Situation and Issues of Development of Antimicrobial Drugs in Japan and Europe and United States

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It is no exaggeration to say that the pandemic of a new coronavirus infection (COVID-19)[1] that occurred in 2019 has drastically changed people's awareness of infectious diseases. The new coronavirus infection occurs when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects humans,[2] but infectious diseases are also caused by infection with various microorganisms other than viruses.[3] Among therapeutic drugs for infections, in particular, antimicrobial drugs used for the treatment of bacterial infections (in this article, systemic antibiotics, synthetic antimicrobial drugs, and drugs mainly used for the antimicrobial action are referred to as "antimicrobial agents"[4]), slowing down of development has been discussed in Japan and overseas in recent years. It has come to be recognized as an important issue in Japan as well. However, new reports on extensive investigation of the situation of development of antimicrobial drugs in Japan are limited.

In this article, in order to widely understand the situation related to the development of antimicrobial drugs in Japan, we will investigate and report the following 3 points: (1) changes in the number and percentage of approved antimicrobial drugs and the status of drug lag in Japan in the past 20 years, (2) situation of development in Japan of new antimicrobial drugs approved overseas in the past 10 years, and (3) situation of development of new antimicrobial drugs in Japan and Europe/US. We would also like to organize and present the issues related to development of antimicrobial drugs.

1. Introduction

1-1. Infections and AMR

Infectious diseases are diseases in which pathogenic microorganisms invade the body to cause symptoms, and pathogenic microorganisms are classified into bacteria, viruses, fungi, and parasites depending on their size and structure.[3] Antimicrobial resistance (AMR) means that drugs used to eradicate these pathogenic microorganisms become ineffective, in other words, acquire resistance.[5] If the drug resistance rate to existing antimicrobial drugs increases, the clinical efficacy decreases, and the types of infectious diseases that become difficult to treat increase.

AMR is an important global public health crisis. In 2016, it was estimated that 700,000 people die from AMR in the world every year.[6] The 700,000 people according to this estimate include the number of deaths attributable to nonbacterial AMR, such as human immunodeficiency virus and malaria. An article published in 2022[7] estimated that 1.27 million people died directly from bacterial AMR in 2019. Although the overall number of deaths due to AMR in Japan is unknown, according to an article published in 2020, the number of deaths due to bloodstream infections caused by methicillin-resistant *Staphylococcus aureus* and fluoroquinolone-resistant *Escherichia coli* was estimated to be more than 8,000 per year.[8]

Not only clinical impact but also medical economic impact of AMR has been reported. According to the report by the Organization for Economic Cooperation and Development, AMR is estimated to cause medical costs of 3.5 billion US dollars (annual) in the analyzed

1) World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
2) World Health Organization. Clinical care for severe acute respiratory infection: toolkit: COVID-19 adaptation
3) AMR Clinical Reference Center. What is a basic infection?: https://amr.ncgm.go.jp/general/1-1-1.html
4) Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare. Guide for proper use of antimicrobial drugs Version 2. December 5, 2019
5) AMR Clinical Reference Center. What is AMR?: https://amrcrc.ncgm.go.jp/020/010/index.html
6) O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. May 2016: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf
7) Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet.2022.DOI:10.1016/s0140-6736(21)02724-0
8) Tsuzuki S, Matsunaga N, Yahara K, et al. National trend of blood-stream infection attributable deaths caused by *Staphylococcus aureus* and *Escherichia coli* in Japan. J Infect Chemother.2020;26(4):367-371.

countries (33 countries).[9] Moreover, according to comparison of the data for EU/European Economic Area (EEA) countries in 2007 and this report, the impact of AMR on healthcare budgets in EU/EEA countries was estimated to have increased by 60% in about 10 years.[9] Research results on the impact of an increase or decrease in AMR on medical economics in Japan were reported. It was reported that a 50% reduction in the drug resistance rate of gram-negative bacteria (main 3 species with high isolation frequency) compared with the current rate would reduce inpatient medical expenses by 2.5 billion to 6.4 billion yen (per year).[10]

Such a situation of global crisis drives global efforts to address AMR threats. In 2015, the World Health Organization (WHO) released the "Global action plan on antimicrobial resistance," which calls for immediate, harmonized action worldwide.[11] The Japanese government released the "National Action Plan on Antimicrobial Resistance (AMR)"[12] in 2016 and has been working on its implementation. Because the target period of this action plan was up to 2020, early revision is expected.

1-2. Background of Development of Antimicrobial Drugs in Japan and Overseas

Despite awareness of the threat of AMR and the need for countermeasures, the slowdown of development of new antimicrobial drugs is a global challenge.[13]

In the United States, an effort called "The 10 × '20 Initiative[14]" was started in 2010, and the goal was set to create 10 new antimicrobial drugs by 2020 through collaboration of industry, academia, and government. According to an article in 2021 that showed changes in the number of FDA-approved antimicrobial drugs that contains a new molecular entity (NME) after 1980 and acts on the whole body, the number steadily decreased from 1980 to 2009. However, compared to the period, the number in the period from 2010 to 2019 increased although it was not sufficient.[15]

On the other hand, the number of antimicrobial drugs approved in Japan between 2010 and 2019 was smaller than that in Europe and the US, and the number of approvals was tied for second worst place among the 14 investigated countries.[16] In a report on a survey of the status of unapproved drugs in Japan,[17] 265 unapproved drugs in Japan as of the end of December 2020 were organized by therapeutic category. As a result, antineoplastic drugs (52 products, 20%) were ranked at the top, followed by gastrointestinal and metabolic drugs (32 products, 12%) and systemic anti-infective drugs (32 products, 12%) (tie for second place).

As shown above, one of the reasons for the small number of approvals can be the severity of the environment surrounding the business of antimicrobial drugs. The details will be discussed later in this article.

2. Survey 1 (Changes in the Number and Percentage of Approved Antimicrobial Drugs and Status of Drug Lag in Japan)

2-1. Method of Survey 1

Regarding NMEs that were approved in Japan between 1990 and 2019 and were classified into therapeutic categories[18] 61 (antibiotic agent) and 62 (chemotherapy agent), we investigated the number of approvals and the percentage out of the total number of NMEs (drugs) approved during the same period. "List of Approved Products[19]," "Yakumu-Koho (Bulletin for Pharmaceutical Affairs[20]," and "Asu-no-shinyaku (New Drugs for Tomorrow)[21]" were used to search. In order to investigate systemic antimicrobial drugs for bacterial infections, those falling under the therapeutic category No. 617 (mainly those acting on molds) and 625 (antiviral agents), and topical drugs were excluded. The drug lag was calculated as the difference between

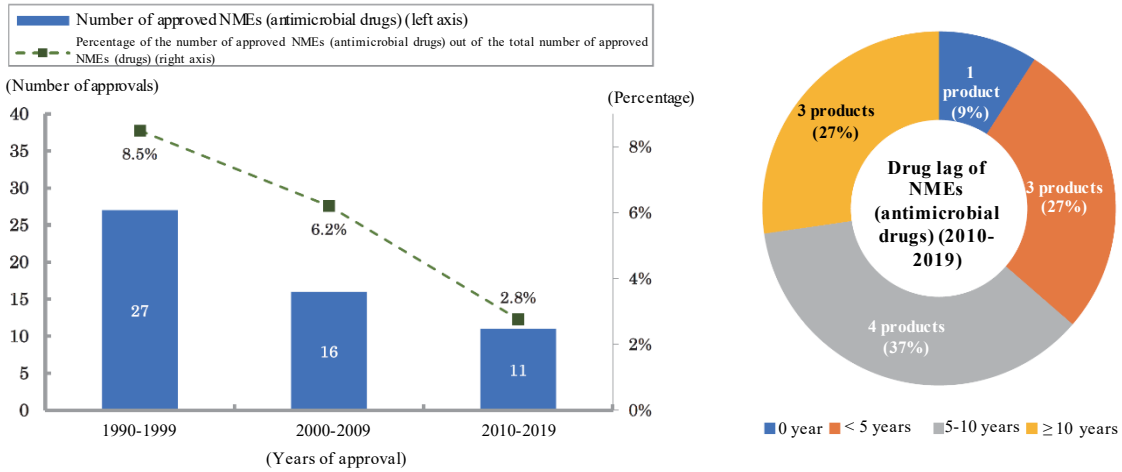
9) OECD. Stemming the Superbug Tide. November 07,2018: https://www.oecd.org/health/stemming-the-superbug-tide-9789264307599-en.htm
10) Matsumoto T, Yuasa A, et al. Estimating the Economic and Clinical Value of Reducing Antimicrobial Resistance to Three Gram-negative Pathogens in Japan. Journal of Health Economics and Outcomes Research.2021; 8:64-75.
11) World Health Organization. Global action plan on antimicrobial resistance: https://www.who.int/publications/i/item/9789241509763
12) Cabinet Meeting on Measures against Infections That Are Global Threats. National Action Plan on Antimicrobial Resistance (AMR) 2016-2020. April 2016: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000120769.pdf
13) Vickers RJ, Bassetti M, Clancy CJ, et al. Combating resistance while maintaining innovation: the future of antimicrobial stewardship. Future Microbiol.2019;14(15):1331-1341.
14) Infectious Diseases Society of A. The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020.Clin Infect Dis.2010; 50:1081-3.
15) Dheman N, Mahoney N, Cox EM, et al. An Analysis of Antibacterial Drug Development Trends in the United States, 1980-2019.Clin Infect Dis.2021; 73:e4444-e50.
16) Outterson K, Orubu ESF, Rex J, et al. Patient access in fourteen high-income countries to new antibacterials approved by the FDA, EMA, PMDA, or Health Canada, 2010-2020.Clin Infect Dis.2021.
17) Office of Pharmaceutical Industry Research. "Drug Lag: Situation and Characteristics of Unapproved Drugs in Japan." OPIR Views and Actions No. 63 (July 2021)
18) Ministry of Internal Affairs and Communications. Japanese Standard Commodity Classification: Therapeutic Category No. (Revised in June 1990): https://www.soumu.go.jp/toukei_toukatsu/index/seido/syouhin/2index.htm
19) Pharmaceuticals and Medical Devices Agency. List of Approved Products: https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html
20) Yakumu-Koho (Bulletin for Pharmaceutical Affairs). Yakumu Koho: http://yakumukohosha.co.jp/
21) TECHNOMICS. Asu-no-shinyaku (New Drugs for Tomorrow): http://www.technomics.co.jp/en/business/

the date of the earliest approval in Japan, the US and Europe and the date of approval in Japan.

2-2. Results of Survey 1

The results are shown in Figure 1. When the number of NMEs (antimicrobial drugs) approved in Japan was divided into 3 categories by periods from 1990 to 1999, from 2000 to 2009, and from 2010 to 2019, the number was 27, 16, and 11 products, respectively, showing decreases. In addition, the percentage of NMEs (antimicrobial drugs) to all NMEs (drugs) was 8.5%, 6.2%, and 2.8%, respectively, showing decreases similarly to the number of approved products (left figure). When the timing of approval was compared between Japan, US and Europe for 11 products approved between 2010 and 2019, it was confirmed that 7 products (64%) had a lag of 5 years or longer since approval in Europe and the US. (Right figure). The results up to 2019 were summarized to equalize the number of years in each category, but it was confirmed that no relevant drugs were approved in 2020.

Figure 1 Changes in the Number and Percentage of Approved Antimicrobial Drugs and the Status of Drug Lag in Japan



Note: The product approved only in Japan was classified as "year 0."
Source: Prepared at the Office of Pharmaceutical Industry Research based on the List of Approved Products, Yakumu-Koho, Japanese Standard Commodity Classification: Therapeutic Category Number (revised in June 1990), and Asu-no-shinyaku.

3. Survey 2 (Situation of Development in Japan of New Antimicrobial Drugs Approved Overseas)

3-1. Method of Survey 2

The antimicrobial drugs identified in the preceding study [16] were included in the survey, and the situation of development of these drugs in Japan as of December 2021 was investigated using the information published in Asunoshinyaku.[21]

New antimicrobial drugs used in the preceding study were defined as follows. (1) NMEs that are categorized as J01 (systemic antimicrobial drugs) in the WHO Anatomical Therapeutic Chemical (ATC) classification system, (2) products which do not fall under any of the following categories: generic drugs, topical drugs, drugs classified as other categories in the ATC Classification, and combination products not containing NME, and (3) the date of the approval by the United States Food and Drug Administration(FDA), the European Medicines Agency (EMA), the Health Canada, or the Ministry of Health, Labour and Welfare, whichever is earliest, was within the period from January 1, 2010 to December 31, 2019. EMA uses the New Active Sub-stance (NAS) as the term corresponding to NME, but NMEs are consistently used in this article.

Bezlotoxumab (J06) and Fidaxomicin (A07), which are therapeutic agents for *Clostridioides difficile* infection, were included in this survey in the same way as on the preceding study, although they did not fall under J01.

Websites of the FDA,[22] EMA,[23] and the Pharmaceuticals and Medical Devices Agency (PMDA)[19] were additionally searched for the same period (January 2010 to December 2021) to prevent missing data. In addition, the antimicrobial spectrum of the target antimicrobial drugs was investigated. The antimicrobial drugs to be investigated were classified into Priority 1 and Priority 2 presented by the AMED Public and Private Partnerships for Infectious Diseases R&D in the "Priority Pathogens Lists for R&D of New

22) U.S. Food and Drug Administration. Novel Drug Approvals for 2021: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2021
23) European Medicines Agency. Medicines: https://www.ema.europa.eu/en/medicines

Antibiotics (2021 version)"[24] (AMED list) compiled by the Japan Agency for Medical Research and Development (AMED). The drugs that do not fall under these categories were classified as "not applicable." An excerpt of the AMED list is shown in Table 1.

Such lists of pathogenic microorganisms for which development of new antimicrobial drugs should be prioritized (Priority Pathogens List) have also been issued by WHO[25] and the Centers for Disease Control and Prevention (CDC)[26]. However, the AMED list is prepared in consideration of clinical practice issues in Japan.

Table 1 Priority Pathogens Lists for R&D of New Antibiotics (2021 version)

Pathogen	AMED Public and Private Partnerships for Infectious Diseases R&D	Pathogen	AMED Public and Private Partnerships for Infectious Diseases R&D
Multidrug-resistant *Acinetobacter baumannii* (MDRA)	Priority1	*Clostridioides difficile* (*C. difficile*)	Priority2
Multi-drug resistant *Pseudomonas aeruginosa* (MDRP)	Priority1	Vancomycin-resistant *Enterococci* (VRE)	Priority2
Carbapenem-Resistant *Enterobacterales* (CRE)	Priority1	Methicillin-resistant *Staphylococcus aureus* (MRSA)	Priority2
Cephalosporin-resistant *Enterobacterales* (ESBL+) (ESBL)	Priority1	Vancomycin-resistant *Staphylococcus aureus* (VRSA)	Priority2
Drug-resistant *Neisseria gonorrhoeae*	Priority1	Penicillin non-susceptible *Streptococcus pneumoniae* (PNSP)	Priority2
Mycobacterium tuberculosis (multidrug-resistant/extensively drug-resistant) (MDRTB/XDRTB)	Priority1	Drug-resistant *Mycoplasma genitalium*	Priority2
Nontuberculous mycobacteria (NTM)	Priority1	*Drug-resistant candida*	Priority2
Candida auris	Priority1	Azole-resistant *Aspergillus fumigatus*	Priority2

Source: The table was prepared by extracting Priority 1 and Priority 2 from the Priority Pathogens Lists for R&D of New Antibiotics (2021 version)

In the AMED list, Priority 1 is a category of pathogens that are given a higher priority in development in the drug discovery research of AMR drugs, and antimicrobial drugs that have an antimicrobial spectrum for pathogens falling under multiple Priority categories were classified in the higher Priority category. The antimicrobial spectrum that a product unapproved in Japan is estimated to have was judged based on the overseas approval information, etc.; therefore, it should be noted that the spectrum might be different from the indicated bacterial species to be approved in the future.

3-2. Results of Survey 2

The results are shown in Tables 2 and 3. As a result of additional search of websites of FDA, EMA, and PMDA, 18 products were included in the survey similarly to the preceding study.

Of the 18 products, 6 were approved in Japan as of December 2021, and 2 products were currently under development in Japan. The history of development in Japan was confirmed but the development was suspended or discontinued for 4 products, and the history of development in Japan was not confirmed for 6 products. The reason for discontinuation or suspension of the 4 products for which development was suspended or discontinued could not be confirmed from the released information. After exclusion of the 6 products approved in Japan and 2 products under development, among the remaining 10 products that have not been developed in Japan, a total of 9 products fell under Priority 1 or Priority 2; 4 products and 5 products, respectively.

24) AMED Public and Private Partnerships for Infectious Diseases R&D. Priority Pathogens Lists for R&D of New Antibiotics (2021 version): https://id3catalyst.jp/apid/en/list.html

25) WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Prioritization of Pathogens to Guide Discovery, Research and Development of New Antibiotics for Drug Resistant Bacterial Infections, Including Tuberculosis.2017.

26) CDC, ANTIBIOTIC RESISTANCE THREATS in the United States.2019.

4. Survey 3 (Situation of Development of New Antimicrobial Drugs in Japan and Europe/US)

4-1. Method of Survey 3

Antimicrobial drugs currently under development in Japan and overseas were identified using the following 3 lists or websites: (1) Antibiotics Currently in Global Clinical Development[27] (a list of antimicrobial drugs which contain at least 1 ingredient that has not been approved in low-molecular-weight compounds that act on the whole body, and may be used for severe infections), (2) Nontraditional Products for Bacterial Infections in Clinical Development[28] (a list of products with antimicrobial effects under development which contain at least 1 ingredient that has not been approved in modalities (antibodies, nucleic acid drugs, etc.) other than low-molecular-weight compounds acting on the whole body, and which may be used for severe infections, and (3) Asunoshinyaku.[21]

The definition for search in Asu-no-shinyaku is NMEs falling under Therapeutic Category Number 61 (antibiotics preparations) and 62 (chemotherapeutic drugs), and the drugs with systemic action against bacterial infection are investigated. So, those corresponding to Therapeutic Category Number 617 (mainly acting on mold) and 625 (antiviral drugs) and external drugs were excluded. Because the search using Asu-no-shinyaku was conducted in December 2021, it should be noted that the information contained in this survey reflects the information posted on the website as of December 2021.

After these three lists were combined, the following were excluded: (1) Drugs listed redundantly when the lists were combined; (2) drugs included in the drugs for which results were presented in "Situation of Development in Japan of New Antimicrobial Drugs Approved Overseas" in Survey 2 and drugs which were not included but have already been approved in Japan; (3) drugs mainly acting on fungi and viruses; and (4) drugs which have not been developed in Japan, US, or Europe.

In addition, the situation of development of each developed product and the antimicrobial spectrum were investigated. The drugs were classified by the same method as Survey 2. However, the drugs under development were investigated in Survey 3; consequently, a category "not applicable/unknown" was created by adding "unknown" to "not applicable."

27) The Pew Charitable Trusts. Antibiotics Currently in Global clinical Development. March 2021: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2014/antibiotics-currently-in-clinical-development

28) The Pew Charitable Trusts. Nontraditional Products for Bacterial Infections in Clinical Development. March 2021: https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development

Table 2 Situation of Development in Japan of New Antimicrobial Drugs Approved Overseas 1

Generic name	Priority in AMED List	Pathogen with antimicrobial spectrum*	United States (Date of approval / development situation)	EU (Date of approval / development situation)	Japan (Date of approval / development situation)
Cefiderocol	Priority 1	CRE, MDRA, MDRP, ESBL	11/14/2019	4/23/2020	Under development (Application under preparation)
Imipenem/cilastatin/relebactam		CRE**	7/16/2019	2/13/2020	6/23/2021
Omadacycline		NTM, MRSA, VRE	10/2/2018	Under development (Phase 3)	Not developed
Eravacycline		CRE, ESBL	8/27/2018	9/20/2018	Not developed
Plazomicin		CRE, ESBL	6/25/2018	Development discontinued/suspended	Not developed
Meropenem/vaborbactam		CRE**, ESBL	8/29/2017	11/20/2018	Not developed
Avibactam/ceftazidime		CRE**, ESBL	2/25/2015	6/23/2016	Under development (Phase 3)
Ceftolozane/tazobactam		ESBL	12/19/2014	9/18/2015	1/8/2019
Lascufloxacin	Priority 2	PRSP	Not developed	Not developed	9/20/2019
Lefamulin		MRSA, VRE, PNSP	8/19/2019	7/27/2020	Not developed
Delafloxacin		MRSA	6/19/2017	12/16/2019	Development discontinued/suspended
Bezlotoxumab		*C. difficile*	10/21/2016	1/18/2017	9/27/2017
Oritavancin		MRSA, VRE, PNSP	8/6/2014	3/19/2015	Development discontinued/suspended
Tedizolid		MRSA, VRE, PNSP	6/20/2014	3/23/2015	3/23/2018
Dalbavancin		MRSA	5/23/2014	2/19/2015	Development discontinued/suspended
Fidaxomicin		*C. difficile*	5/27/2011	12/5/2011	7/2/2018
Ceftaroline		MRSA, PNSP	10/29/2010	8/23/2012	Development discontinued/suspended
Sarecycline	Not applicable	-	10/1/2018	Not developed	Not developed

* Only pathogens listed in the AMED List were included. See Table 1 for the names of pathogens.
** Excluding metallo-β-lactamase-producing strains.
Source: Prepared by the author based on information from the 6 citations presented in Section 3-1.

Table 3 Situation of Development in Japan of New Antimicrobial Drugs Approved Overseas 2

	Total	Priority1	Priority2	Not applicable
Approved in Japan	6	2	4	0
Under development in Japan	2	2	0	0
History of development in Japan was confirmed, but the development was suspended or discontinued.	4	0	4	0
No history of development in Japan	6	4	1	1
Total	18	8	9	1

Source: Prepared by the author based on information from the 6 citations presented in Section 3-1.

The antimicrobial spectrum of the product under development was determined based on the information obtained in the development phase (including the results of basic research); therefore, it should be noted that the spectrum might be different from the indicated bacterial species to be approved in the future.

4-2. Results of Survey 3

The results are shown in Table 4. Sixty products under development were identified according to the method. Of the 60 products under development, the history of development in Japan was not found for 51 products. Two products for which development was discontinued, etc. (development suspended / development discontinued / approval withdrawn / development information not updated for 5 years or more) were excluded. Among the remaining 7 products for which the history of development in Japan was confirmed, 1 product (Solithromycin) under application in Japan was identified, but the status of information disclosure had not been updated since the application for approval was filed in Japan in April 2019, and the current status was unknown. In Europe and the United States, development of the product was discontinued or suspended after application. In addition, phase 1 studies were found to be ongoing for 2 of these 7 products (Gepotidacin and Nacubactam) in Japan, and a phase 3 study was ongoing in the US for the former, but development in the US had been discontinued for the latter.

Among the 60 products, 2 products were under application and 11 products were being examined in phase 3 studies in Europe and the US. The situation of development of these 13 products in Japan was as follows: not developed, 11 products; development discontinued, etc., 1 product; and under phase 1 studies, 1 product.

Table 5 shows the situation of development in Europe and the United States for 51 products for which the history of development could not be confirmed in Japan. The status for 17 products was also development discontinued, etc. in Europe and the US. Among the remaining 34 products, the status in the US or Europe for 24 products was under application (1 product), under phase 3 studies (10 products), and under phase 2 studies (13 products). The antimicrobial spectrum of 1 product under application and 10 products under phase 3 studies was examined. The results showed that each product might fall under the AMED list; 5 products in Priority 1 and 6 products in Priority 2.

5. Summary of Survey Results and Issues Related to Development of Antimicrobial Drugs

In this article, the results of the following surveys are presented: changes in the number and percentage of approved antimicrobial drugs and the status of drug lag in Japan (Survey 1); the situation of development in Japan of new antimicrobial drugs approved overseas (Survey 2); and the situation of development of new antimicrobial drugs in Japan and Europe/US (Survey 3).

Survey 1 showed that the number of antimicrobial drugs approved in Japan decreased over time, and more than 60% of approved drugs had a lag (delay) of more than 5 years after approval in Europe and the United States. Survey 2 showed that, among the 18 products of new antimicrobial drugs that can be used in Europe or the US, only 6 products of antimicrobial drugs can be used in Japan as of December 2021. There are 2 aspects in drug lag: one is "unapproved drugs," which means that the drug is approved in other countries but is not approved in Japan, and the other is a "lag (delay)," which means that the drug has been approved in Japan, but the time required for approval was longer than in other countries.[17)]

Table 4 Situation of Development of New Antimicrobial Drugs in Japan and Europe/US

	Under application	Phase 3	Phase 2	Phase 1	Pre-clinical	Development discontinued, etc.*	Not developed	Total
Japan	1	0	0	2	4	2	51	60
US and Europe	2	11	13	9	2	20	3	60

* Development discontinued / development suspended / development information not updated for 5 years or more / approval withdrawn

Source: Prepared by the author based on 4 lists presented in Section 4-1 and information obtained from websites.

Table 5 Situation of Development in Europe and the United States for 51 Products for Which the History of Development Could Not Be Confirmed in Japan

	Under application	Phase 3	Phase 2	Phase 1	Pre-clinical	Development discontinued, etc.*	Total
US and Europe	1	10	13	9	1	17	51

* Development discontinued / development suspended / development information not updated for 5 years or more / approval withdrawn
Source: Prepared by the author based on 4 lists presented in Section 4-1 and information obtained from websites.

The results of Surveys 1 and 2 showed that both aspects of lag exist in the development of antimicrobial drugs in Japan. Survey 3 showed that, among 60 products under development that have not been approved in Japan, the US, and Europe, 2 products were under application, and 11 products were under phase 3 studies in Europe and the US, while 1 product was under application and no products were under phase 3 studies in Japan.

Many discussions have been held on the reasons why the development of new antimicrobial drugs is difficult. Many issues such as difficulty in drug discovery of antimicrobial drugs with new mechanisms of action and difficulty in enrolling patients with AMR infections in clinical studies are mentioned. For details of each issue, refer to many preceding reviews, etc.[29, 30, 31, 32] Among these issues, we would like to focus our discussion on "low profitability of antimicrobial drugs" in this article. This is because it is considered an important point as the reason why the development of antimicrobial drugs is delayed in Japan compared to Europe and the US.

Usually, more strict promotion of proper use is required for antimicrobial drugs, especially those with a broad antimicrobial spectrum and those expected to be effective for AMR, than for drugs in other disease areas. One of the reasons for this is that inappropriate use of antimicrobial drugs is known to be one of the factors that cause the increase in AMR.[33] In light of these mechanisms by which AMR occurs/increases, it is important to adopt the concept of antimicrobial stewardship (AS)[34] for supporting the proper use of antimicrobial drugs as a measure for coping with AMR, and to provide the maximum therapeutic effect while properly managing the patients receiving administration of the antimicrobial drug and the dosage/administration period. In other words, even if pharmaceutical companies succeed in the research and development of new antimicrobial drugs with broad spectrum, antimicrobial drugs expected to be effective for AMR should be reserved for AMR infections. As a result, it is difficult to expect profits in accordance with the "amount of use or sales."[35]

In 2021, an estimate that the annual global sales of 1.9 billion US dollars at peak would be necessary to establish the development and sales of antimicrobial drugs as a business was reported.[35] However, among the antimicrobial drugs launched after 2000, only 2 products showed peak global sales exceeding 1 billion US dollars: Zyvox (sales of 1.353 billion US dollars in 2015; launched in April 2000[35]) and Cubicin (sales of 1.312 billion US dollars in 2016; launched in November 2003[35]). Thus, it is not easy to achieve the peak sales of 1.9 billion US dollars.

Among the 60 products under development identified in Survey 3, the history of development in Japan could not be confirmed for 51 products (85%, including 20 products for which development was already discontinued or suspended in Europe and the US Europe). When the companies developing these 51 products were confirmed, it was found that most of them were developed by bio-ventures other than "Mega Pharma" or equivalent companies, which are not directly performing business in Japan. This point has been suggested in the past analysis of unapproved drugs in Japan.[17] In order for overseas developing companies to start the development of such products under development directly in Japan, or for companies operating in Japan to introduce such drugs in Japan and start the development, a system to enhance the predictability of the antimicrobial drug business in Japan is required.

The major economic support mechanisms to increase the predictability of the antimicrobial drug business are

29) Tateda K. III. Various problems with antimicrobial drugs. 1. To break the stagnation in development of antimicrobial drugs. The Journal of the Japanese Society of Internal Medicine. 2013; 102.
30) Matsumoto T. Educational Lecture. 9. Development of new antimicrobial drugs. The Journal of the Japanese Society of Internal Medicine .2014; 103.
31) Yagisawa M. Current situation and future of antimicrobial drugs for AMR measures. Journal of Healthcare-associated Infection. 2019; 12.
32) Hirai K. History and future prospects of development of antimicrobial drugs in Japan. Japanese Journal of Chemotherapy. 2020; 68.
33) Altarac D, Gutch M, Mueller J, et al. Challenges and opportunities in the discovery, development, and commercialization of pathogen-targeted antibiotics. Drug Discov Today.2021; 26:2084-89.
34) Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, Clinical Infectious Diseases, Volume 62, Issue 10,15 May 2016.
35) Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Affairs. 2021; 40:1758-65.

"push incentives" to support until approval is obtained and "pull incentives" to support after approval is obtained.[35] There are many overseas organizations engaged in activities to collect funds necessary for push incentives and to promote research and development of antimicrobial drugs, and they support the research and development of antimicrobial drugs mainly by university research institutions and bio-ventures. The activities of push incentives are more active in foreign countries than in Japan, which may have a considerable influence on the difference in the number of antimicrobial drugs developed in Japan and Europe/US. In July 2020, the AMR Action Fund[36] was established by more than 20 major pharmaceutical companies including Japanese pharmaceutical companies. The purpose of the foundation is to produce 2 to 4 new antimicrobial drugs to deliver patients by 2030. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) takes the initiative for this fund, and the Japan Pharmaceutical Manufacturers Association (JPMA) has contributed to the founding of the fund as an IFPMA member organization. In the future, Japanese pharmaceutical companies and bio-ventures are also expected to use this fund to promote the research and development of antimicrobial drugs in Japan.

On the other hand, the scale of the amount of pull incentives is mentioned in the proposal compiled by the AMR Subcommittee of the Asia Africa Medical Innovation Consortium.[37] In the Subscription Model (SM), which is a system to continuously pay a fixed amount separately from the profit based on the amount of sale, the amount necessary for a product in Japan is suggested to be about 2 to 8 billion yen per year, and the payment period is assumed to continue for 10 years after the launch. Another method is the Market Entry Reward (MER) system. In this system, pharmaceutical companies can obtain profits in accordance with the sales volume of antimicrobial drugs, and separately from that, a certain amount of money is guaranteed for investment in the research and development of antimicrobial drugs. It has been proposed that the scale of this system should be 10 to 30 billion yen per product. These amounts were estimated for domestic use in Japan, and the aforementioned paper[35] reported that for the entire world, SM requires 3.1 to 4.2 billion US dollars (total of 10 years) and MER requires 1.6 to 2.2 billion US dollars (one payment). In the US and the United Kingdom (UK), the submission of bills supporting the development of antimicrobial drugs, including pull incentives,[38, 39] or pilot introduction[40] has been started, and the governments have already started discussions on the amount required for pull incentives in their countries. The situation of efforts in the US and UK (England) is shown in Table 6.

It is difficult to estimate the number of antimicrobial drugs to be developed in Japan from the results of the surveys in this article. However, it is considered urgently necessary to start the development in Japan from the viewpoints of public health and safety assurance for at least a total of "9 products" (including "4 products" shown in Survey 2, which have been approved in Europe and the US but have not been developed in Japan and fall under Priority 1 in the AMED List, and "5 products" shown in Survey 3, which are under application/phase 3 studies in Europe/US but have not been developed in Japan, and might fall under Priority 1 in the AMED List). The details of the 9 products are shown in Table 7. In addition, the AMED List states, "Breakthroughs are always required in the area of AMR; therefore, it is necessary for AMR research to support approaches from a new viewpoint regardless of Priority." Development support is required regardless of priority not only for antibiotics that act on pathogens with high priority, but also for development of innovative antibiotics that have a non-conventional mechanism of action.

The survey results presented in this article include the following limitations.

36) AMR Action Fund. Website: https://www.amractionfund.com/ja/
37) AMIC, AMR Subcommittee. Strengthening AMR Countermeasures to Respond to Health Crises. Recommendations to the Japanese Government on Establishing a Pull Incentive System for the Antimicrobial Market. March 24, 2021: https://www.amralliancejapan.org/en/2021/03/news1550/
38) H.R.4100-116th Congress: DISARM Act of 2019: https://www.congress.gov/bill/116th-congress/house-bill/4100/text
39) S.4760-116th Congress: The PASTEUR Act.2020: https://www.congress.gov/bill/116th-congress/senate-bill/4760/text?r=2&s=1
40) National Institute for Health Care Excellence and National Health Service. Antimicrobial Resistance: Developing and testing innovative models for the evaluation and purchase of antimicrobials: https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials

Table 6 Situation of Efforts in the United States and the United Kingdom (England)

Country	Name (bill/system)	Contents	Situation
United States	DISARM Act (The Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms)	Increase payment from Medicare to medical institutions for the use of antimicrobial drugs. This increases demand for innovative antimicrobial drugs and allows pharmaceutical companies to actively invest on research and development of antimicrobial drugs.	The bill was submitted to Congress in 2019.
United States	PASTEUR Act (Pioneering Antimicrobial Subscriptions to End Up Surging Resistance)	The government pays utilization fees to pharmaceutical companies for a certain period of time (subscription method) in order to improve the situation where patients cannot easily receive treatment with new antimicrobial drugs because of a slowdown in the number of antimicrobial drugs developed. Regulatory authority can facilitate the development of new antimicrobial drugs, while pharmaceutical companies can appropriately recover development costs without marketing large amounts of antimicrobials.	The bill legislation was submitted to Congress in 2020.
UK (England)	Subscription-based payment model	The antimicrobial drugs eligible for this system are evaluated and determined from the viewpoint of clinical practice, supply, expenses, etc. The amount of remuneration will be discussed between the marketing authorization holder and the government on a case-by-case basis. In addition, the National Institute for Health and Clinical Excellence (NICE) conducts a Health Technology Assessment (HTA), and the results of the assessment will be taken into consideration when the amount of remuneration is determined.	As of December 2021, 2 products are being evaluated as pilot cases.

Table 7 Nine Products That Might Fall Under Priority 1 in the AMED List and Have Been Approved / Under Application / Under Phase 3 Studies in Europe/US and Have Not Been Developed in Japan

Generic name	Pathogen with antimicrobial spectrum*	United States (Date of approval / development situation)	EU (Date of approval / development situation)
Omadacycline	NTM, MRSA, VRE	10/2/2018	Under development (Phase 3)
Eravacycline	CRE, ESBL	8/27/2018	9/20/2018
Plazomicin	CRE, ESBL	6/25/2018	Development discontinued/suspended
Meropenem/vaborbactam	CRE**, ESBL	8/29/2017	11/20/2018
Cefepime/taniborbactam***	CRE, ESBL, MDRP	Under development (Phase 3)	Not developed
Cefepime/enmetazobactam***	CRE, ESBL	Under development (Phase 3)	Under development (Phase 3)
Sulbactam/durlobactam***	CRE, MDRA	Under development (Phase 3)	Under development (Phase 3)
Cefepime/zidebactam***	CRE, MDRP, ESBL	Under development (Phase 3)	Not developed
Zoliflodacin***	Drug-resistant *Neisseria gonorrhoeae*, MRSA	Under development (Phase 3)	Not developed

* Only pathogens listed in the AMED List were included. See Table 1 for the names of pathogens.
** Excluding metallo-β-lactamase-producing strains.
*** The antimicrobial spectrum was estimated from the information during development (not approved at present).
Source: Prepared by the author based on information from the 6 citations presented in Sections 3-1 and 4-1.

The first limitation is that, although information on development in Japan and abroad was investigated using the released information as well as Asu-no-shinyaku that cites released information, there may be development information or products under development for which the company has not publicly

released information. As a result, in Survey 3, there were more drugs under phase 2 or phase 3 studies than the drugs under preclinical studies or phase 1 studies. The second limitation is that, because this article is intended to investigate the situation of development of antimicrobial drugs in Japan, US, and Europe, the drugs approved only in China, India, Australia, etc., and the drugs under development were excluded from the survey. The third limitation is that whether or not the products under development correspond to AMR drugs or the AMED List was estimated based on the information at the development stage (including the results of basic research). If they are developed and approved in Japan, the indications and applicable microorganisms may differ.

6. Conclusion

Development of drugs for AMR infections is a pressing issue especially in Japan, and awareness of the necessity of economic incentives to promote the development of antimicrobial drugs is increasing in Japan as well. Financial resources are required for economic incentives, but the amount obviously smaller compared to the economic impact and damage caused by infectious diseases. The COVID-19 pandemic has made us deeply aware of the importance of investing in advance and taking countermeasures. Costs for development of antimicrobial drugs including drugs for treating AMR infections and financial resources required for economic incentives should be regarded "not as costs but as investment related to national security." On the other hand, there are slight differences among countries regarding which pathogens should be given priority in development of therapeutic drugs for AMR. Therefore, Japan needs to make preparation appropriate for its situation.

We hope that such an economic incentive system will be introduced in Japan, and research, development, and launch of new antimicrobial drugs will be promoted to proceed preparations for AMR called a silent pandemic.

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