AMR Alliance Japan

POLICY BRIEF

Establishing incentive models to encourage R&D for antimicrobials

Executive summary

- Low profits and complex regulations have disincentivized the research and development (R&D) of antimicrobials, resulting in a "discovery void" since the 1980s.
- In Japan, despite efforts made by the Japan Agency for Medical Research and Development (AMED) and the private sector to increase investments, the market for antimicrobials continues to shrink.
- Antimicrobial R&D has stagnated worldwide and large multi-national corporations have been exiting the market, leaving the responsibility to small and medium-sized enterprises.
- A combination of push and pull incentives are needed to finance research and development, in addition to other new financing mechanisms.

Introduction

As a result of weak market conditions, no antimicrobials with a novel mechanism of action have been discovered since 1987.[1] Profits margins for antimicrobial are a fraction of those for alternative products, incentivizing companies to devote R&D efforts to more profitable markets. As a result, despite £520 million in global public spending for antimicrobial R&D since 2016, the antimicrobial market continues to shrink.[2] Between 2016 and 2019, Sanofi, Novartis and AstraZeneca have shuttered their antibiotic-development divisions.[3] In 2019, Achaogen, a US-based biotech firm that launched Zemdri (plazomicin) for adult urinary tract infection, declared bankruptcy.[4]

Incentives are needed to stimulate antimicrobial development. These incentiveThese incentives can be broadly grouped into two categories: "push" and "pull" incentives.[5] "Push" incentives fund inputs, such as grants, tax credits, or regulatory reform. "Pull" incentives reward new antimicrobials, such as patents and market entry rewards. In addition, there has been ongoing debate about whether there should be "negative" push and pull incentives to penalize pharmaceutical companies that do not engage in antimicrobial R&D.

Background of the Issue: Japan

For years, Japan drove innovation in the development of antimicrobials, discovering antimicrobials such as cefazolin, clarithromycin, levofloxacin, meropenem, peracillin, and tazobactam.[6] However, despite previous success, the market for antimicrobials in Japan has declined since the 1990s. The market for systemic antimicrobials decreased from ¥965.5 billion to ¥200 billion from 1989 to 2018.[7] Furthermore, the market for infectious disease drugs is expected to decline by 30.2% to ¥552.2 billion in 2024 compared to 2015.[8]

The lack of antimicrobial discovery in Japan is part of a global trend in antimicrobial markets. The low revenue for antimicrobials cannot compensate for the cost of R&D, leading private entities to either pull out of the market or in some cases, face the need to declare bankruptcy. From the 1950s to the 1980s, there was a steady rise in the number of antimicrobials developed. More than 25 new antimicrobials were discovered and approved in the 1980s (Figure 1). However, since the 1990s, there has been a gradual decrease in production. In the 2010s, only five antimicrobials have been discovered and approved.

From a scientific perspective, there have been difficulties in finding new targets for antimicrobials. Japanese pharmaceutical companies excel in the chemical synthesis and optimization of antimicrobials. [9] However, even with full genome sequencing, new antimicrobial targets remain difficult to find. It is necessary to create, through incentives, an environment that encourages the discovery of new targets.

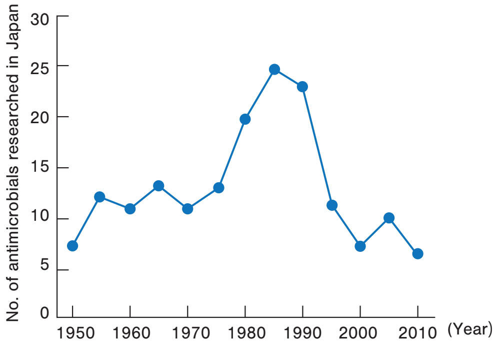

Figure 1. Overcoming the stagnation of antimicrobial drug development; Journal of the Japanese Society of Internal Medicine 102: 2908-2914

Stakeholders and Countermeasures: Japan

Stakeholder	Countermeasure
The Japan Agency for Medical Research and Development (AMED)	• Cyclic Innovation for Clinical Empowerment (CiCLE) - funding in creating an environment for fostering innovation; research and development. [10] ▶ Funding of up to ¥100 million to ¥10 billion yen per project for improving the environment for medical R&D and R&D. ¥100 million to ¥5 billion for practical realization development ▶ Research Project to Promote the Development of Innovative Drugs for Emerging and Re-Emerging Infectious Diseases - provide funding for seventeen areas of infectious disease research, including antimicrobial resistance organisms. [11] ▶ Annual funding for antimicrobial resistance can range from ¥10 million to ¥20 million per project and may be granted for up to 3 years.
Ministry of Health, Labour, and Welfare	• Scheme to expedite unapproved drugs for antimicrobial resistant diseases to incentivize development. [12] ▶ If the drug meets criteria, drugs that usually undergo regulatory consolation for about a month, will be accepted immediately, and the total review period will be decreased from 12 months to 9 months.
Private sector	• Partnerships – Takeda Pharmaceutical Company, Ltd. Eisai Co., Ltd, and Global Antibiotic Research Development Partnership (GARDP) to screen chemical libraries and discover components with antibacterial activity. [13] • AMR Industry Alliance - Sumitomo Dainippon Pharma Co., Shionogi & Co. Ltd., Japan, Japan Pharmaceutical Manufacturing Association (JPMA), Meiji Seika Pharma Co., Ltd., Japan, and Otsuka members of international alliance to strengthen antimicrobial development. [14]
Public-academic partnership	• Faculty at Chiba University, with the support of AMED, is working on the development of a novel antimicrobial against multidrug-resistant enterococci. [15]

Background of the Issue: Global

Alexander Fleming discovered penicillin in 1928, revolutionizing the way that the world treated infectious diseases. The 1950s was a period of major innovations in antimicrobials, with the discovery of pleuromutilin, macrolides, glycopeptides, nitroimidazoles, streptogramins, cycloserine, novobiocin, rifamycin.[1] This boom in innovation continued until the 1980s, contributing to a major decrease in the global burden of infectious diseases.

However, as brand name drugs began to be replaced by generics, profits for antimicrobials fell. The global cost of developing a new, targeted, antimicrobials, excluding post launch studies, was calculated at US$1.58 billion (at 2011 price levels).[16] However, only 5 of 16 antimicrobials introduced between 2000 and 2015 achieved annual US sales of $100 million or more.[17] Given such marginal rates of return, the only way a company can pay for the development of new antimicrobials is by making use of income from other, more profitable pharmaceuticals. This has led companies to focus more of their R&D efforts away from antimicrobials overall. As of July 2018, a total of 44 antibiotics (including combinations) were in clinical development.[18] This perils in comparison to the over 1,100 cancer drugs in development as of May 2018.[19]

Since large companies are able to pursue more profitable pipelines, the research and development of antibiotics relies mostly on small and medium size enterprises. In 2019, of the 314 research and development institutes working on at least one preclinical antimicrobial program, 255 (81%) were small and medium-sized enterprises with less than 1,000 employees.[20] Such small and medium-sized enterprises are vulnerable, as they tend to have a narrow set of expertise, depend on the success of a single or a few priority projects, and need a continuous flow of funding.

While solving commercial and regulatory issues is critical, it is not enough as scientific barriers hinder the discovery of new antimicrobials. A review by Dr. Lynn Silver describes two major scientific challenges for antimicrobial discovery: 1) proper target selection that is not prone to rapid resistance development; and 2) improvement in chemical libraries to overcome limitations of diversity.[1] In fact, according to a 2019 WHO report, none of the 60 products under development bring significant benefit over existing treatment, and very few target the most important antimicrobial resistant bacteria.[22] Additionally, for innovative drugs, it takes years to reach patients.[23,24] Therefore, in addition to changing market conditions to favor the development of antimicrobials, investment is needed to facilitate scientific progress in these areas.[25]

Stakeholders and Countermeasures: Global

Stakeholder	Countermeasure
World Health Organization (WHO) and Drugs for Neglected Diseases initiative (DNDi)	• Global Antibiotic Research and Development Partnership (GARDP) – supports development of antimicrobials by providing governance, scientific environment and infrastructure, resource mobilization, communication, finance, and human resources.[26] ▶ Focus on gram-negative drug-resistant infections in children, newborns with sepsis, and sexually transmitted diseases (STIs) ▶ Received funding from Germany, Netherlands, South Africa, Switzerland, and the United Kingdom, as well as from Médecins Sans Frontières / Doctors Without Borders (MSF).[27]
US government and non-profits	• Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) - invests up to $500 million to fight antimicrobial resistance, including the research and development of antimicrobials.[28] • The Pioneering Antimicrobial Subscription Upsurging Resistance (PASTEUR) Act: New subscription model to encourage pharmaceutical companies to develop new antimicrobials. The subscription contract ranges from US$750 million to US$3 billion for up to 10 years.[29]
New Drugs for Bad Bugs (ND4BB)	• Part of the EU-funded Innovative Medicine Initiative (IMI) and represents an investment of US$780 million in antibiotic research and development.[30,31] ▶ Combatting Bacterial Resistance in Europe – Molecules against Gram-Negative Infections (COMBACTE-MAGNET)– EU and Industry project to develop new compounds including a β-lactam antibiotic against a broad-range of multi-drug resistant Gram-negative bacteria and a monoclonal antibody active against Pseudomonas aeruginosa (in clinical trial)[32] ▶ European Gam-Negative Antibacterial Engine (ENABLE) – supports universities and small/medium enterprises in early stages of drug development, including apramycin, dabocillin, and thiophene.[33,34]
Joint Programming Initiative on Antimicrobial Resistance	• Sponsored academic and industrial initiatives to develop novel antimicrobial therapy (€14·4 million and repurpose neglected antimicrobials (€4·5 million).[35]
Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR)	• REPAIR Impact Fund – for-profit venture capital for discovering and promoting early stages development of therapies targeting antimicrobial resistant microorganisms.[36] ▶ Budget of $165 million. ▶ Planning an additional $20–40 million for investment in around 20 projects in Europe and the USA across 3–5 years. ▶ Funded and commissioned by Novo Nordsik Foundation.
UK government	• 5-year national action plan for AMR – pull incentive to pay companies for public health value of new antimicrobials.[37] • The NHS offered a subscription contract for two new antimiocrobials.[38]
Private sector	• AMR Industry Alliance – industry alliance to curb AMR. ▶ In 2016, the investment by a subset of AMR Industry Alliance companies was more than $2 billion - four times more than the aggregate investments of the global public sector during the same year. • AMR Action Fund – partnership by more than 20 pharmaceutical companies with the goal of developing 2 to 4 new antimicrobial agents by 2030. Invested more than US$1 billion.[40]

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AMR Alliance Japan Recommendations

- Pull incentives should be implemented to encourage the development of antimicrobials. Specifically, market entry rewards, transferable exclusivity extensions, purchase guarantee systems, and pre-examination pricing systems based on drug profiles should be considered.
- Japan should consider the introduction of new domestic financing mechanisms to promote R&D of novel antimicrobials, and thereby assume global leadership on antimicrobial development.

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