% of responding economies indicated that incentives are provided for antimicrobial R&D.

These incentives include the 4 overarching classes of antimicrobials: **Bacterial, Fungal, Viral & Parasitic** and are economic incentives.

Case Example from Canada: Canada invests in AMR R&D, but funding has mostly been for basic research in the academic sector, with little support for Canadian companies (SMEs).

The AMR Global Hub's Dynamic Dashboard outlines Canadian investments totaling USD173 million. 54% of Canadian investments are for basic research – which often does not translate to commercialized products.

Case Example from Indonesia: Indonesia provides incentives but not specific to AMR, e.g. tax reduction policies—including a tax holiday for investments above USD33.8 million, tax allowance for investment of USD6.75 - 33.8 million, and a super tax deduction for research and development.

Case Example from the Philippines: The Department of Science and Technology (DOST) - Philippine Council for Health Research and Development (PCHRD) has been granting cash rewards pursuant to Republic Act 7459 or otherwise known as “Investors and Invention Incentives Act of the Philippines”, to patented inventions in the Philippines ranging from PHP20,000 to PHP100,000. Moreover, tax incentives and tax exemptions for the income derived from the inventions for the first 10 years from the date of first sale and an Inventions Development Assistance Fund is also in place. For R&D, if and when the DOST/PCHRD co-funds an R&D by a private local pharmaceutical company for AMR therapeutics, detection, and other modalities, they will have the right to first refusal in accordance with the Philippine Technology Transfer Act. DOST may also extend assistance to its supported projects/institutions for Intellectual Property protection.

Case Example from Russia: Economic incentives are provided within the framework of various funds, government programs and grants:

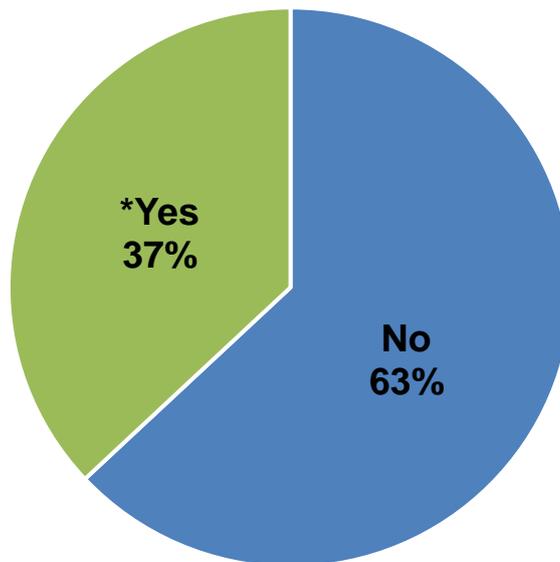
1. A set of process measures "Research and experimental design work in order to ensure the chemical and biological safety of the Russian Federation".
2. Financing within the framework of the program of the comprehensive plan of scientific research to reduce antimicrobial resistance, including the study of the mechanisms of antimicrobial resistance, the development of antimicrobial drugs and alternative methods, technologies and tools prevention, diagnosis and treatment of infectious diseases.
3. State program of the Russian Federation: Development of pharmaceutical and medical industry of the Ministry of Industry and Trade of Russia.
4. Foundation for Advanced Research, etc.

Case Example from the United States: The U.S. government provides a variety of grants and other financial mechanisms (e.g., contracts, cooperative agreements, other transactional agreements) to support research and development of a wide range of antimicrobial products. Amounts provided vary by funding agency, and are distributed by competitive mechanisms to private organizations, academic institutions, and non-profits. The National Institutes of Health (NIH) provides grant and contract funding and contributes in-kind services to CARB-X. The Biomedical Advanced Research and Development Authority (BARDA) within the Administration for Strategic Preparedness and Response (ASPR) provides funding and technical support for early-stage development through the CARB-X program and funding and technical support to a portfolio of advanced research and development projects sponsored by pharmaceutical and biotech companies.

Production and Maintenance

Q2.1: Does your economy help offset the cost for the production and/or maintenance of antimicrobials?

Offset Costs for Antimicrobial Production and/or Maintenance

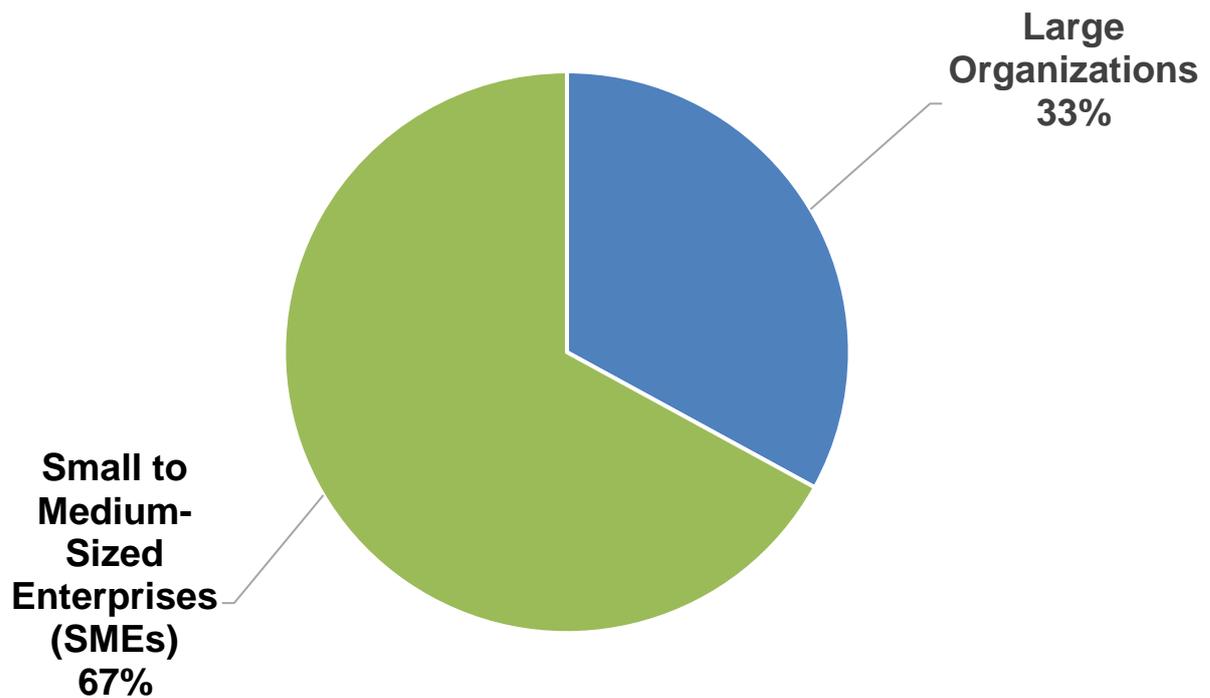


37% of economies help offset the cost for the production and/or maintenance of antimicrobials.

***Two** economies reported to offset the cost of **both production and maintenance**, while **one** economy reported **only offsetting the cost of production**.

Q3: Do the antimicrobial manufacturers within your economy trend towards small and medium-sized enterprises (SME)* or large organizations?

Size of Antimicrobial Manufacturers' Workforce



33% of economies trend towards small and medium sized enterprises (SME) < 500 employees. Two economies selected both answers.

**While the definition of a small or medium enterprise varies among APEC economies, it is typically a company with less than 250-500 total employees worldwide.*

Comment from the United States: Research and development of new antimicrobial products is largely done by SMEs within the U.S. but approved branded and generic antimicrobials are often marketed by large organizations.

Data

Q4a: As your economy funds data collection on antimicrobial use, is the data gathered by stewardship programs and/or domestic regulatory requirements?

75% of economies gather data through stewardship programs. **50%** of economies gather data through domestic regulatory requirements.

21% of economies gather data through **other means**. The two 'other' reports included: Economy-specific Programs, and analysis from consulting companies. One economy gathers data through IQVIA.

All economies except Indonesia, reported that their economy funds data collection that helps stakeholders identify potential populations that are at increased risk of resistant infection.

Comment from Indonesia (edited for clarity): In 2023, the Antimicrobial Resistance (AMR) or Antimicrobial Consumption (AMC) efforts were funded through a grant provided by the World Health Organization (WHO). The data on Antimicrobial Use (AMU) was collected through two distinct programs:

Stewardship Program: AMU data was gathered from a study focused on the use of antimicrobials in health facilities.

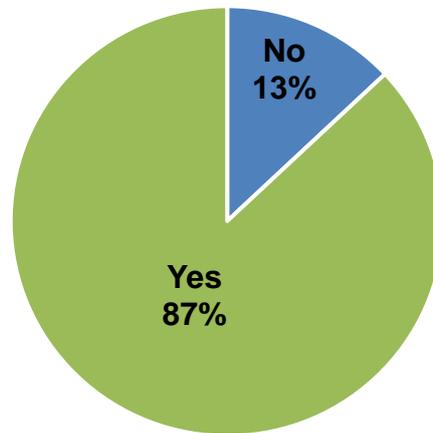
Domestic Regulatory Requirement Program: AMU data was collected from the existing reporting system, which was not specifically tailored to antimicrobial use. The reporting included drug use information from health facilities in collaboration with National Insurance (BPJS). Additionally, data on the production and distribution of drugs from industry and Pharmaceutical Big Companies was also included.

However, it is important to note that the current data cannot provide insights into the potential impact on the population due to the lack of analysis related to antimicrobial resistance in the population.

Comment from the United States: Antimicrobial use in human healthcare settings is collected under several data sources; the primary source supported by the U.S. government is the National Healthcare Safety Network (NHSN), which is administered by the Centers for Disease Control and Prevention (CDC). Antimicrobial use and resistance data from NHSN can be used by individual reporting hospitals to monitor their use over time and compare with other similar facilities to guide antimicrobial stewardship efforts. The FDA's Center for Veterinary Medicine collects data on the amount of antimicrobial products sold for use in food-producing animals, to assist FDA in its continuing analysis of antimicrobial resistance, among other issues.

Q5.1: If yes, does this data help stakeholders identify potential populations that are at increased risk of resistant infection?

Data Collection Aides in Identifying Populations At-Risk for AMR



87% of economies answered that the data helps stakeholders identify potential populations that are at increased risk of resistant infection.

Case Example from Canada: For antimicrobial use in humans, the Public Health Agency of Canada monitors human antimicrobial purchases from healthcare sectors and antimicrobials dispensed from retail pharmacies as a proxy for human antimicrobial consumption. It is based on two **IQVIA** products: the Canadian Drugstore and Hospital Purchases and the Canadian Compuscript.

Case Example from the Philippines: The Philippines has the Antimicrobial Resistance Surveillance Program (ARSP) which monitors the current levels and developing trends of AMR of aerobic bacteria of public health importance and performs reference laboratory functions related to AMR, with the goal of utilizing such data as basis for rational antimicrobial use by utilizing clinical data gathered through hospital sentinel sites. With this, DOST supports R&D detection of AMR through the one health approach by funding research which aims to synergistically work with the ARSP program for the detection of AMR from various sources such as waste-water, animals, food, and soil to determine and identify the risk factors for resistant infections or resistance. Through the one health approach, the DOST funds research on the detection and surveillance of AMR in various sources which may play a part in the increase of resistant infections.

Case Example from Thailand: Data on antimicrobial consumption in humans and animals has been collected and analyzed at multiple levels. At the domestic level, Thailand surveillance of antimicrobial consumption was developed to monitor trends and situations of domestic consumption of antimicrobials in humans and animals. Data are used to benchmarked with the domestic goals. At the healthcare settings, the rate of antimicrobial prescription for targeted diseases has been monitored to ensure that it shall not exceed the National Targets.

Crisis Preparedness and Response

Q8: Are your antimicrobial supply chains diversified, i.e., are there additional sources for alternative products, if needed?

62% of economies answered that their antimicrobial supply chains are diversified. One economy responded “other: major importing economies include China; Japan; India; Denmark; Korea, etc.”

100% of economies reported that their economy does have an AMR action plan.

AMR Action Plan for Canada: Last updated 2023

AMR Action Plan for Indonesia: Last updated 2021

AMR Action Plan for Malaysia:

1st Edition: Malaysian Action Plan on Antimicrobial Resistance 2017-2021

2nd Edition: Malaysian Action Plan on Antimicrobial Resistance 2022-2026

AMR Action Plan for the Philippines: The Philippines is currently implementing the Philippine National Action Plan (PNAP) 2019-2023 to combat AMR through One Health Approach. The first action plan was reviewed in 2018 and the PNAP 2019-2023 was published the following year (2019).

AMR Action Plan for Thailand: In 2016, the government of Thailand endorsed the first domestic strategic plan on antimicrobial resistance 2017-2021, which was later extended to 2022 in order to align with a timeframe of the domestic strategy.

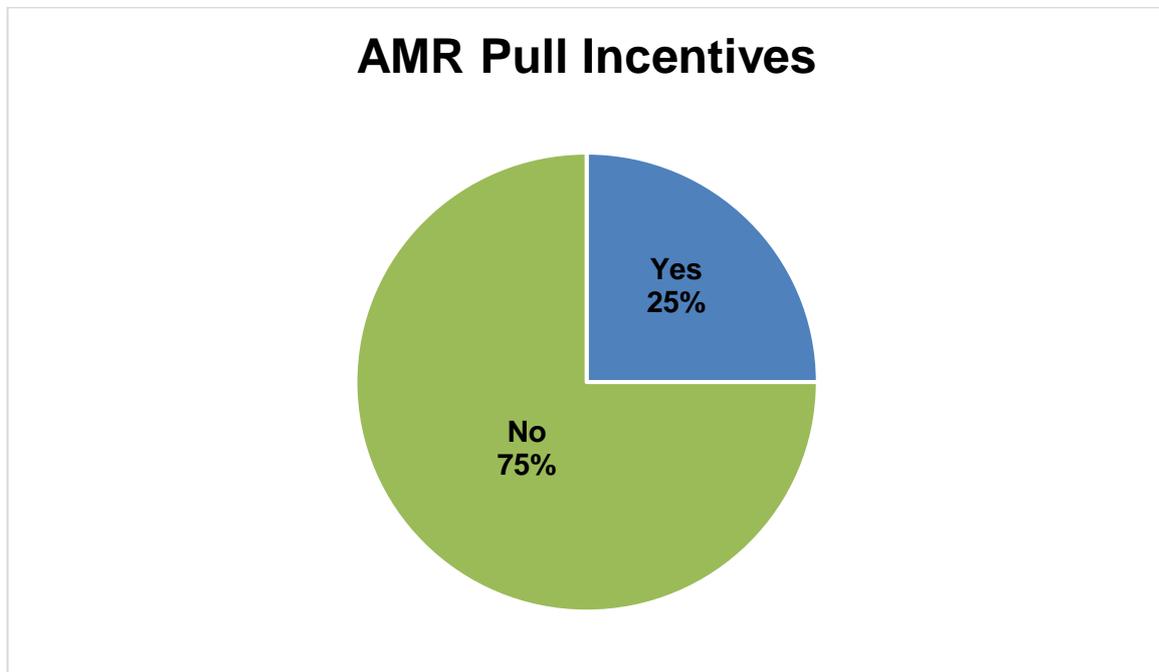
The published plan can be found online at www.amrthailand.net and <https://www.who.int/publications/m/item/thailandnational-strategic-plan-on-antimicrobial-resistance-2017-2021>.

Currently, the second National Action Plan on AMR 2023-2027 is in a finalization process for being submitted to the cabinet for endorsement.

AMR Action Plan for Russia: Decree of the Government of the Russian Federation № 604-r dated 30.03.2019

Pull Incentives

Q9. Does your economy offer pull incentives?



Additional Explanation from Russia: Our economy offers a number of additional incentives aimed at financial support for the development and production of antimicrobial drugs. As a rule, these are grants or government assignments, as well as support from state and non-state funds.

Priorities in the selection and evaluation of products - in case of emergencies (pandemics, epidemics) - support in the form of files, funds, government assignments, grants. The amount of funding depends on the importance and relevance of the products. In some cases, the assessment is carried out by examination of scientific and technical reports by experts of the Russian Academy of Sciences.

Control of compliance of the developed products with the requirements of technical specifications and calendar plans. Production rights, intellectual property rights.

Additional Explanation from the United States: GAIN Act provisions provide QIDP-designated drugs with a five-year extension to any marketing exclusivity that the application qualifies for upon approval.

ASPR/BARDA recently awarded contracts through the Project BioShield special reserve fund for late-stage development and potential procurement of two products. These procurements expand the U.S. preparedness posture and provide commercial stability to the sponsor companies. The revenue from PBS procurements also reduces a company's runway to cash neutral and enables them to retain staff and intellectual capital, ultimately positioning them to reinvest in future R&D opportunities and address future drug resistant organisms. In order to incentivize the appropriate use of novel antimicrobial drugs despite

their relatively higher cost compared to generic products, the Centers for Medicare and Medicaid Services (CMS) have taken several actions recently to increase reimbursement to hospitals for novel AM drugs. Through the Inpatient Prospective Payment System (IPPS), CMS increased New Technology Add-on Payments (NTAP) for certain antimicrobial products from 50 to 75 percent and increased payments to hospitals treating patients with resistant infections by updating their severity level designation, among other actions.

FDA is authorized to designate certain antimicrobial products as QIDPs if they are “an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by (1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens; or (2) qualifying pathogens listed by the [HHS] Secretary”. Project BioShield funding is used to address domestic security threats as identified by the Department of Homeland Security’s Material Threat Determination process. Generally, for antimicrobial products to be eligible for NTAP, the technology must be new, generally defined as within two to three years following FDA approval or market introduction, or if later than two to three years, the existing CMS payment for the service involving the technology must be inadequate as demonstrated by meeting thresholds calculated annually by the CMS.

The pull incentives are staggered over a multi-year implementation period. The payment process is explained below:

QIDP designation is considered a pull incentive because it provides market exclusivity, allowing sponsors to price products higher they may be able to with greater competition. Project BioShield payments are processed based on the terms of individual awards. NTAP payments are provided to hospitals to provide greater reimbursement for their use of qualifying products, and therefore are considered pull incentives because they are intended to facilitate appropriate use of these products and therefore facilitate revenue for sponsors.

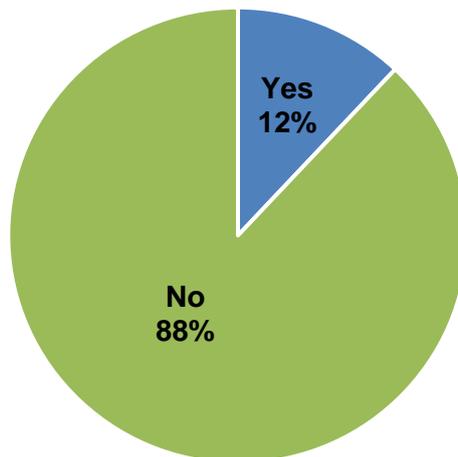
There are contractual conditions for the receipts of pull incentives: In the case of Project BioShield awards, contracts can support ongoing product development both commercial and threat based, FDA post-marketing requirements associated with product approval, U.S. onshoring and manufacturing security requirements, and the procurement of treatment courses. The contracts are structured such that achievement of specific product development milestones triggers payments.

The intention of the pull incentives are (1) to support local access/launches of antimicrobials (outcome- based); (2) to contribute to a sustainable return on investment to the AMR pipeline (lego-regulatory based); (3) expand the USG preparedness posture to biological threats including AMR.

Reimbursement

Q11. Does your economy have a targeted reimbursement process for antimicrobials?

Targeted Reimbursement for Antimicrobials



12% of economies answered that their economy has a targeted reimbursement process for antimicrobials.

Thailand, who answered 'yes' further elaborated stating: "Antimicrobials listed in the National List of Essential Medicines can be fully reimbursed by all public health insurance schemes including the universal health coverage."

Experience Sharing

In Canada, the current approach to drug valuation requires several steps following Health Canada's approval of the drug. After that, a company pays CAD74,030 to apply for a Health Technology Assessment (HTA). This HTA is a prerequisite for public funding of the drug through provincial healthcare systems.

The Canadian government has two separate bodies weighing in on drug pricing; they represent the valuation decided by the Canadian government.

(1) PMPRB (Patented Medicines Price Review Board) provides stakeholders with price, cost, and utilization information to help them make pricing, purchasing, and reimbursement decisions. It also acts as a check on the prices of patented medicines. The price is set by comparing clinical data between new drugs and existing standards of care, as well as prices in economies with similar economic metrics.

(2) CADTH (Canadian Agency for Drug and Technologies in Health) is an economy-wide organization that provides recommendations on drug usage and prices. To assess the "need" for the drug and the drug's efficacy and cost-effectiveness CADTH will review a drug's HTA as submitted during the application. CADTH reviews drugs for all provinces and territories except Quebec. In the province of Quebec, a separate review process is processed by its *Institut National d'Excellence en Sante et en Services Sociaux* (INESS). Like CADTH, INESSS is a Quebec-based organization that recommends whether a drug should be reimbursed with public funding. While INESSS' jurisdiction extends to hospitals, CADTH's does not.

Canada

There is also the pan-Canadian Pharmaceutical Alliance which conducts joint price negotiations for brand name and generic drugs for the provinces & territories public drug plans, cancer agencies, and federally for Non-Insured Health Benefits (NIHB), Correctional Services of Canada (CSC), and Veterans Affairs Canada (VAC). Their jurisdiction excludes hospitals.

In terms of how the three interact, price negotiations are held between the pCPA and manufacturers. The pCPA uses the price ceiling provided by the PMPRB and the recommendations made by CADTH/INESSS to establish a Product Listing Agreement (PLA) that sets the price at which a manufacturer agrees to sell its product to the provinces and territories. As the pCPA's objective is to reduce costs for Canadians, the price is typically a reduction from what CADTH recommended — or at least from what PMPRB set as the ceiling.

Difficulties:

PMPRB sets the maximum prices companies can charge.

CADTH makes the approval of a new agent conditional to its target price being no higher than CAD50,000 per quality adjusted life-year (QALY) gained by the new therapy. In the case of some drugs, the threshold often results in a price reduction. This depends on the marginal cost of a QALY. The explicit cost effectiveness threshold is based on the opportunity cost associated with displacing the least cost-effective health technology in the Canadian health system. Calculations are carried by expert health economists and revised periodically to reflect changing market conditions.

Antimicrobials are not currently viewed as drugs for rare diseases.

The set threshold value is not currently adjusted by other key factors that are not yet considered like; the absence of any other therapies (unmet clinical need), the severity of the illness, reward for risk-taking, innovation, patient values, societal values, end-of- life adjustments and other policy and economic factors.

The Philippines

In 2021, HIV-related drugs such as Tenofovir/lamivudine/dolutegravir(TLD), dolutegravir (DTG), and Oral Pre-Exposure Prophylaxis (PrEP) were the antimicrobials (specifically antiretrovirals) assessed by the HTA Council. The acceptability of the patients and program implementers was solicited. Difficulty in handling the sensitive nature of the topic was encountered. There was also a limited volume of available drug resistance incidence data from the reference reviews. Nevertheless, these were recommended by the HTA Council.

For topic prioritization activity in 2022, where antimicrobials were nominated and processed, there were difficulties encountered in identifying the disease burden for the specific indication of the drug, especially that data available are usually on a broader spectrum of infections versus specific antimicrobial indications.

Malaysia

1. Most of the studies were conducted in-vitro but not in a clinical setting.
2. Most of the studies did not capture wider value to population or public health because the focus was on patient specific outcome.
3. No follow up once initial recommendation or evidence made. e.g., evidence on safety or limited number of patients.
4. Difficult to identify the suitability of clinical trials design.
5. Lack of meaningful clinical endpoints and scarce comparative effectiveness.
6. Newer entity comes with much higher cost.

Russia

Difficulties in predicting mid-and long-term perspectives for particular antimicrobials due to potential emerging and spread of new resistance mechanisms.

Insufficient data on activity against particularly difficult-to-treat pathogens.

Thailand

AMR data are essential input for HTA but these data are generally varied across geography (economy-wide vs. local), by setting (hospital vs. community) and so on.

Q13: Please share any identified opportunities for improved HTA/value assessments for antimicrobials:

Canada	<ol style="list-style-type: none"> 1. Engage with regulatory agencies to facilitate application process by asking if regulatory fees and HTA-related fees can be reduced for priority antimicrobials. 2. Examining alternative HTA frameworks that incorporate Public Health value for antimicrobials: <ol style="list-style-type: none"> I. Perform a cost-analysis model to estimate what an adjusted HTA with key factors that show value to society means for antimicrobials, and what would ultimately be the cost in Canada. II. If costs are too high or cannot be calculated due to lack of expertise, a suggestion was made to use a qualitative framework with a points-based scoring system to determine the contract value for an antimicrobial, instead of using health economic modelling to estimate QALYs. III. Capture STEDI (spectrum, transmission, enablement, diversity and insurance) values in the model, which are seen as central to quantifying the additional value of antimicrobials compared with other types of therapies. Of the STEDI values, enablement and insurance values are important drivers of value and modelling work in these areas should be encouraged. Insurance and diversity values, overlaps the public health imperative and would double count benefits. 3. Review the definitions for orphan drugs and drugs for rare diseases and assess if antimicrobials can be part of that definition. 4. Join other world economies to justify the pooled valuation of antimicrobials.
Malaysia	<ol style="list-style-type: none"> 1. Understanding the value of clinical and public health value of antimicrobial agents. 2. Recognize the role of specific tools e.g., epidemiological modeling and structured expert judgments. 3. Recognize the needs of diverse stakeholders and decision makers. 4. Recognize the role and value of supporting policies and targets.
The Philippines	<p>Include review of local AMR surveillance data and improve data collection for disease burden in HTA assessments</p>
Russia	<p>Revision of the requirements to the clinical trials of antimicrobials designed to treat infections due to multi-resistant pathogens</p>
Thailand	<p>A guideline for HTA/value assessment for antimicrobials especially for less developing economies should be developed to assist the economies</p>

Q14: Please share any difficulties in reimbursement/financing/payment for antimicrobials that you have encountered:

Canada	<p>The reimbursement process is complex as it includes both private and public systems. In Canada, the main purchasers of prescription drugs are third-party payers, such as public and private drug plans, patients and hospitals. Private health insurance plans act as passive payers, typically reimbursing plan members (who normally must pay out-of-pocket first and then seek reimbursement) for the costs of prescribed medicines, less any cost-sharing amount.</p> <p>Provincial, territorial, and federal drug plans define reimbursement prices for pharmaceutical products covered under their formularies and, in some instances, use different methodologies for determining reimbursement amounts. The reimbursed prices may differ from manufacturer's list prices.</p> <p>Canadian hospitals operate under fixed budgets and/or payment per case, which they use to procure drugs provided free-of-charge to their patients. Hospitals typically use group purchasing programs to establish group contracts for set prices. The hospital then buys directly from the manufacturer at the contract price.</p> <p>Difficulties:</p> <p>Fragmented system: Private payers account for 38% of prescription drug spending in Canada; Public plans, account for 45% of drug spending in Canada; Out of pocket payers make up the remaining 17% of drug spending. The reimbursement arrangements may or may not cover the dispensing fee charged by the pharmacist.</p> <p>Canadians have the world's 4th highest drug prices. Canadian list prices of patented medicines remained among the highest in the Organization for Economic Co-operation and Development (OECD), ranking 4th, well behind the US and just marginally lower than Switzerland and Germany.</p>
Malaysia	<ol style="list-style-type: none">1. Malaysia has no National Insurance Scheme which made the reimbursement initiatives difficult.2. Some of the antimicrobials are expensive.3. Maintaining the sustainability of domestic funding is challenging.
The Philippines	<p>Limited involvement of stakeholders from the private sector in R&D of antimicrobials possibly due to lack of incentives and profitability compared to other drugs.</p> <p>Although AMR is part of the R&D priorities of the DOST, there is no dedicated allocation for AMR R&D which makes funding for AMR research subject to competition with non- AMR topics.</p> <p>Lack of legislative support for R&D for AMR.</p>
Russia	<p>Absence of reimbursement for outpatient use of antimicrobials makes the registration of the new antimicrobials for outpatients use unattractive for the industry.</p>

Q15: Please share any identified opportunities for improved reimbursement/financing/payment for antimicrobials:

Canada	<p>The government of Canada has charged a panel of experts (the Council of Canadian Academies) to evaluate the feasibility of Pull Incentives for High-Value Antimicrobials in Canada</p> <ul style="list-style-type: none">• The Public Health Agency of Canada (PHAC) has asked the CCA to undertake an expert panel assessment on Pull Incentives for High-Value Antimicrobials.• The assessment will answer the following question: What economic pull incentives have the greatest potential for success in encouraging the market entry and sustained market availability of high-value antimicrobials for use in humans in Canada? <p>Canada has established an advisory group (AG) on antimicrobial resistance as an important step in mobilizing and maintaining the momentum required to address AMR in Canada. The primary focus of AG's activities will be to provide advice on work related to the development and implementation of policies and initiatives that target AMR in Canada and globally.</p> <ul style="list-style-type: none">• AG will provide expert advice on specific medical, scientific, technical, policies and programs related to AMR and antimicrobial use to the new AMR Task Force from the Public Health Agency of Canada. <p>This advice includes the identification of priority needs for securing access to effective antimicrobials</p>
Indonesia	<p>APEC should provide assistance for economies to develop and implement economic incentives to develop new antimicrobials and preserve the efficacy of currently available products.</p>
Malaysia	<p>Pooled procurement of drugs between public and private healthcare sectors.</p>
The Philippines	<p>On-going legislation of the Vaccine and Virology Institute of the Philippines (VIP) is seen as an opportunity to allow for advanced R&D to combat AMR especially in viruses.</p> <p>As one of the multi-pronged approach in addressing AMR, the global interest in the topic generates coalitions and networks at the international, regional and local level. The Philippines has established the Inter-agency Committee on AMR to create synergy among different stakeholders in combating AMR, thus, member-agencies of the Committee are authorized to charge against their current appropriations such amounts as deemed necessary for the implementation of the NAP.</p> <p>Provide incentives such as paying or rewarding the innovations made by R&D companies/institutes.</p>
Russia	<p>Implementing new coefficients for the treatment of infections caused by difficult to treat pathogens.</p> <p>For new antimicrobials that are crucial for the solution of the unmet medical needs - prospective procurement assurance program.</p>

Q16: If you have any comments or suggestions, please provide them here:

Canada's strength is in academic basic research:

- Mostly in basic research (push incentives) in academic endorsements.
- Global Hub's Dynamic Dashboard outlines Canadian investments totaling USD173 million.
- Canada has not yet invested in pull incentives to create a viable market for antimicrobials.

Canada also has some advanced funding options for large scale industry projects:

- The Strategic Innovation Fund provides funding for large projects (above CAD20 million) and domestic innovation ecosystems that involve industry and academia.
- Serves all sectors of the economy, focused on investments with low financial risk and revenue generating business entities.
 - So far, it has not funded clinical trials outside COVID-19.

Canada's has also contributed financial support (CAD0.3 million) for the SECURE initiative to increase global AMR preparedness and support:

Canada

- SECURE is a newly created initiative with the mission to expand access to essential, life-saving antimicrobials for economies and populations in need and ensuring their appropriate use.
- SECURE's efforts will address the burden of infectious diseases and AMR in low and middle-income economies.
- SECURE was developed by GARDP and the WHO, with support from UNICEF and the Clinton Health Access Initiative (CHAI).

In May 2023, Canada's Minister of Health announced an investment of CAD6.3 million to CARB-X in support of global and domestic antimicrobial innovation.

- Through this investment, Canada aims to support Canadian research groups and industry in their research and development efforts for therapeutic and diagnostic solutions to fight AMR and to help support global innovation by strengthening the discovery and development of new antimicrobial drugs needed to ensure patients can continue to rely on these life-saving medicines.

Thailand

Thailand has joined the GARDP for research and development of new antimicrobials for resistant *N. gonorrhoeae*.

Identified Gap: Pull Incentives

AMR Action Plans

Australia	<p>2016: “Subscription model implemented for increased access to hepatitis C antivirals (though pending expansion to AMR therapeutics)”²</p> <p>2020: “Innovative ways will be needed to fund, or stimulate, the discovery and development of new approaches to the prevention, detection and containment of antimicrobial resistance, in both the public and private sectors. This includes alternative funding models such as Product Development Partnerships (PDPs) and Public-Private Partnerships (PPPs). However, for Australia to benefit from investments in research and development, findings will need to be transferrable to the grass-roots level across all sectors”³</p>
Canada	<p>“The global community (e.g. G7 and G20) has made commitments to research and innovation and is seeking effective solutions such as antimicrobial development, alternative medicines, vaccines, diagnostics, economic incentives for research and development, and collaboration across economies and sectors. Substantial investments are being made to forge collaborative partnerships to maximize existing and future AMR efforts and to pool financial resources. Canada and other economies must consider new approaches to treat resistant infections and examine ways to encourage large drug companies to re-enter the AMR research and development field.”⁴</p>
Japan (2016-2020)	No mention of pull incentives
Korea (2016)	No mention of pull incentives
The Philippines (2022)	<p>“To address this issue, all responsible agencies are expected to exert political commitment and leadership in taking initiatives to protect our nation from the threat of AMR. There is a need to implement rational use of antimicrobials in both human medicine and animal husbandry, provide incentives for research and development of both new antimicrobials and vaccines, strengthen our economy's monitoring and surveillance of AMR, strengthen infection prevention and control programs, and develop additional or more complex measures to hinder the further spread of this phenomenon. This is an attainable endeavor with the help of both international and local partners working towards a common goal.”⁵</p>
Malaysia (2022)	Mention of Strategy 4.4 [“Introduction of incentives to optimize appropriate use of antimicrobial agents.” This strategy is to “facilitate market access and

² Advancing Antimicrobial Development: A Practical Framework for Developing Novel Antimicrobials," published by LEK Consulting and sponsored by MSD

³ Australia's National Antimicrobial Resistance Strategy – 2020 and beyond

⁴ Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action

⁵ THE PHILIPPINE ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE: ONE HEALTH APPROACH

promotion of MyGAP certified products to optimize appropriate use of antimicrobial agents.”⁶

Russia	No mention of pull incentives
Thailand (2017-2021)	“In recent years, the problem of antimicrobial resistance (AMR), especially resistance to antimicrobials, has increased significantly. Unless drastic action is taken, it is expected that this trend will continue. The further spread of resistance threatens the effectiveness of existing antimicrobials: a situation that is compounded by a lack of incentives for the pharmaceutical industry to invest in research and development of new antimicrobials.” ⁷

Economy-level Projects

Australia	“To streamline the supply of drugs, MTPConnect has conducted workshops focusing on improved valuation methods, product development gaps, and stronger push and pull incentives. Alongside MTPConnect, Australia has vastly expanded its reach into AMR innovation through the Australian Strategic and Technical Advisory Group on AMR (ASTAG), the Pharmaceutical Benefits Scheme (PBS), and NPS MedicineWise.” ⁸
Japan	“In 2017, the Japanese Pharmaceutical Manufacturers Association (JPMA) called on the Ministry of Health, Labour and Welfare to fund a public private consortium aimed at advancing antimicrobial development. In 2019, the JPMA specifically called for introducing pull-type incentives. Many pharmaceutical firms have signed the 2016 Davos Declaration and expressed the need for global harmonization of research and increased R&D incentives. Many firms also have also joined the AMR Action Fund, a consortium of companies that seeks to invest in smaller biotech firms developing antimicrobials, with a goal of bringing two to four new antimicrobials to patients by 2030.” ⁹
Korea	“The South Korean intellectual property and patent policy environments are generally favorable and should encourage innovation. However, there are comparatively few ongoing AMR research projects and no antimicrobials in development. Development is further inhibited by a lack of effort to capture the full value of new antimicrobials and to develop effective pull mechanisms.” ¹⁰
United States	Numerous pieces of legislation have been introduced in Congress over the past decade, though the recent reintroduction of the PASTEUR Act, currently under consideration by Congress, is the most serious effort, and would mark a global win for efforts to broaden the antimicrobial pipeline. However, no votes have been scheduled in Congress. Proponents hope that if passed, the bill could offer a template or framework for stimulating the development of antimicrobials both domestically and abroad.

⁶ MALAYSIAN ACTION PLAN ON ANTIMICROBIAL RESISTANCE (MyAP-AMR) 2022-2026

⁷ Thailand’s National Strategic Plan on Antimicrobial Resistance (2017-2021)

⁸ 2021 AMR Preparedness Index: Published by Global Coalition on Aging and Infectious Disease Society of America

⁹ Ibid.

¹⁰ Ibid.

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