



Asian Perspectives on the Control of Antimicrobial Resistance

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Introduction

Infectious diseases still remain the most important threat to human health despite remarkable advances in modern medicine. According to WHO, about 15 million (>25%) of 57 million annual deaths worldwide are estimated to be related directly to infectious diseases.¹ Infectious diseases are the second leading cause of death next to cardiovascular diseases and the leading cause of disability-adjusted life-years worldwide. Among infectious diseases, respiratory infections are the leading killer followed by HIV/AIDS, diarrheal diseases, tuberculosis, malaria, and sexually transmitted diseases. The burden of morbidity and mortality associated with infectious diseases falls most heavily on people in developing countries, and particularly on infants and children. Asia, the largest continent with most population, is the major center of emerging and re-emerging infectious diseases including antimicrobial resistance in major human pathogens.

Emergence of antimicrobial resistance in Asia

1. Global situation of antimicrobial resistance

Most of the cardinal infectious diseases such as respiratory infections, HIV/AIDS, diarrheal diseases, tuberculosis, malaria, sexually transmitted diseases and nosocomial infections have serious problems in the treatment due to widespread emergence of antimicrobial resistance. Although major issues on antimicrobial resistance may be different between hospitals and community or between developed and developing countries, an increasing trend of resistance in major pathogens is consistently observed in any setting. Antimicrobial resistance results in increased morbidity and mortality from treatment failures. A recent meta-analysis showed that methicillin-resistant *Staphylococcus aureus* (MRSA) could increase the mortality by 2 times higher than that in methicillin-susceptible *S. aureus* bacteremia.² More dramatically, vancomycin-intermediate or hetero-vancomycin-resistant *S. aureus* has increased the mortality by 12 times comparing with control group.³ Not only clinical impact but also socioeconomic impact of resistance is also devastating. Socioeconomic impact is more serious in poor, developing countries where incidence of resistance is higher than in developed countries and infrastructures are relatively lacking.

2. Current epidemiology of antimicrobial resistance in Asia

Asia is obviously one of the major epicenters of antimicrobial resistance in major human pathogens.

For the past 10 years, many epidemiologic studies in Asian countries revealed that the prevalence of antimicrobial resistance in major pathogens is remarkably higher in some Asian countries than that in western part of the world. Representative examples of antimicrobial resistance among community pathogens in the Asian region include *Salmonella* or *Shigella* species with multidrug resistance, *Streptococcus pneumoniae* with penicillin and macrolide resistance, *Mycobacterium tuberculosis* with multidrug resistance, and *Neisseria gonorrhoea* with penicillin and tetracycline resistance. Antimicrobial resistance is also a serious problem in nosocomial pathogens such as MRSA, vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacilli, and multidrug-resistant *Pseudomonas aeruginosa*. One of the most prominent examples of antimicrobial resistance in Asia is pneumococcal resistance. From the serial international surveillance studies on pneumococcal resistance among clinical isolates (1996-1997), carriage isolates (1998-1999), and invasive isolates (2000-2001) in Asian countries, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) reported that antimicrobial resistance to penicillin and macrolides in *S. pneumoniae* is much more prominent in Asian countries than in western countries.^{4,6} For instance, more than 70% of clinical isolates of *S. pneumoniae* from Vietnam and Korea were not susceptible to penicillin or macrolides. Prevalence of MRSA is also higher in Asian countries according to the recent international surveillance study. In general, many Asian countries have serious problems in antimicrobial resistance in major pathogens.

3. Major reasons for high prevalence of resistance in Asia

Basic driving force for the emergence of antimicrobial resistance is antimicrobial consumption, particularly inappropriate use of antibiotics. Antimicrobial agents are frequently abused or misused in many Asian countries, even without doctor's prescriptions in some countries. Counterfeit drugs which are very common in some countries are another form of antimicrobial abuse. Antibiotics are abused not only in patients but also in food animals, fish farms, and agriculture. After emergence of resistance, resistant strains can spread within the region or to geographically remote areas or different countries. Molecular epidemiologic studies showed that the spread of the Taiwan^{19F} clone and the Spain^{23F} clone could be among the major reasons for rapid increases in antimicrobial resistance in *S. pneumoniae* in the Asian region.⁷ In addition to these basic factors, lack of relevant information on resistance, lack of awareness of the situation of resistance, and lack of systems for the control and prevention of resistance have been making the situation worse in the region for the past 2 decades.

Strategy to control antimicrobial resistance in Asia

Antimicrobial resistance in major pathogens will continue to emerge, leading to unpredictable epidemics and difficult challenges to public health and to microbiology and allied sciences. Strategic planning for the control and prevention of antimicrobial resistance is urgently required, especially in the Asian region where the burden of the problem is peaking and the infrastructure to control the problem is underdeveloped.

The major pillars of the public health strategy for confronting resistance are surveillance and monitoring of resistance, rational use of antimicrobial agents, effective infection control, and research and development of new drugs.

1. Surveillance and monitoring of resistance

Surveillance of resistance must be the first link in the chain of public health action against antimicro-

bial resistance, as it is aiming to identify the existing problems of resistance, to assist health providers in making rational clinical decisions, to assist health policy makers in implementing policies and regulations for antibiotic use, and to support pharmaceutical industry in the discovery, preparation, and marketing of new drugs. Surveillance activity should be performed at different level in Asian countries; local hospital, nationwide, and an international level. Local-level surveillance in individual hospitals is the basis for infection control procedures, hospital antibiotic control, and quality improvement of patient care. Creation of an efficient and strong national surveillance system is very difficult, but it is very important to have the national data on antimicrobial resistance in making and implementing the policies and strategies. Only few countries in Asia have nationwide surveillance systems for this purpose. In Korea, for example, the National Antimicrobial Resistance Safety Management Program (NARMP) was established in 2002 as an official governmental system to deal with the problem of antibiotic resistance. NARMP has been performing basic surveillance of resistance in the hospitals and in food animals in Korea since 2002. Based on these surveillance data, NARMP will make or revise the policy and regulations to improve antibiotic use and to control antimicrobial resistance in Korea. The Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) and the Korean Network for Studies on Infectious Diseases (KONSID) are private nationwide network systems to perform multi-center surveillance of resistance. International surveillance is also very important because antimicrobial resistance can spread between countries. In the western part of the world, there are a couple of international networks for surveillance of resistance.⁸ Some of them are organized by industries such as the Alexander Project (GSK), MYSTIC (AstraZeneca), SENTRY (BMS), TSN (Focus Technologies), PROTEKT (Aventis), and LIBRA (Bayer), while others are organized by academia or governments such as EARSS (European Antimicrobial Resistance Surveillance System), ESAR (European Surveillance of Antibiotic Resistance), INSPEAR (International Network for the Study and Prevention of Emerging Antimicrobial Resistance), and WARN (World Antibiotic Resistance Network). But, in the Asian region, ANSORP (Asian Network for Surveillance of Resistant Pathogens) is the only international network for studies on antimicrobial resistance and infectious diseases. Since 1996 when ANSORP was first organized by Asian investigators, ANSORP has been continuously expanded to have 31 centers in 18 cities in 12 countries in Asia and the Middle East as of 2004. ANSORP has successfully performed international surveillance of pneumococcal resistance, MRSA and VRSA, VRE, enteric pathogens, and community-acquired pneumonia. ANSORP system will have more than 80-100 centers in Asia until 2010. Through this network, ANSORP will perform not only multinational studies but also education, strategic planning, and promotional activity for control and prevention of infectious diseases and antimicrobial resistance in the region. ANSORP will be the center of biomedical research on infectious diseases and antimicrobial agents and resistance in the Asia-Pacific region.

2. Strategic plan for control of resistance in the region

1) Rational antibiotic use

Given the impact of inappropriate use of antibiotics on the emergence of antimicrobial resistance, rational antibiotic use is very critical for the control and prevention of antibiotic resistance in the Asian region. Antibiotics should be used appropriately not only in patients but also in food animals. To promote rational use of antibiotics, education of physicians, pharmacists, and patients is a very basic measure. Standard treatment or prophylaxis guidelines of antimicrobial use are also required to encourage appropriate use of antibiotics. Public campaign or use of mass media could be useful to provide information about the danger of antibiotic resistance and antibiotic abuse. All these measures to promote rational use of antibiotics should be based on the epidemiologic data in the region.

2) Prevention of the spread of resistant clones

Strict infection control procedures are essential to prevent the spread of antibiotic-resistant clones within the hospital or between the regions. Basic molecular epidemiologic research to document the spread of resistance should be performed to prepare the strategies of infection control.

3) Policy and regulation

Necessary policy and regulation to control antibiotic use should be implemented both at local hospitals and at national level. This would be particularly important in many Asian countries where relevant regulation of antibiotic use is not established. As an alternative to regulations, certain types of incentives for hospitals and pharmaceutical companies such as tax breaks or extension of patent rights could be considered.

4) Development of new drugs and vaccines

Development of new antimicrobial agents which can eradicate resistant pathogens is vital. However, it is very difficult to discover new classes of antibiotics by conventional methods of drug development, with the oxazolidinones being the latest example to successfully launched in the clinical practice. Unfortunately, considering the past history of antimicrobial resistance, antimicrobial resistance could ultimately emerge against any kinds of antibiotics. Although vaccination could be an ultimate solution for the control of antimicrobial resistance, investment of time and capital needed to develop new vaccines are substantial and not every type of infectious disease lends itself to this type of prevention.

Conclusion

Antimicrobial resistance is an inevitable phenomenon. It is clearly anticipated that the problem of antimicrobial resistance will be getting worse in many parts of the world, especially in Asian countries. Continued surveillance of resistance through local, national, and international networks should be performed in the region. Based on the information, strategic plan for the control and prevention of resistance is urgently required in the Asian region.

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