Antimicrobial resistance: Shionogi advocates policy change to address the public health threat

SHIONOGI

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Antimicrobial resistance (AMR) has become a serious threat to the effective prevention and treatment of infections caused by bacteria, viruses, fungi and parasites. AMR is a global issue with potentially devastating consequences to those infected with resistant pathogens and high direct and indirect costs to society. The ongoing coronavirus (COVID-19) pandemic has demonstrated how devastating infectious diseases can be. Although AMR is a slower-moving threat, it is no less dangerous than COVID-19: every year, drug-resistant microbes are responsible for an estimated 700,000 deaths and future projections for the impact of unresolved AMR are as high as 10 million deaths per year by 2050 (ref. 1).

"AMR is a slow tsunami that threatens to undo a century of medical progress," says Tedros Adhanom Ghebreyesus, director-general at the World Health Organization (WHO). Antibiotic resistance is perhaps the most important component of AMR because effective antibiotics underpin much of modern-day healthcare, from common surgeries to chemotherapy and organ transplants. We are slowly losing the race to stay ahead of bacterial resistance mechanisms and, without action, we face a future in which lack of effective antibiotics could make routine medical procedures dangerous, make more complex interventions and procedures impossible, and reduce our ability to respond to outbreaks of infectious diseases. Antibacterial resistance is a predictable and preventable crisis – but only if we act now. AMR, and in particular antibacterial resistance, must be regarded as an urgent global, regional and national priority for governments and health organisations.

INFECTIOUS DISEASE INNOVATION

Shionogi is a global pharmaceutical company established more than 140 years ago in Osaka, Japan. Shionogi is committed to prioritising patients and the company recognises the importance of continued investment in infectious disease research. In the Access to Medicine Foundation's 2020 Antimicrobial Resistance Benchmark survey, Shionogi was found to invest a greater proportion of revenue in antimicrobial research and development (R&D) than similar companies evaluated.

Highlights of Shionogi's antibacterial research achievements include:

- 1959: sulfamethoxazole, a sulfonamide antibacterial still in clinical use today and listed on the WHO Model Lists of Essential Medicines in combination with trimethoprim.
- 1982: moxalactam (latamoxef), the world's first oxacephem antibiotic.
- 1988: flomoxef, the world's second oxacephem antibiotic.
- 1992 and 1997: ceftibuten and cefcapene, new oral cephem antibiotics.
- 2005: doripenem, a new carbapenem antibiotic.
- 2019: cefiderocol, the world's first approved siderophore cephalosporin antibiotic.

Shionogi has also discovered important antiviral products and has therapeutic, vaccine and diagnostic programmes to address severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the causative pathogen for COVID-19). Highlights of Shionogi's antiviral research include:

- 2013: dolutegravir, an integrase inhibitor for human immunodeficiency virus (HIV).
- 2018: baloxavir marboxil, the world's first cap-dependent endonuclease inhibitor for influenza virus.

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Bacterial infections secondary to viral infections such as influenza and SARS-CoV-2 can be extremely serious. Most of the deaths in the 1918 influenza pandemic, as well as the 1957 and 1968 pandemics, likely resulted directly from secondary bacterial pneumonia[2]. Bacterial infections secondary to SARS-CoV-2 have also been reported,

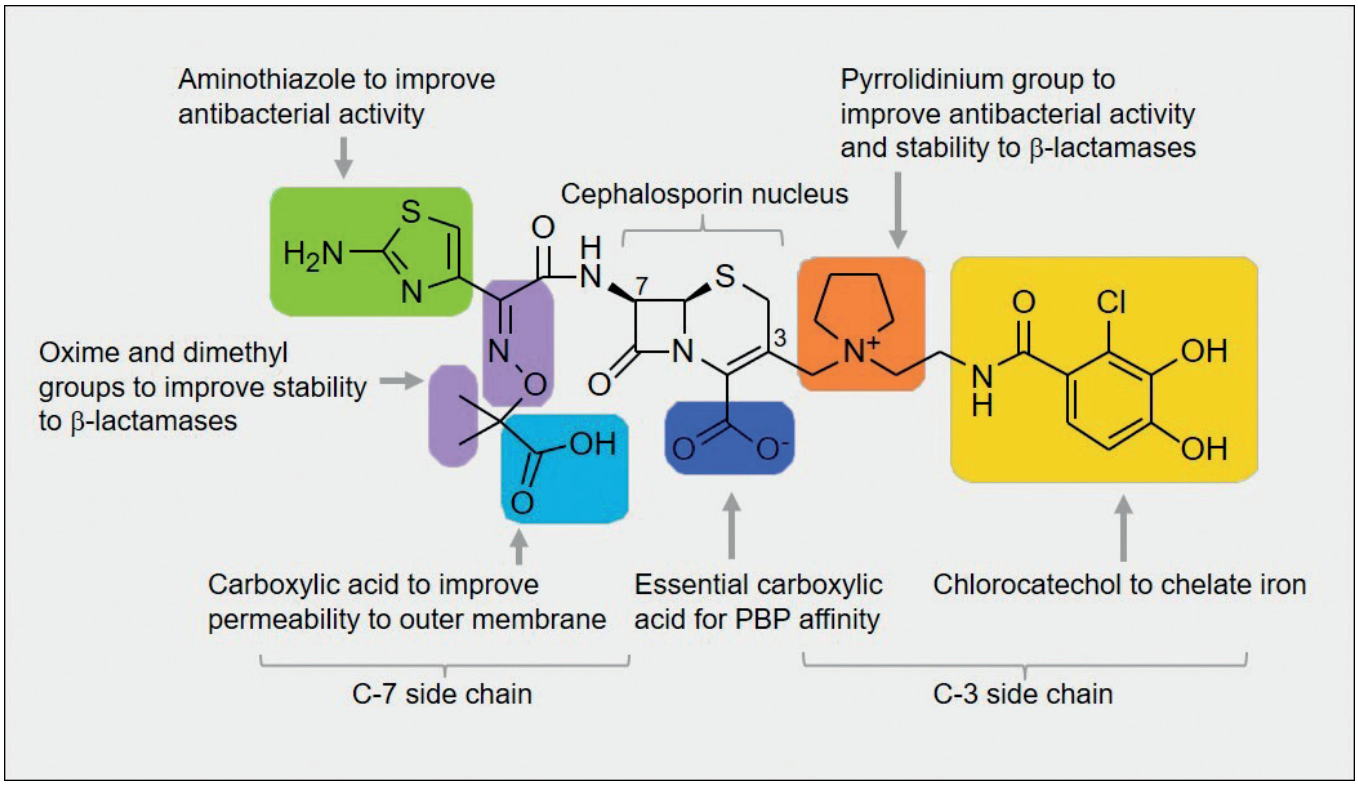

Figure 1. The structure of cefiderocol. PBP, penicillin-binding protein[10].

although extensive prophylactic use of antibiotics has limited the incidence. Recent analysis of Shionogi's Early Access Program for cefiderocol in Europe suggests that between April and July 2020, 35% of requests for cefiderocol were from patients with SARS-CoV-2, driven largely from southern Europe during the peak of the COVID-19 pandemic (data on file).

PROBLEM PATHOGENS

Bacteria are classified into two categories, Gram-positive and Gram-negative, based on a method of staining developed in 1882 by Hans Christian Gram. Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus* species, have a thick peptidoglycan layer and no outer membrane; in contrast, Gram-negative bacteria, such as *Klebsiella*, *Pseudomonas* and *Acinetobacter* species, have a thinner peptidoglycan layer and an outer membrane, an asymmetric bilayer consisting of phospholipids and lipopolysaccharides. The difference in membrane structure between Gram-positive and Gram-negative bacteria and the wide diversity of enzymes that bacteria produce to counter antibiotics determine whether a specific antibiotic can effectively treat a specific bacterial strain.

Drug-resistant bacteria, sometimes described as multidrug resistant (MDR) or as 'superbugs' or 'nightmare' bacteria, are a growing issue in all parts of the world. MDR bacteria are resistant to multiple classes of antibiotics. The WHO has categorised the most problematic bacteria as critical, high or medium priority. The pathogens labelled as critical are:

- *Acinetobacter baumannii*, carbapenem-resistant.
- *Pseudomonas aeruginosa*, carbapenem-resistant.
- Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant. (Enterobacteriaceae include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.)

Bacteria listed as critical are all Gram-negative. Carbapenems are a class of antibiotics and are the workhorses for treating the most serious Gram-negative infections in hospitals. Twenty years ago, carbapenems were almost always effective, but resistance is becoming common; for example, in Korea the resistance rate of *A. baumannii* to imipenem (a commonly used carbapenem) increased to 85% in 2015 (ref. 3).

Gram-negative bacteria have three major resistance mechanisms to carbapenem antibiotics: porin channel mutations to prevent cell entry, efflux pumps to expel antibiotics and beta-lactamase enzymes to inactivate beta-lactam antibiotics. New antibiotics must overcome resistance mechanisms using more efficient penetration through the outer membrane and improved stability over the ever-increasing diversity of acquired or intrinsic enzyme-based mechanisms.

Carbapenem-resistant infections are not only a cause of high patient mortality, they are also expensive. Infection with *A. baumannii* is associated with prolonged hospital stays, often requiring patients to be admitted to the intensive care unit[4]. In the United States (US), treatment of a single patient with a carbapenem-resistant Enterobacteriaceae infection is estimated to cost between $22,000 and $65,000 (ref. 5). Outbreaks of carbapenem-resistant infections at specific institutions can be expensive. A carbapenem-resistant *K. pneumonia* outbreak affecting 40 patients across five hospitals in west London, United

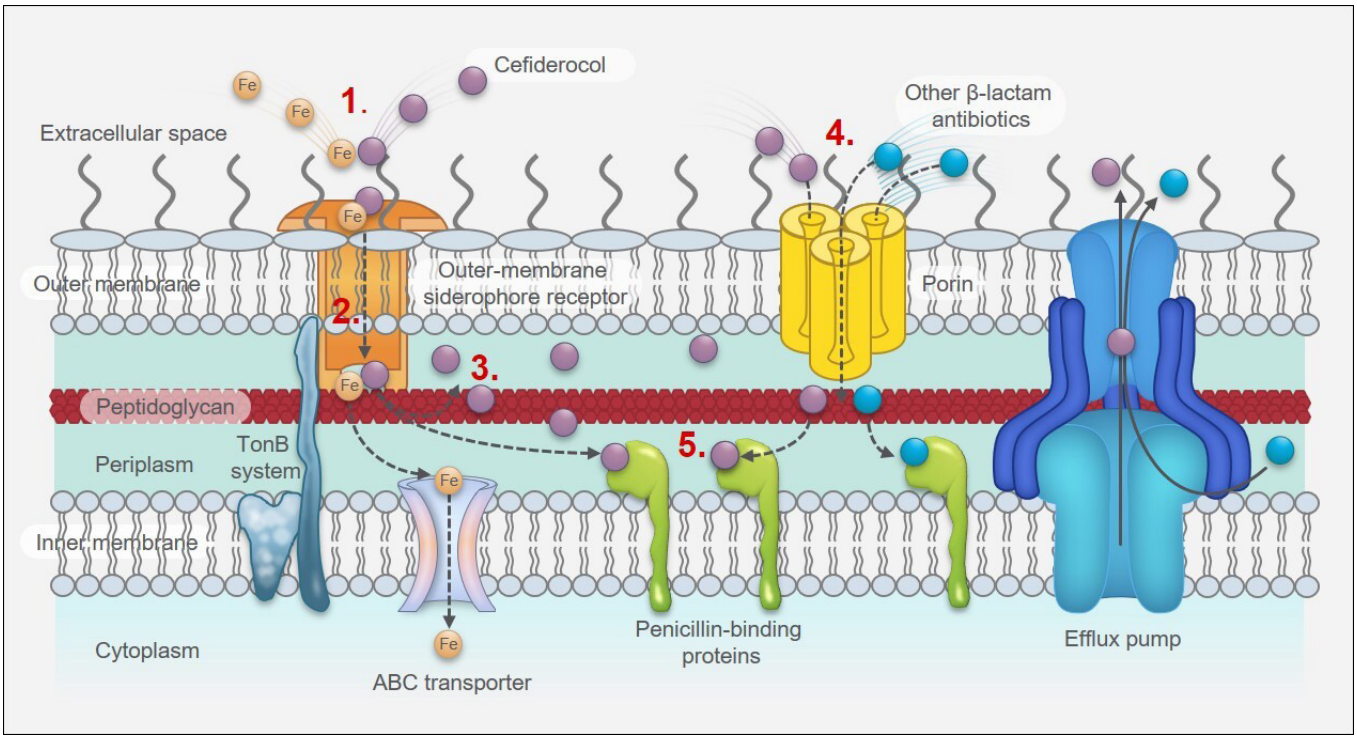

Figure 2. Cefiderocol can enter Gram-negative bacterial cells via their iron uptake mechanism. 1. Cefiderocol chelates extracellular iron. 2. The chelated complex is actively transported into the periplasm by outer-membrane receptors. 3. Once in the periplasm, cefiderocol dissociates from the iron ions. 4. In common with other beta-lactam antibiotics, cefiderocol enters the periplasm via diffusion through porins. 5. Once inside the periplasm, cefiderocol binds and inhibits penicillin-binding proteins.

Kingdom (UK), between 2014 and 2015 resulted in costs totalling €1.1 million[6]. Unless addressed now, increases in antibacterial resistance will further strain already stretched healthcare budgets and ultimately affect patient care.

CEFIDEROCOL – A 'TROJAN HORSE'

Shionogi has developed cefiderocol, an antibiotic recently approved by both the US Food and Drug Administration[7] and the European Medicines Agency[8] that targets Gram-negative bacteria including those identified by the WHO as critical priority pathogens. Cefiderocol is the first of a novel class of siderophore-conjugated cephalosporin antibiotics. Iron is an essential micronutrient required by bacteria to grow. Siderophores are natural iron-chelating compounds secreted by bacteria and other microorganisms to acquire and transport iron across the cell membrane. Cefiderocol works by mimicking naturally occurring siderophore molecules and chelating with iron. The chelated complex is actively transported across the outer membrane of the bacterial cell into the periplasmic space through specialised iron transporter channels. Cefiderocol's 'Trojan horse' method of cell entry enables more efficient penetration by overcoming certain intrinsic or acquired antibiotic resistance mechanisms[9].

Research into synthetic beta-lactams conjugated with siderophores was started in the 1980s (ref. 9), but early attempts to develop antibiotics of this type were unsuccessful. In the early 1990s, Shionogi identified two siderophore cephalosporins with potent antibacterial activity against Gram-negative pathogens but chose to focus on the development of carbapenem antibiotics with broader antibacterial spectrums, including both Gram-positive and Gram negative bacteria. Work on siderophore-conjugated antibiotics resumed in the early 2000s, when reports of carbapenem resistance emerged and the need for new antibiotics became clear. Further research by Shionogi led to the identification of cefiderocol[10].

Cefiderocol was designed with a cephalosporin nucleus and a catechol side chain to mimic siderophores and thereby facilitate cell entry. The addition of side chains to the cephalosporin nucleus enhances its potency and stability against beta-lactamase enzymes (**Fig. 1**). The catechol side chain enables the formation of a chelating complex with ferric iron, enabling the antibiotic/iron complex to cross the outer membrane through active iron transporters. Once inside the periplasmic space, the iron dissociates and the cefiderocol molecule binds to penicillin binding proteins (PBPs), thereby disrupting cell wall synthesis and killing the bacteria (**Fig. 2**).

In view of the growing challenges of antimicrobial resistance and cefiderocol's novel mechanism of cell entry, Shionogi has made cefiderocol available to patients with the most urgent need prior to commercial launch through expanded access programmes (commonly referred to as compassionate use or special access programmes, for patients with life-threatening infections who have no other treatment options). As of July 2020, more than 200 patients from more than 10 countries have been provided with cefiderocol.

POLICY CHANGE IS CRITICAL

In 2015, the WHO issued a document titled 'Global action plan on antimicrobial resistance', stating that "Without harmonized and immediate global action, the

world is heading towards a post-antibiotic era where common infections could once again kill". Shionogi supports the call to action and advocates six policy pillars (**Fig. 3**) to address the AMR crisis:

1. Create a predictable and sustainable market for AMR products through economic incentives, such as payments that are not associated with (are delinked from) the volume of product sold (known as pull incentives), and establish new, antibiotic-specific, value assessments for reimbursement.
2. Harmonise global regulations for development and approval of new antibiotics. Despite progress, regulatory agencies around the world still have different requirements for development programmes and approve new agents with different product labelling.
3. Establish clinical trial networks to help execute clinical studies more efficiently. Operationalising clinical studies for new antibacterial products is difficult and extremely expensive. Development costs to bring one new product to approval exceed US$1 billion[11].
4. Ensure appropriate use of antibiotics through regulation of animal use, stewardship and timely surveillance of resistance epidemiology. New diagnostics and enhanced surveillance are needed to guide appropriate use and better understand where resistant pathogens are an issue.
5. Make effective medicines available for patients in need directly or through alliance partners. In parts of the world, basic medical care and common antibiotics are not readily available. Improving access to the healthcare infrastructure that many people take for granted should be a high priority.
6. Reduce environmental impact from the manufacture of antibiotics. New standards have been developed to measure and control of the discharge of antibiotics into the environment during manufacturing. Biopharmaceutical companies belonging to the AMR Industry Alliance have made commitments to appropriately control their manufacturing processes, and others should follow.

A BROKEN MARKET

Developing antibiotics is a long, complex and risky process, with many failures along the way. Appropriate use initiatives, including stewardship by health-care practitioners, aim to slow the rate of resistance development by restricting the use of new antibiotics and targeting their use to instances in which treatment options are limited. Although appropriate use of antibiotics is essential, the consequence is a low level of use for new agents, which in turn limits revenue to support continued commercialisation and a healthy pipeline of new antibiotics. The uncertainty around market size, combined with the increasingly challenging task of discovering and developing novel antibiotics, has led many large manufacturers to exit or scale back their antibiotics development programmes[12] and to focus their activities on more predictable areas. Of equal concern, a number of smaller companies with commercialised antibiotics have had to file for bankruptcy or seek acquisition, negatively impacting market diversification and career opportunities for skilled researchers. In April 2019, Achaogen filed for bankruptcy after launching plazomicin, and all assets were sold; in December 2019, Melinta Therapeutics filed for bankruptcy; and in July 2020, Tetraphase Pharmaceuticals was acquired by La Jolla Pharmaceutical Company. Simply put, the market for antibiotics that address AMR is broken.

Shionogi strongly supports the introduction of new incentives, funding, and value assessment models for reimbursement to restore a viable commercial market and maintain innovation in this critical field. Shionogi advocates for incentives for R&D (push incentives) and incentives for commercialisation (pull incentives), as well as other value assessment and reimbursement reforms to stimulate the market for novel antibacterial agents. Shionogi is excited to see visible progress with respect to push incentives,

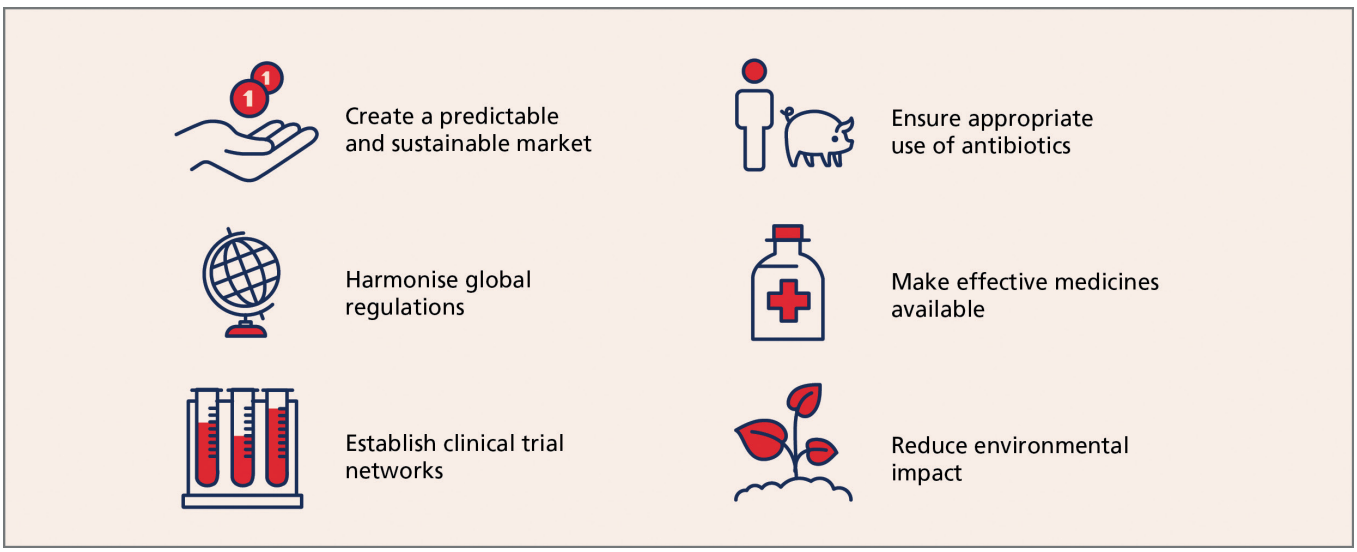

Figure 3. Six policy pillars required to address antimicrobial resistance.

such as the US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) Broad Spectrum Antimicrobials Program, the global non-profit partnership Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), and a programme launched by the Innovative Medicines Initiative called New Drugs for Bad Bugs. Since its inception in 2013, Shionogi has participated in the Global Health Innovative Technology Fund, Japan's first public–private partnership fund created to advance the research and development of innovative medicines for the treatment of infectious diseases in the developing world.

Although push funding is important, pull incentives are crucial to ensure that new antibiotics are made available to consumers. To date, there has been a lot of discussion but little tangible action in terms of pull incentives. Shionogi recognises that pull incentives have to fit country and regional situations and supports selection and implementation from a suite of pull incentives, such as partially delinked or fully delinked market-entry rewards, subscription payment schemes, and government purchases, in addition to innovative, antibacterial-specific, value based pricing and reimbursement initiatives, such as diagnosis-related group-linked reimbursement reform. Shionogi appreciates the ongoing discussion of pull incentives by governments and other organisations and strongly advocates moving quickly from discussion to implementation. Shionogi also supports the implementation of measures that address manufacturing issues as part of the overall development and commercialisation need.

INDUSTRY IS ALIGNED. WHAT IS NEXT?

The biopharmaceutical industry has made significant progress aligning on the need to address AMR and committing to tangible action. However, AMR is a complex issue requiring collaboration across multiple sectors and stakeholders. We note progress with new initiatives by organisations such the WHO, the Food and Agriculture Organization of the United Nations, and the World Organisation for Animal Health to lead and coordinate the global One Health response to AMR in cooperation with the United Nations and other agencies.

In 2016, Shionogi and more than 100 life-sciences companies and associations signed a declaration on AMR at the World Economic Forum calling for collective action to create a sustainable and predictable market for antibiotics, vaccines and diagnostics, while emphasising the need for conservation of new and existing treatments. Together with 12 other leading companies, Shionogi went further, signing an Industry Roadmap that includes action plans for antibiotic research and appropriate use, access and manufacturing. The companies involved subsequently formed the AMR Industry Alliance, a private sector coalition that unites biotechs, diagnostic manufacturers, generic drug manufacturers, and leading research-based pharmaceutical companies.

In July 2020, Shionogi partnered with more than 20 biopharmaceutical companies to launch an initiative known as the AMR Action Fund to help small biotechnology companies bridge the financial gap that will continue to exist until implementation of new market-based policy reforms that support antibiotics. Industry has stepped up, committing nearly US$1 billion to bring two to four antibiotics to market this decade. Although this action buys time, it does not solve the issue that the antibiotics market is broken and requires urgent action by governments around the world.

Two countries have taken a leadership role in addressing the need for action. The UK has announced a pilot programme for delinked purchase of two antibiotics. NHS England will pay a company a fixed fee for an antibiotic that targets AMR and in return will receive the antibiotic whenever needed at no additional cost. If the pilot is successful, rollout of these purchasing arrangements is expected across the UK's National Health Service. Sweden is implementing a pilot programme designed to guarantee access to medically important antibiotics, providing an annual payment to a company for access to an antibiotic in addition to the usual reimbursement. Shionogi applauds the UK and Sweden for piloting new AMR policies.

In addition to pull incentives, novel approaches are needed to the assessment processes that many countries use to determine the value of antibiotics. Health technology assessments evaluate benefits versus costs of new medicines, but they tend to exclude population-level benefits, such as reduced transmission, reduction in resistance rates and enablement of other medical procedures. The COVID-19 pandemic has demonstrated the threat of societal transmission of infectious diseases and hopefully it will spur change towards a harmonised, dedicated, value assessment for antibiotics across countries.

OUR CALL TO ACTION

SARS-CoV-2 was largely unknown until early 2020, but AMR is a threat we know and understand. We know the priority pathogens for which there is an urgent need for new treatments, and we know how to develop agents to treat them. Shionogi recognises that establishing mechanisms to incentivise development and commercialisation of new antibiotics, such as pull incentives and novel value assessments or reimbursement systems, will take time, stakeholder engagement and political goodwill at national and global levels. To help prevent another infectious disease crisis we must take action to address AMR. At Shionogi we are proud of our commitment to addressing infectious diseases and will take a leadership role to ensure that new antibiotics are available to benefit individual patients and society as a whole.

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ACKNOWEDGEMENTS

The authors would like to thank colleagues from Shionogi for their help in the development of this white paper, in particular Hiroyuki Yoshida, Yusuke Ariyoshi, Andrew Koren, James Bond, Lisa Butkowski and Kelli Smith.