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Review

Antimicrobial resistance: Japan's and Thailand's perspectives

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Juntra Karbwang,[1] Kiyoshi Kita,[2] Kenji Hirayama,[2] Taeko Moriyasu,[3] Thanawat Khongyot,[2,4] Yoshimasa Tanaka,[5] Tsuyoshi Kihara,[6] Kesara Na-Bangchang[1,7]*

[1]Drug Discovery and Development Center, Thammasat University (Ransit Campus), Pathumtanee, Thailand.
[2]School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan.
[3]Office for Global Relations, Nagasaki University, Nagasaki, Japan.
[4]School of Pharmacy, Walailak University, Nakhon Si Thammarat, Thailand.
[5]Center for Medical Innovation, Nagasaki University, Nagasaki, Japan.
[6]Shiongi Global Infectious Diseases, Nagasaki University, Nagasaki, Japan.
[7]Graduate Studies, Chulabhorn International College of Medicine, Thammasat University (Ransit Campus), Pathumtanee, Thailand.

*Corresponding Author
Email kesaratmu@yahoo.com

Tel:+66218111678

The emergence and rapid spread of antimicrobial resistance (AMR) threaten global public health. AMR is promoted by many factors, including inadequate infection prevention and control, a lack of sanitation, failing waste management systems, limited access to vaccines, diagnostics, and quality and affordable medicines, and a lack of awareness and knowledge regarding AMR and its burdens. AMR countermeasures include minimization of the risk of AMR development through the rational use of antibacterial drugs. Significant critical gaps include fast AMR tracking, new drug research and development, and simple and rapid diagnostic tests to detect AMR microorganisms. Wastewater-Based Epidemiology (WBE) is a potential approach for early warning and sentinel surveillance of AMR. Promising sources of antimicrobial agents include marine microbes and shark-derived nanobodies from shark-farming systems.

Keywords: Antimicrobial Resistance (AMR), Antimicrobial Stewardship, Research and Development

INTRODUCTION

The global emergence and rapid dissemination of antimicrobial resistance (AMR) threaten human health worldwide. This leads to prolonged illness, disability and death (Lim et al., 2016; Naylor et al., 2018; Cassini et al., 2019; Antimicrobial Resistance Collaborators, 2022). AMR impacts the economy of individuals and public health expenditures (Velazquez-Meza, 2011). The WHO has developed a priority pathogens list to guide and promote new drug discovery, research and development. The list focuses on gram-negative bacteria resistant to multiple drugs, e.g., including carbapenem-resistant *Acinetobacter, Pseudomonas,* and third-generation cephalosporin-resistant

Enterobacteriaceae (WHO, 2017). New approved antibacterial drugs and candidates are still insufficient (WHO 2021a; WHO, 2021b; WHO, 2021c).

The review article highlights the presentations and discussions during the Nagasaki University and Thammasat University symposium held on December 14, 2022. The main objective was strengthening collaborative surveillance networks, raising better awareness, education, and stewardship, conducting social research, and developing rapid diagnostics and research and development (R&D) for new antibacterial drugs to address AMR.

DISCUSSION

Antibacterial R&D Landscape in Japan

Japan's government and private sectors, such as the Japan Agency for Medical Research and Development (AMED), have established a push incentive and financial support to promote basic and clinical research to address the issues of AMR. The regulatory authority has improved its application process to facilitate antibacterial drug approval and sustainability of antimicrobials after their launch, as well as access and delivery to needy countries.

AMR: One Health Perspective

The Thailand National Strategic Plan 2017-2021 aimed to resolve AMR in an integrated manner, with the objective of developing structures and sustaining AMR-related actions. These actions included the establishment of an AMR surveillance system, the implementation of regulations controlling the distribution of antimicrobials, the promotion of infection prevention and control through antimicrobial stewardship in humans, agriculture, and animals, the enhancement of public knowledge about AMR and the appropriate use of antimicrobials, and the development of mechanisms to facilitate the development and sustainability of AMR-related actions.

Surveillance and Monitoring of Antimicrobial Use and Resistance

The AMR Clinical Reference Center of Japan was established in 2017. Several research projects have been conducted on antimicrobial use, disease burdens, and antimicrobial stewardship in Japan. Antimicrobial use in Japan has decreased significantly since the introduction of the plan. Antimicrobial stewardship alone may not be sufficient, and other interventions might be necessary. COVID-19 has more influence on the clinical use of antimicrobials than the promotion of appropriate use of antimicrobials (Li et al., 2024). Continuous antimicrobial use surveillance is required. Information related to AMR indicators majoring in hospitals has been aggregated, providing a comprehensive summary of infectious disease treatment status, infection control approaches, incidence of healthcare-associated and bloodstream infections, emergence of major and AMR bacteria, and information on antimicrobial and disinfectant use.

Wastewater-Based Epidemiology (WBE) is used as an early warning and an unbiased tool through sentinel surveillance for infectious diseases by identifying locations where diseases have already spread and implementing an early intervention to delay the spread of the disease (Mella et al., 2024). The use of WBE for tracking AMR requires further research, as the challenge for this approach is the detection of multiple pathogens in wastewater.

For the prevention and control of hospital-acquired infections in a Resource-Limited Setting (RLS), screening strategies/surveillance of AMR in infectious patients were recommended. This would particularly include the screening for carbapenem-resistant *Enterobacteriaceae* (CRE), *Acinetobacter baumannii (CRAB)*, and *Pseudomonas aeruginosa* (CRPsA*).* However, surveillance cultures of asymptomatic patients should be considered only in patients with previous CRE colonization and those with a history of recent hospitalization in endemic CRE settings or contacted CRE colonized/infected patients. The challenges for improving preventive and control measures and patient outcomes are proper screening strategies and strengthening the microbiology laboratory capacity.

A Need To Stimulate R&D of Antimicrobial Drugs

Marine microbes, sponges and corals have increasingly gained attention as resources for antimicrobial agents. Most species such as *Streptomyces chumphoensis*, *Streptomyces verrucosisporus*, *Micromonospora fluostatini*, *Micromonospora sediminis*, *Micromonospora sediminicola, Micromonospora marina,* and *Micromonospora maritima* were obtained from marine sediment. Tunicamycins from marine-derived *Streptomyces bacillaris* have been shown to inhibit MurNAc-pentapeptide translocase in *Staphylococcus aureus* (Lee et al., 2024). Marine-derived biomolecules extract library was established, which contains small and mid-size biomolecules. These molecules can penetrate cell membranes and interfere with the intracellular protein-protein interaction involved in the development of diseases (Gozari et al., 2021). Screening natural products from these microorganisms is still limited and needs further investigation.

Another source of antimicrobial agents is the shark-derived nanobodies derived from shark-farming systems. The single variable domain (VNAR) fragment from sharks, called a nanobody, can be expressed in *Escherichia coli* and has the properties of an ideal therapeutic candidate for some diseases. It is physically robust and may lead to the development of highly specific, stable, effective, and inexpensive biotherapeutics in the future (Liu et al., 2023).

Drug repurposing is another fast and cost-effective approach for developing drugs against AMR (Azeem et al., 2024). Polymyxin B (PMB) has been used for Gram-negative bacterial infections since 1959. However, its clinical use is limited due to the serious nephrotoxicity and neurotoxicity after parenteral administration. PMB is the last-line treatment for gram-negative bacteria, but there is limited information on optimal drug delivery for treating MDR-Gram-negative bacterial infection. Currently, studies on pulmonary drug delivery systems for polymyxin B include liposomes and innovations that have adapted the route of administration from intravenous to inhalation. Further development of novel strategies for safe and effective inhalation therapy of polymyxin B against MDR-Gram-negative bacterial lung infections is required.

A Need for Simple and Rapid Diagnostic Tests to Detect AMR

A rapid, simple, accurate and low-cost method to diagnose *Mycobacterium tuberculosis* (MTB) resistant microorganisms that can be adopted in developing countries was developed using gene amplification technologies (Ilina et al., 2013). These techniques enable rapid, simple, accurate and low-cost genotyping of MTB. Targeted next-generation sequencing (tNGS) can be used to perform *Mycobacterium tuberculosis* (MTB) complex-specific amplification or target capture directly from sputum samples, yielding simultaneous coverage of many genes and DNA regions associated with antimicrobial resistance (AMR) (Zhang et al., 2024). To address AMR issues effectively, novel, faster, standardized, sensitive, and specific methods with reliable results need to be introduced into microbiological laboratory practice. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) could be considered a rapid screening technique for AMR.

Conclusion

Although AMR occurs naturally over time, usually through genetic changes, it is accelerated by the misuse and overuse of antimicrobials in humans, animals, and plants. The rapid spread of AMR is further promoted by inadequate infection prevention and control, together with a lack of clean water and sanitation, failing waste management systems, limited access to vaccines, diagnostics and quality and affordable medicines, as well as a lack of awareness and knowledge of AMR and its burdens (WHO, 2021a; WHO 2021b). A holistic approach is required to tackle AMR and its rapid spread. While more diagnostics and drug R&D for AMR are vital, better access and appropriate use of existing and future antibiotics in humans, animals, and plants, as well as better-coordinated surveillance and tracking of AMR and prevention of infections and spreading are equally important.

Conflict of interest

No conflict of interest exits in the submission of this manuscript.

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