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Strengthening AMR Countermeasures to Respond to Health Crises

Recommendations to the Japanese Government on Establishing a Pull Incentive System for the Antimicrobial Market: Creating an Ecosystem for Sustainable Antimicrobial Development to Protect the Lives of the Public

Executive Summary

Nikkei FT Communicable Diseases Conference
Asia Medical Innovation Consortium (AMIC)
AMR Consortium

Antimicrobial resistance (AMR) is an internationally recognized health crisis. It requires a strong policy response. To promote such responses, the World Health Organization released a WHO policy package to combat antimicrobial resistance[1] in 2011. In 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance.[2] Following the release of these documents, Japan created its own National Action Plan on AMR 2016-2020[3] in 2016.

Despite these measures, the threat of AMR as a 'silent pandemic' is growing. In 2019, it was estimated that already approximately 8,000 deaths are occurring annually in Japan due to blood-stream infections attributable to just two antimicrobial-resistant organisms, methicillin-resistant *Staphylococcus aureus* (MRSA) and fluoroquinolone-resistant *Escherichia coli* (*E. coli*) (Figure 1).[4] While the number of infections attributed to MRSA has been trending downward since 2011, Japan still maintains a high number of infections compared with other countries. Meanwhile, the number of fluoroquinolone-resistant *E. coli* infections is on the rise,[5] as are infections due to carbapenem-resistant *Enterobacteriaceae* (CRE) bacteremia, which is estimated to kill 20% to 40% of the people it infects.[6] In the past, the number of domestic CRE infections was stable. Japan saw around 1,600 cases between 2015 and 2017.[7] This number suddenly jumped to 2,289 cases in 2018 (resulting in 71 deaths). This increase coincided with a rise in the percentage of infections caused specifically by overseas strains of CRE, which rose from 1.4% in 2017 to 2.5% in 2018. At the same time, Japan began to see a larger variety of prefectures reporting the appearance of these strains. In 2017, overseas strains of CRE were reported in just six prefectures (with three prefectures reporting cases involving people with no or unknown overseas travel history). By 2018, that figure rose to 16 prefectures, with 12 prefectures reporting cases involving people with no or unknown overseas travel history (Figure 2).[8] Although MRSA case numbers are currently falling in Japan, increases are being seen overseas, and it is plausible that a spread of MRSA infections could spread from abroad to Japan in the future. Rapid measures to deal with the AMR are urgently needed.[9]

[1] https://www.who.int/bulletin/volumes/89/5/11-088435/en/
[2] https://apps.who.int/iris/bitstream/handle/10665/193736/9789241509763_eng.pdf?sequence=1
[3] https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000120769.pdf
[4] National trend of blood-stream infection attributable deaths caused by Staphylococcus aureus and Escherichia coli in Japan. https://www.sciencedirect.com/science/article/pii/S1341321X19303356. Accessed September 16, 2020.
[5] Nippon AMR One Health Report (NAOR) 2019. https://www.mhlw.go.jp/content/10900000/000571551.pdf. Accessed September 7, 2020.
[6] Treating carbapenem-resistant Enterobacteriaceae infections. https://www.niid.go.jp/niid/ja/allarticles/surveillance/2439-iasr/related-articles/related-articles-468/8619-468r05.html. Accessed September 7, 2020.
[7] Notifications of carbapenem-resistant Enterobacteriaceae infections submitted according to the Infectious Diseases Control Act, 2018. https://www.niid.go.jp/niid/ja/cre-m/cre-idwrs/9781-cre-191227.html. Accessed September 7, 2020.
[8] Detected carbapenemase gene-positive strains originating from locations overseas in carbapenem-resistant Enterobacteriaceae (CRE) pathogen surveillance, 2017-2018. https://www.niid.go.jp/niid/ja/cre-m/cre-iasrd/9125-475d02.html. Accessed September 7, 2020.
[9] Fix the antibiotics pipeline. https://www.nature.com/articles/472032a.pdf. Accessed September 14, 2020.

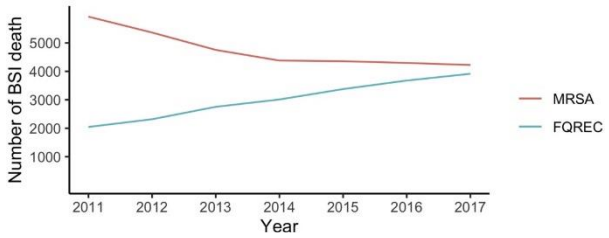

Figure 1: Estimated annual BSI deaths attributable to MRSA and FQREC

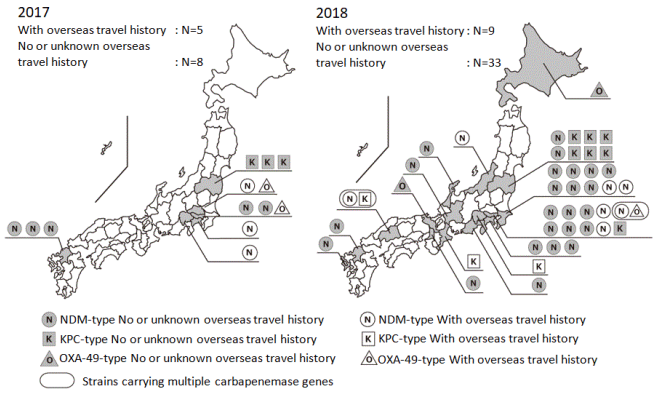

Figure 2: Regions reporting carbapenemase gene-positive strains originating from overseas

That said, the number of new antimicrobials in development has been declining worldwide since the 1980s. In response to this problem, "The 10×'20 Initiative" was launched in the United States with the goal of encouraging the production of ten new antimicrobials between 2010 to 2020. Following on the start of that initiative, in 2011, the U.S. Food and Drug Administration (FDA) passed the Generating Antibiotic Incentives Now Act (GAIN), which promotes the development of new antimicrobials to combat AMR by granting them accelerated FDA review and approvals, as well as five-year extensions on market exclusivity upon approval. Financial support for antimicrobial development is also being provided by the Biomedical Advanced Research and Development Authority (BARDA) of the U.S. Department of Health and Human Services (HHS), which grants public funds for basic research on AMR countermeasures, and Combating Antibiotic-Resistant Bacteria (CARB-X), a public-private partnership (PPP) focused on addressing the threat of AMR. CARB-X has announced it will invest up to US$500 million in AMR countermeasures in the United States and abroad from 2016 to 2021.[10] With the support of these initiatives, twenty new antimicrobial agents were approved in the U.S. between 2010 and 2020 (Table 1).[11]

However, not all of the new antimicrobials have been launched successfully. Shortly after the approval of Plazomicin in 2018, the biotech venture company that developed it, Achaogen, Inc., went bankrupt.[12] That event highlighted the major financial challenges that firms aiming to develop new antimicrobials face after obtaining approval. These include issues related to maintaining sufficient funding to cover post-marketing costs, and expenses related to the creation of a manufacturing system in order to ensure the stable and continuous provision of antimicrobials to the market.[13]

To help address these challenges, discussions have begun in the United States, the United Kingdom, and elsewhere to examine the introduction of new pull incentives that could help companies secure continued funding for new antimicrobials even after approval. The Pasteur Act, which calls for antimicrobial subscriptions, was submitted to the US Congress in April 2004. In the United Kingdom, a pilot is underway that aims to test a delinked subscription model in which the prices paid for new antimicrobials selected by the National Health Service (NHS) will not depend on the

[10] CARB-X is a non-profit partnership. https://carb-x.org/partners/funding-partners/. Accessed September 7, 2020.
[11] Current status and prospective of antibacterial agents regarding countermeasure against antimicrobial resistance (AMR). http://www.thcu.ac.jp/uploads/imgs/20191226090752.pdf. Accessed September 7, 2020.
[12] https://www.nature.com/articles/d41573-019-00085-w. Accessed September 8, 2020.
[13] The history and future prospects of antimicrobial drug development in Japan. http://journal.chemotherapy.or.jp/detail.php?-DB=jsc&-recid=5561&-action=browse. Accessed September 8, 2020.

volume sold. Two antimicrobials were selected for this pilot in December 2020.[14] Likewise, in Sweden, discussions on the introduction of a delinked subscription model have been held since 2018, and a pilot study on the subject is currently being carried out.[15] Pull incentives will not succeed without collaboration and coordination within the international community. Solving the problems of antimicrobial development will require pull incentives in a range of countries that are designed to suit local healthcare systems and regulations.

AMR countermeasures must be built upon efforts supporting the appropriate use of antimicrobials. It is important to provide antimicrobials only to the patients who need them and only during the periods they are needed, based on testing. From a public health standpoint, the use of new antimicrobials must be carefully controlled. All of these points have consequences for antimicrobial manufacturing. Because of the nature of antimicrobial stewardship requirements, even if pharmaceutical manufacturers successfully develop new antimicrobials, they cannot expect profits based on high usage or sales volume, and it is impossible to predict revenue. There is an additional element to this issue in Japan, in that compared to other countries, relatively few people have experienced antimicrobial-resistant infections domestically. This, combined with pharmaceutical pricing issues, makes the prospect of developing and manufacturing new antimicrobials unattractive for pharmaceutical companies in Japan. All of these issues have contributed to the creation of a drug lag for antimicrobials in Japan. Among the twenty new antimicrobials developed as a result of the 10x'20 Initiative in the U.S., only five have been approved for use in Japan. Furthermore, it took an average of 51.2 months for any one of those products to get approved in Japan compared to when they were first approved overseas (Figure 1). The Japanese Government must adopt policies to allow for the rapid and steady introduction of new antimicrobials moving forward.

In 2020, the rapid spread of Coronavirus Disease 2019 (COVID-19) reminded societies around the world of the importance of being prepared for infectious diseases. Worldwide efforts to develop vaccines and therapeutic agents advanced rapidly. Countries around the world, including Japan, are rushing to secure a share of the pharmaceuticals developed. The world is racing against time to deliver the developed pharmaceuticals to their populations in order to save as many lives from COVID-19 as possible.

AMR is at least as large of a threat as COVID-19. It is projected that if serious measures aren't taken against AMR, by 2050, as many as 10 million people could be dying each year from AMR-related causes.[16] The WHO has recognized AMR as a critical health issue.[17] **Japan too must recognize that infectious disease-related health crises are not limited to just emerging and reemerging infectious diseases, but also include AMR, and as such, the Japanese Government should increase support for AMR countermeasures as means of responding to future health crises.**

[14] Mark Perkins, David Glover, "How the 'NHS model' to tackle antimicrobial resistance (AMR) can set a global standard," https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/ Accessed: February 18, 2021
[15] Public Health Agency of Sweden, "Availability of antibiotics." https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/ Accessed: March 17, 2021
[16] TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. Accessed September 14, 2020.
[17] WHO, "10 Global Health Issues to Track in 2021" https://www.who.int/news-room/spotlight/10-global-health-issues-to-track-in-2021 Accessed: February 18, 2021

In an effort to push AMR countermeasures forward, the WHO[18] and the U.S. Centers for Disease Control and Prevention (CDC)[19] created Priority Pathogens Lists (PPL) in 2017 and 2019, respectively. These lists catalogue the pathogens that each organization considers to be the greatest threat to humanity. In Japan, the Agency for Medical Research and Development (AMED), the chairman of the Japan Infectious Diseases Society, the chairman of the Japan Chemotherapy Association, and members of the Japan Pharmaceutical Manufacturers Association have come together to form the AMED Industry-Academia-Government Liaison Committee for Infectious Disease Drug Discovery, which aims to develop a Japanese PPL.[20] Table 2 shows an updated version of the PPL, which was presented at the 13th joint meeting of Seven Academic Societies[21] and the Drug Discovery Promotion Review Committee in March 2021. This list will continue to be revised based on feedback from various sectors of society. The Japanese PPL should be the starting point for the selection of the antimicrobials that should be eligible for a pull incentive.

This proposal provides specific recommendations for ensuring that the few antimicrobials that are expected to be developed globally in the coming decade reach the Japanese public. The measures in these recommendations will also help to establish market conditions that allow domestic pharmaceutical makers to sustain continuous investment in antimicrobial R&D. This document is a compilation of the opinions of experts from industry, government, academia, and civil society who voluntarily lent their knowledge in support of the aforementioned goals. It is presented in the hope of providing useful information for future discussions on AMR countermeasures held within the Japanese Government toward the protection of public health and strengthening of national security.

[18] Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/. Accessed September 14, 2020.
[19] ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed September 14, 2020.
[20] Study on the development of pharmaceuticals against infectious diseases and pathogens in Japan and overseas. https://www.amed.go.jp/content/000064113.pdf. Accessed September 8, 2020.
[21] The seven academic societies are the Japanese Society of Chemotherapy, The Japanese Association for Infectious Diseases, the Japanese Society for Clinical Microbiology, the Japanese Society for Bacteriology, the Japanese Society for Infection Prevention and Control, the Pharmaceutical Society of Japan, and the Japanese Society of Veterinary Science

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Table 1 - Development of antimicrobial agents worldwide since 2010

Antimicrobial name	Strain	Date of approval [**Bold**: initial approval date] (Delay, months)		
		Japan	U.S.	Europe
Ceftaroline fosamil	CEP	---	2010/10	2012/08 (+22)
Fidaxomicin	CDI	2018/07 (+86)	2011/05	2011/12 (+7)
Bedaquiline	TB	2018/01 (+61)	2012/12	2014/03 (+15)
Delamanid	TB	2014/07 (+3)	---	2014/04
Dalbavancin	GLP	---	2014/05	2015/02 (+9)
Tedizolid phosphate	OXZ	2018/03 (+45)	2014/06	2015/03 (+9)
Oritavancin	GLP	---	2014/08	2015/03 (+7)
Finafloxacin	QL	---	2014/12	---
Tazobactam + Ceftolozane	BLI+CEP	2019/01 (+61)	2014/12	2015/09 (+9)
Avibactam + Ceftazidime	BLI+CEP	---	2015/02	2016/06 (+16)
Ozenoxacin	QL	2015/09	2017/12 (+27)	2019/01 (+40)
Delafloxacin	QL	---	2017/06	MAA
Vaborbactam+Meropenem	BLI+CPN	---	2017/08	2018/11 (+15)
Secnidazole	NIZ	---	2017/09	---
Plazomicin	AG	---	2018/06	MAA
Eravacycline	TC	---	2018/08	2018/09 (+13)
Sarecycline	TC	---	2018/10	---
Omadacycline	TC	---	2018/10	MAA
Rifamycin	RIF	---	2018/11	---
Relebactam + Imipenem	BLI+CPN	---	2019/07	MAA
Pretomanid	TB	---	2019/08	---

CEP: cephalosporin, CDI: *Clostridium difficile* infections, TB: anti-tubercular drug, GLP: glycopeptide, OXZ: oxazolidinone, QL: quinolone, BLI: β-lactamase inhibitor, CPN: carbapenem, NIZ: nitroimidazole, AG: aminoglycoside, TC: tetracycline, RIF: rifamycin, MAA: marketing authorization application

Table 2 - Priority Pathogens Lists for R&D of New Antimicrobials (FINAL DRAFT by AMED ID R&D PPP)

Pathogen	WHO(2017)	CDC(2019)	AMED ID R&D PPP DRAFT
MDR *Acinetobacter*	Critical	Urgent(Carbapenem-R)	Priority1
MDR *Pseudomonas aeruginosa*	Critical	Serious(MDR)	Priority1
Carbapenem-R *Enterobacterales*	Critical	Urgent(Carbapenem-R)	Priority1
Ceph-R (ESBL+) *Enterobacterales*	Critical	Serious Ceph-R (ESBL+)	Priority1
Drug-R *Neisseria gonorrhoeae*	High	Urgent(drug-R)	Priority1
MDR/XDR *Mycobacterium tuberculosis*	–	Serious(drug-R)	Priority1
Nontuberculous Mycobacterium (NTM)	–	–	Priority1
Clostridioides difficile	–	Urgent(drug-R)	Priority2
Vancomycin-R *Enterococci* (VRE)	High	Serious(drug-R)	Priority2
Methicillin-R *Staphylococcus aureus* (MRSA)	High	Serious(MRSA)	Priority2
Vancomycin-R *Staphylococcus aureus*	High	–	Priority2
Penicillin non-susceptible *Streptococcus pneumoniae* (PNSP)	Medium	Serious(drug-R)	Priority2
Drug-R *Mycoplasma genitalium*	–	Watch list	Priority2
Candida auris	–	Urgent	Priority1
Drug-R *Candida*	–	Serious(drug-R)	Priority2
Azole-R *Aspergillus fumigatus*	–	Watch list	Priority2

Priority 1: Bacterial or fungal infections which are difficult to treat using existing antimicrobials domestically and internationally [1)] for which the development of new antimicrobials is urgently needed
Priority 2: Bacterial or fungal infections which are clinically treatable by combinations of existing antimicrobials domestically and internationally for which new antimicrobial development will be needed in the near future.
Priority 3 : Bacterial or fungal infections other than the above which require continuous surveillance and basic research in order to prepare for the possibility that new antimicrobial development might be needed in the future
[1)]Based on information from MHLW, NIID, MOFA, WHO and CDC

Priority 3
- Drug-R *Helicobacter pyroli*
- Multi-drug resistant *Bacteroides fragilis*
- Drug-R *Campylobacter*
- Drug-R *Salmonella*
- Fluorloquinolone-resistant *Shigella*
- β-lactamase-nonproducing ampicillin resistant *Haemophilus influenzae*
- Erythromycin-R group A *Streptococcus*
- Clindamycin-R group B *Streptococcus*

WHO	Critical	High	Medium	
CDC	Urgent	Serious	Concerning	Watch
AMED ID PPP	Priority 1	Priority 2	Priority 3	
–	No description			

- Pathogens not listed in this table are categorized "Priority 3" at this moment.
- This Priority Pathogen List will be updated when necessary.
- In recognition of the fact that breakthroughs are always needed related to AMR, it is important that new approaches to research be supported regardless of the above priority list

Provisional translation

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Key Messages

- **Antimicrobial Resistance (AMR) is a health crisis. Japan must deal with it urgently.**

- It has been estimated that **AMR infections** (MRSA and fluoroquinolone-resistant *E. coli*) **already cause at least 8,000 deaths in Japan annually**. In comparison, COVID-19 has caused 8,227 deaths in Japan (as of March 7, 2021).

- **Infections that are resistant to last-resort antimicrobials (such as carbapenem) are on the rise**, and **the number of infections caused by bacterial strains from outside of Japan is rapidly increasing** (based on data from 2017 to 2018).

- Antimicrobial development peaked in the 1980s. **Only six antimicrobials have been approved in Japan since 2010** (compared to over 20 antimicrobials in the U.S.).

- To promote the development of new antimicrobial agents, **we have developed specific recommendations on the creation of a pull incentive**
  - ✧ There are three types of pull incentives that should be considered in Japan:
    - **Market entry rewards**
    - **Delinked subscription model**
    - **Profit guarantee scheme**
  - ✧ Budgetary scope:
    - **Total costs per product depending on the model selected**: **20 to 80 billion yen** (over a ten-year payment period, this equates to payments of **2 to 8 billion yen annually**).

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