AMR Alliance Japan

POLICY BRIEF

Stabilizing the supply of antimicrobials

Executive summary

- Fragmented antimicrobial supply chains, with very few players at some stages of the chain, increases the risk of global antimicrobial shortages.
- High labor costs and low profits have reduced Japan's antimicrobial market, leading to a situation in which Japan is dependent on overseas manufacturers for the continued supply of antimicrobials.
- Fragmented supply chains and weak market conditions are global problems. Antimicrobial shortages account for 15% of all global drug shortages.
- A risk-management perspective is needed to help companies and countries stabilize antimicrobial supply chains. Responses should include efforts to ensure that multiple routes exist for regularly used antimicrobials.

Introduction

Many different players are involved in antimicrobial supply chains, moving the product from manufacturers to consumers. Put very simplify, active pharmaceutical ingredients (APIs) and excipient manufactures deliver their products to drug manufactures. From there, antimicrobials are manufactured and then sent out for packaging. The completed drug is distributed to primary or secondary wholesalers, which deliver the antimicrobials to hospitals, pharmacies, and patients.

However, the supply chains for antimicrobials are highly fragmented, consisting of many players at some stages of the chain and very few players at other stages. This is especially the case for APIs, the biologically active ingredients of each pharmaceutical. For example, China provides 40% of global APIs.[1] Therefore, if an overseas API manufacturer halts production due to contamination, it can cause a bottleneck in the supply chain, resulting in global antimicrobial shortages. Such antimicrobial shortages are already happening throughout the world, including Japan.

During antimicrobial shortages, many doctors are forced to use suboptimal alternatives. In the US, 55% of physicians indicated that they used less effective, more toxic, or costlier alternative and second line agents during antimicrobial shortages, potentially causing accelerated antimicrobial resistance. [2]

Background of the Issue: Japan

In 2019, Japan faced a major shortage of cefazolin, an "essential" antibiotic used to prevent infections related to surgeries.[3] While the Ministry of Health, Labour, and Welfare provided a list of alternative drugs, these substitute agents were also in short supply. About 42% of physicians claimed that the cefazolin shortage had an effect on their practice.[4] According to a survey of Japanese hospitals that faced cefazolin shortages, the proportion of prescriptions that would be considered appropriate antimicrobial use decreased, whereas the proportion of prescriptions of broad spectrum antimicrobials increased, suggesting that the shortage had an impact on antimicrobial stewardship. [5]

The cefazolin crisis exemplifies many of the issues regarding the supply of antimicrobials in Japan. Prior to the drug revision in April 2020, the price of 0.5g cefazolin is about ¥96 compared to its manufacturing cost of around ¥120. [6] Therefore, companies were selling cefazolin at loss, making continued production unsustainable. While the price was raised to ¥156 in response to the crisis, the Four Academic Society has expressed concerned about acquiring antimicrobials during an emergency.

Furthermore, labor costs are too high in Japan for companies to enter the active pharmaceutical ingredients (APIs) market. As a result, Japan depends heavily on manufactures based in countries where labor costs are lower, such as China and India. A

failure at any of these off-shore manufacturing plants can lead to a national shortage of antimicrobials.

Despite efforts by the public and private sector to stabilize antimicrobial supplies domestically, it has not been enough stop the decline of Japan's antimicrobial market. The market for systemic antimicrobials decreased from ¥965.5 trillion to ¥200 trillion from 1989 to 2018.[7] Therefore, it is essential that Japan continues to take more action to improve market conditions by implementing strategies to incentives investment. [8]

Stakeholders and Countermeasures: Japan

Stakeholder	Countermeasure
Nichi-Iko Pharmaceutical Company, ltd.	• $15 million investment into its factory in Shizuoka. [9]
Four Academic Societies (Japan Society for Infection Prevention and Control. Japan Society of Chemotherapy, the Japan Association of Infectious Diseases, and Japan Society of Clinical Microbiology)	• Four Academic Society's Policy Recommendations for the stable supply of antimicrobials- list of ten key drug, as well as proposals for understanding the current situation of antimicrobial drug production and systems, developing an environment for national manufacturing of antimicrobials, and reviewing the price of existing antimicrobials. [6]
Government (G20)	• Okayama Declaration of G20 Health Ministers - the declaration highlighted the need for private market incentives to guarantee the sustainable access of new and existing essential antibiotics. [10]

Background of the Issue: Global

Around the world, antimicrobial shortages occur frequently, accounting for around 15% of all drug shortages.[9] From 2001 to 2013, 148 national antimicrobial shortages occurred in the US alone,[12] and as of June 29, 2020, 10.5% of all antimicrobials are in short supply.[13] Currently, a penicillin shortage is affecting at least 39 countries. As well as its effects on health outcomes, the estimated economic cost of an antimicrobial shortage is between €20-€30 million (¥2.9 billion to ¥4.3 billion). [14]

While unnecessary antimicrobial use contributes to these shortages, long-lasting shortages are primarily due to weak market conditions. The US Food and Drug Administration (FDA) stated that 62% of all drug shortages in the US are a result of manufacturing and quality issues. [15] When profits are low, companies either exit the market or relocate manufacturing to countries where production costs are lower. For example, China accounts for approximately 40% of global active pharmaceutical ingredient (APIs) production. [1,16] Also, Puerto Rico is home to 49 pharmaceutical companies and more than 70 medical device manufacturers because labor costs are the lowest of any US territory.[17] Notably, more than 30 drugs and 10 biologics without good therapeutic alternatives were made primarily or exclusively on the island. Consequently, if only one or two producers exists, any failure along these supply chains can result in rapid regional or global shortages.

Antimicrobial shortages are not restricted to high-income countries, but also have major impacts for low- and middle-income countries. Weak supply chains, a lack of oversight and regulation, and high medical costs prevent many people in low- and middle- income countries from accessing antimicrobials. Currently, a lack of access to antimicrobials kills more people than antimicrobial resistance in low- and middle- income countries. Of the 21 new antibiotics entering the market between 1999 and 2014, less than five were registered in Sub-Saharan Africa. [18] In addition, the greatest increases in demand for antimicrobials have been observed in low- and middle- income countries. In 2015, four out of six countries with the highest antibiotic consumption rates were low- and middle- income countries (Turkey, Tunisia, Algeria, and Romania).[16] Therefore, it is important to ensure that antimicrobial supply chains are also reaching low- and middle- income countries.

Stakeholders and Countermeasures: Global

Stakeholder	Countermeasure
CARB-X	• Global public-private partnership focused specifically on antimicrobial innovation. CARB-X is investing more than $500 million between 2016-2021, including the development of antimicrobials. [20]
Access to Medicine Foundation	• White paper highlights the underlying causes of the antibiotic shortage and recommendations for government, regulators, the pharmaceutical industry and others. The paper focuses primarily on three countermeasures: demand planning, ensuring uninterrupted supply, and strengthening the distribution chain. [12]
United Kingdom's five-year plan on antimicrobial resistance	• First national pull-incentive to increase antimicrobial prices depending on their public health value. [21]

Stakeholder	Countermeasure
Drive-AB	• Joint undertaking between the European Union and European Pharmaceutical Industry Association, including 15 public and 7 private partners from 12 countries. Created policy recommendations strengthening antibiotic pipelines. [22]
UK's AMR Centre and Shionogi & Co., Ltd.	• Public-private partnership on the antimicrobial COT-143. The AMR Centre will be responsible for manufacturing the complex active ingredient and will work on future strategies to commercialize the drugs once clinical trials have been successfully completed. [23]
GlaxoSmithKline	• Works with WHO in anticipating supply and demand needs of antimicrobials. [17]
AMR Industry Alliance	• According to a 2020 report, 81% of member companies have comprehensive strategies to improve access and 63% have partnered with NGOs, industry trade groups, local healthcare institutions, and others to expanded patient access to AMR-relevant products. [24]

AMR Alliance Japan Recommendations

- The Government should invest appropriately to help companies realize the stable supply of antimicrobials, based on a risk-management perspective (including through the consideration of increasing the premiums attached to antimicrobials within the medical fee system).
- The Government should support companies in their efforts to ensure that multiple production routes exist for regularly used antimicrobials, and to make it possible to increase the supply of antimicrobials when needed.

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