

ANTIMICROBIAL RESISTANCE CONTROL IN ASIA

JAE-HOON SONG, PROFESSOR OF MEDICINE, DIVISION OF INFECTIOUS DISEASES, SAMSUNG MEDICAL CENTER, SUNGKYUNKWAN UNIVERSITY SCHOOL OF MEDICINE, SEOUL, KOREA; CHAIRMAN, ASIA PACIFIC FOUNDATION FOR INFECTIOUS DISEASES (APFID) AND ORGANIZER, ASIAN NETWORK FOR SURVEILLANCE OF RESISTANT PATHOGENS (ANSORP)



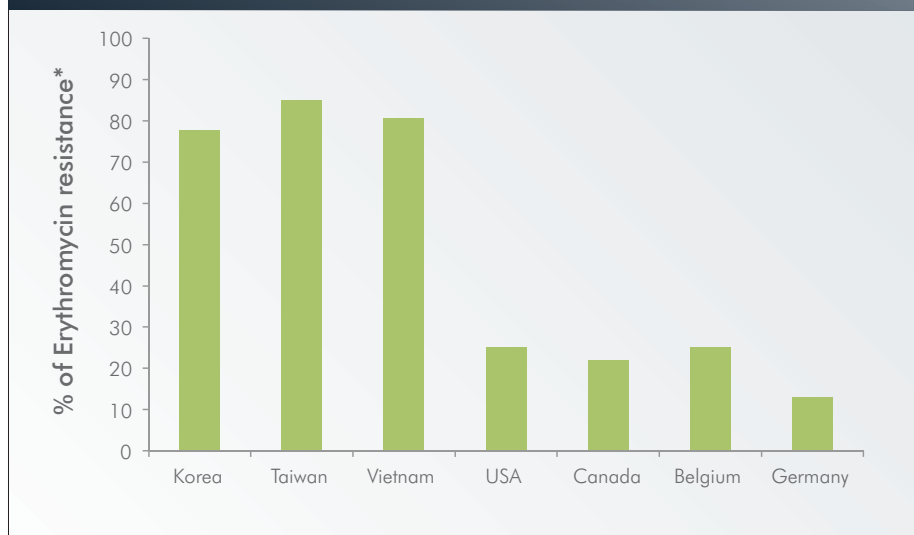
Antimicrobial resistance (AMR) is a very critical health-care, social and economic problem worldwide. In particular, the Asian region shows the seriousness of the AMR problem due to its high prevalence rates of AMR in major bacterial pathogens and lack of effective efforts to combat AMR. Although AMR should be considered the national priority, it has not been recognized as an important health-care issue in most Asian countries. Given the clinical and socioeconomic impact of AMR, comprehensive strategies and action plans based on the national efforts and international collaboration are urgently required to control and prevent AMR in the region.

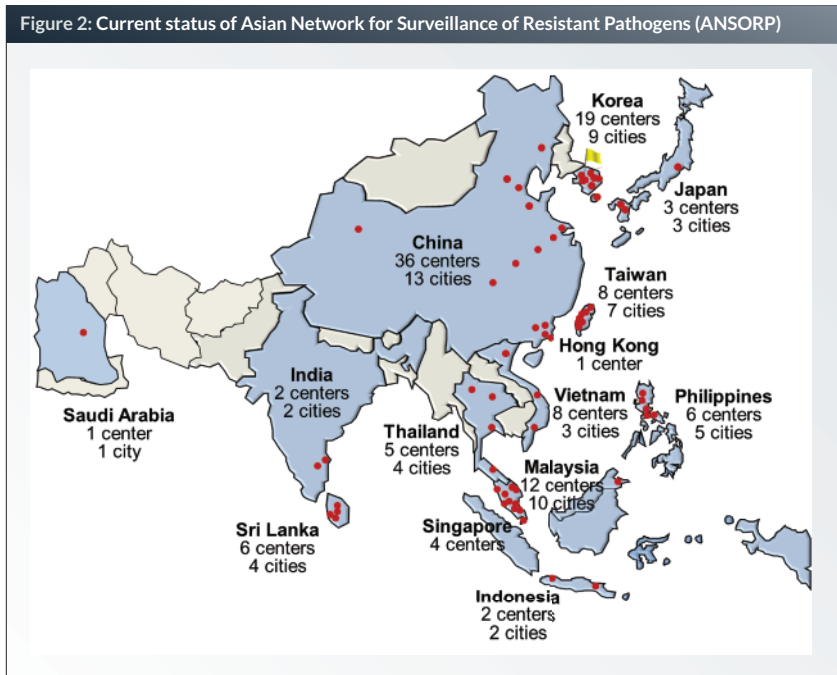
Treatment of infectious diseases is becoming more difficult due to widespread emergence of antimicrobial resistance (AMR) in major pathogens, particularly in bacteria, which results in treatment failure, prolonged illness, disability and greater risk of death. AMR is considered responsible annually for >23,000 deaths in the United States, 25,000 deaths in the European Union and >38,000 deaths in Thailand (1). AMR can spread rapidly between patients, regions, and countries. Recently, New Delhi metallo- β -lactamase-1 (NDM-1)-producing bacteria which originated from India in 2008 have spread throughout the world (2, 3). Since AMR can spread across the borders, this is not a local problem but an international issue. Furthermore, AMR can cause enormous economic loss. Overall societal costs for AMR are estimated to be US\$ 35 billion as direct and indirect cost in the United States, € 1.5 billion in the European Union, and US\$ 1.3 billion in Thailand (1). Given that most of the low- and middle-income countries which might have even more serious problems of antibiotic abuse and AMR do not have the data. The global impact of AMR on clinical, social, and economic aspects is unprecedented.

Current situation of AMR in the Asian region

Based on the published reports, the Asian region is evidently an epicenter of AMR globally with the highest prevalence of resistance in major bacterial pathogens (Table 1) (4-8). Multi-drug-resistant pathogens have been widely disseminated both in hospitals and in the communities in many Asian countries. For instance, *Streptococcus pneumoniae* which is the most common pathogen of community-acquired pneumonia, shows an extremely high prevalence rate to macrolide antibiotics in Asian countries (Fig. 1) (5, 9-12). Unusually high prevalence rates of AMR in major bacterial pathogens in Asian countries are affected by several factors.

Figure 1: Prevalence of *Streptococcus pneumoniae* resistant to macrolide in Korea, Taiwan, and Vietnam (2008–2009); USA (2007–2009); Canada (2008); Belgium (2007–2009); and Germany (2008)





antibiotics and may pose a risk to human health worldwide due to the scale of the livestock industry and the largest volume of antibiotics is produced and consumed in China (14). Once AMR emerges, these resistant pathogens can easily and rapidly spread unless effective control measures are implemented. However, inadequate health-care infrastructures and infection control programmes in most of the low- and middle-income Asian countries prevent effective control and prevention of the emergence and spread of AMR.

Strategies and action plans to control AMR in Asia

International efforts to combat AMR in Asia
International efforts to perform surveillance of AMR and to prepare the

The most important reason is antibiotic abuse and misuse both in the clinical practice and in animal husbandry in Asian countries. Although antibiotics are universally abused throughout the world, these special therapeutic agents are very frequently and widely abused in the Asian region where antibiotics can be purchased as over-the-counter drugs in many countries. Counterfeit antibiotics are another inducer of AMR: 78% of counterfeit antibiotics are made in Southeast Asian countries where 44% of these drugs are consumed (13). Antibiotics are also widely abused in animal husbandry in many Asian countries. In China, the use of antibiotics for disease treatment and as growth promoters in animals is unmonitored which leads to the overuse of

international strategies have been pursued only by limited groups and organizations in the Asian region despite the critical situation of AMR. In 1996, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) was organized by Asian physicians (organizer: Professor Jae-Hoon Song, Korea) to perform international surveillance of AMR in the Asian region (www.ansorp.org). ANSORP has collaborated internationally to identify the problems of AMR in major bacterial pathogens by activating 113 hospitals in 65 cities in 14 Asian countries/areas (Fig. 2). In order to support the ANSORP activities and other programmes, the Asia Pacific Foundation for Infectious Diseases (APFID) was founded in 1999 which organizes and

Table 1: Prevalence of resistance in major bacterial pathogens

Pathogen	Disease	Antibiotic	Resistance ¹ %	Focus area
Community				
<i>Streptococcus pneumoniae</i>	CAP ²	Macrolide	73%	Asia
<i>Escherichia coli</i>	UTI ³	3rd cephalosporins	95%	Asia
<i>Salmonella Typhi</i>	Enteric infection	Ciprofloxacin	84%	Asia
Hospital				
<i>Staphylococcus aureus</i>	HAP ⁴ , bacteremia	Methicillin	82%	Asia
<i>E. coli</i>	HAP, bacteremia	Ciprofloxacin	96%	Asia
<i>Klebsiella pneumoniae</i>	HAP, bacteremia	3rd cephalosporins	81%	Asia
<i>Pseudomonas aeruginosa</i>	HAP	Carbapenem	30%	Asia
<i>Acinetobacter baumannii</i>	HAP	Carbapenem	68%	Asia

¹Highest reported prevalence of resistance to prototype antibiotics
²CAP ; Community-acquired pneumonia
³UTI ; Urinary tract infection
⁴HAP ; Hospital-acquired pneumonia

supports various international efforts to combat infectious disease threats, particularly infections caused by drug-resistant bacteria in the Asia-Pacific region. APFID has been operating four major international programmes; international surveillance of AMR by ANSORP since 1996, international communication of scientific issues by ISAAR (International Symposium on Antimicrobial Agents and Resistance) since 1997, international microbial collection by ABB (Asian Bacterial Bank) since 1996, and international campaign for AMR by Campaign 4 since 2014. APFID and ANSORP have been actively collaborating with the World Health Organization (WHO), Asia Pacific Economic Cooperation (APEC), regional academic societies and health-care organizations in individual countries to prepare international strategies and action plans as well as to establish a platform for effective control and prevention of AMR in the region.

Strategies and action plans for AMR control in Asia

APFID has proposed the international strategies to control and prevent AMR in the Asia-Pacific region in collaboration with APEC as the “APEC guideline to tackle antimicrobial resistance in the Asia-Pacific region” in 2014 (15). The guidelines includes six strategic action plans (Fig. 3):

- Strengthen national and international surveillance activities to identify the problems and issues of AMR and monitoring of antibiotic uses.
- Improve awareness of AMR through campaigns, education and training.

Surveillance of AMR tracks changes in microbial populations, permits the early detection of resistant strains of public health importance, and supports the prompt notification and investigation of outbreaks

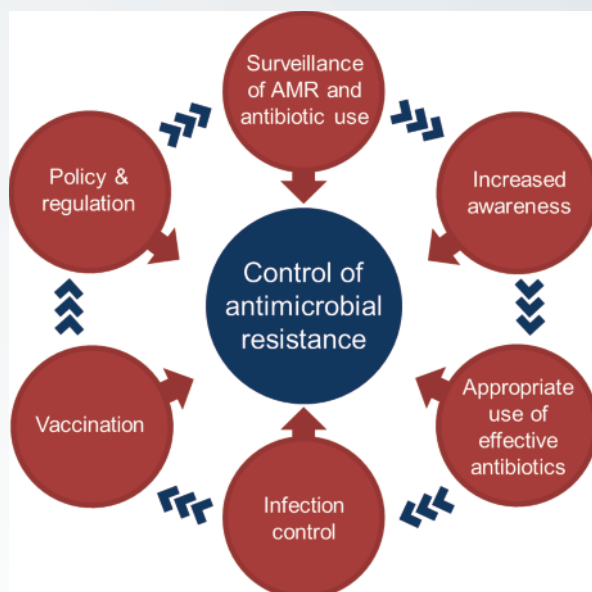
- Promote appropriate uses of antimicrobial agents in human and animal husbandry.
- Strengthen hospital infection control and prevention.
- Promote vaccination programmes to reduce the incidence of bacterial infections.
- Strengthen the national infrastructures and international efforts to combat AMR.

Action plan 1: Strengthen the surveillance of AMR and antibiotics use

Surveillance of AMR is essential for identifying current problems by providing information on the magnitude and trends in AMR. Surveillance of AMR tracks changes in microbial populations, permits the early detection of resistant strains of public health importance, and supports the prompt notification and investigation of outbreaks. Surveillance findings are needed to inform clinical therapy decisions and to guide policy recommendations. First of all,

the national surveillance of AMR should be urgently established in every country in the region. The microbiology laboratory procedures, data collection, and data reporting should be qualified and standardized. Moreover, the international surveillance of AMR in the Asian region should be established because AMR can spread across the borders. ANSORP has been contributing to collecting and reporting the AMR in the Asian region through international collaboration for the past two decades (5, 6, 16, 17). Surveillance is also needed for monitoring the effect of interventions. Monitoring of antibiotic use is also very important because inappropriate taking of antibiotics is the most basic driving force for the emergence of AMR. Given that Asian countries have a very serious problem with antibiotic abuse/misuse not only in patients but also in animal husbandry as well as

Figure 3: Six strategic action plans to control and prevent antimicrobial resistance in Asia



the issues of counterfeit antibiotics, monitoring of antibiotic use is very crucial for proper control and prevention of AMR.

Action plan 2: Improve awareness of AMR

Lack of awareness and knowledge about AMR prevents Asian countries preparing comprehensive strategies to combat AMR. Also, it is one of the main reasons for the inappropriate use of antibiotics. A recent survey in Asia showed that most Asian countries do not have adequate knowledge about AMR or the appropriate use of antibiotics among the general public and health-care professionals (18, 19). However, there has been no adequate educational and campaigning activities for this issue in most Asian countries. APFID is preparing the first international campaign programme – “Campaign 4” – to improve awareness of AMR in the Asian region. Campaign 4 is aiming to deliver four key messages to four major target groups:

- 1) Take prescribed antibiotics only;
- 2) Take antibiotics exactly as prescribed;
- 3) Do not take left-over antibiotics; and
- 4) Do not take antibiotics for the common cold.

The four target groups are the general public (patients), health-care professionals (prescribers), the pharmaceutical industry (providers) and health-care policy-makers. Campaign 4 will be introduced to Asian countries soon using videoclips, leaflets, educational conferences/symposia, media promotions, and e-learning programmes (www.campaign4.org). This campaign will be introduced to Asian countries in collaboration with APEC, WHO and local academic societies as well as public health systems in individual countries. International conferences or meetings are also effective in providing updated information on AMR in the region. ISAAR (www.isaar.org) has been working to disseminate the state-of-the-art knowledge and information on AMR and emerging infectious disease threats biennially since 1997.

Given the rapid increases in extensively-drug-resistant (XDR) or pan drug-resistant (PDR) pathogens throughout the world, the development of new antibiotics that can be effective against these pathogens is critically required

Action plan 3: Promote appropriate uses of antimicrobial agents

Because antibiotic abuse or misuse is the most important factor in the emergence of AMR, appropriate use of antibiotics is the first and basic step for prevention and control of AMR. Given the dearth of new antibiotics in recent decades, appropriate use of the current antibiotics is of the utmost importance. Prudent use of antibiotics should be achieved both at the hospital level and at the national level. In the hospitals, antimicrobial stewardship programmes should be implemented into clinical practice. At the national level, collection of data on the use of antibiotics in humans and animal husbandry, legal control of purchasing and prescribing antibiotics, and governmental regulation to ensure production, licensing, distribution and quality assurance of antibiotics are crucial in Asian countries.

Given the rapid increases in extensively-drug-resistant (XDR) or pan drug-resistant (PDR) pathogens throughout the world, the development of new antibiotics that can be effective against these pathogens is critically required. Since the discovery of new antibiotics is not a major interest for most pharmaceutical companies, however, it should be solved through international collaboration by political, scientific and industrial systems.

Action plan 4: Strengthen hospital infection control

Health-care-associated infections, often caused by antimicrobial resistant bacteria, are an important cause of increased mortality and morbidity. Infection control and prevention in health-care facilities is an effective way to curb AMR by preventing the spread of resistant bacteria within the hospital. Hospital infection control is important not only for the control of AMR in hospitals but also to prevent the emergence of AMR in the community because resistant pathogens can spread out from the hospital to the community. Infection control programmes in health-care facilities in the Asian region should be improved by establishing a secure infrastructure consisting of infection control professionals, continuous support by the hospital leadership, adequate support from the clinical microbiology laboratory and multifaceted education and reinforcement of policies. The antimicrobial stewardship programme (ASP) is another critical component of hospital infection control programmes for preventing the emergence of AMR in hospitals.

Action plan 5: Promote vaccination against bacterial infections

With growing burden of AMR worldwide, fewer antibiotic options are left against resistant pathogens. Preventing the

Given that most Asian countries have serious problems with AMR but weak infrastructures and inadequate responses to meet this threat, AMR should be considered even more important for this region and be urgently managed

occurrence of infection by vaccination would eliminate the need for antibiotic use and can reduce the risk of emerging AMR in bacterial pathogens. Currently, vaccines have been developed for various bacterial pathogens including typhoid fever, cholera, tuberculosis, diphtheria, tetanus, pertussis, *S. pneumoniae*, *Haemophilus influenzae* type b and meningococci. Vaccines targeting MDR pathogens such as *S. aureus* or *P. aeruginosa* are also being developed (20). Among these bacterial vaccines, pneumococcal conjugate vaccine (PCV) is the most representative example of vaccine that can reduce the prevalence of AMR in *S. pneumoniae* by reducing the incidence of pneumococcal infections. Therefore, national and international efforts should be exerted to promote the vaccination programmes available against bacterial infections.

Action plan 6: Strengthen the national infrastructures and international efforts

Control of AMR should be a “national priority” since AMR is a more serious health-care issue than any other single infectious disease with regard to the clinical and economic impact. Given that most Asian countries have serious problems with AMR but weak infrastructures and inadequate responses to meet this threat, AMR should be considered even more important for this region and be urgently managed. National policies and action plans for control of AMR should be based on a multidisciplinary approach consisting of medical, legal, social, economic and public measures. The most important national policies are establishing relevant policies and regulations for production, quality control, circulation and use of antibiotics, nationwide surveillance of AMR, evaluation of the clinical and economic impact of AMR, and public implementation of various interventional measures. One of the most important policies to control antibiotic abuse is the separation of prescribing from dispensing antibiotics by law, which can prevent the general public purchasing over-the-counter antibiotics

without a doctor’s prescription. Antibiotic uses in animal husbandry should also be monitored and regulated by appropriate regulations. In addition to national efforts, international collaboration is also crucial with regard to international surveillance, improving awareness, prevention of counterfeit drugs, development of new antibiotics, and exchanges of information. In the Asia region, private organizations such as APFID/ANSORP, public health-care systems such as the Center for Disease Control and Prevention (CDC) or ministry of health in individual countries and international organizations such as WHO (WHO Western Pacific Region, WPRO and WHO South-East Asian Region (SEARO) or APEC should collaborate to create effective control and prevention of AMR in the region. Given that many Asian countries do not have adequate financial and human resources to improve their health-care infrastructures to control AMR, it would be important in the Asian region to establish an international coalition to combat AMR.

Conclusion

Given a growing crisis of AMR worldwide, particularly in the Asian region, strenuous efforts to tackle AMR should be urgently implemented through international and multisectoral collaboration. This is very crucial because effective prevention and control of AMR can be achieved only by multifaceted international collaborations based on strong national and international initiatives. The six major action plans to control and prevent AMR in the Asian region can provide Asian countries with the guide to establishing the strategies to address the growing threats of AMR and can contribute to reducing the economic and clinical burden of AMR in the Asian region. ●

Dr Jae-Hoon Song, PhD is currently President and CEO of the Samsung Medical Center and Professor of Medicine, Division of Infectious Diseases, Sungkyunkwan University School of Medicine in Seoul, Korea. He is Founder and Chairman of the Asia Pacific Foundation for Infectious Diseases (APFID). He organized the Asian Network for Surveillance of Resistant Pathogens (ANSORP) in 1996 and has been leading international collaboration for surveillance of antimicrobial resistance and major infectious diseases in the Asian region.

References

- Global Risks 2013 Eighth Edition. Geneva, Switzerland: World Economic Forum, 2013.
- Kumarasamy KK1, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, Chaudhary U, Doumith M, Giske CG, Irfan S, Krishnan P, Kumar AV, Maharjan S, Mushtaq S, Noorie T, Paterson DL, Pearson A, Perry C, Pike R, Rao B, Ray U, Sarma JB, Sharma M, Sheridan E, Thirunarayan MA, Turton J, Upadhyay S, Warner M, Welfare W, Livermore DM, Woodford N. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis.* 10(9):597-602, 2010.
- Berrazeg M, Diene S, Medjahed L, Parola P, Drissi M, Raoult D, Rolain J. New Delhi Metallo-beta-lactamase around the world: an eReview using Google Maps. *Euro Surveill.* 19(20), 2014.
- Antimicrobial resistance : Global report on surveillance. Geneva, Switzerland: World Health Organization, 2014.
- Kim SH, Song JH, Chung DR, Thamlikitkul V, Yang Y, Wang H, Lu M, So TM, Hsueh PR, Yasin RM, Carlos CC, Pham HV, Lalitha MK, Shimono N, Perera J, Shibl AM, Baek JY, Kang CI, Ko KS, Peck KR; ANSORP Study Group. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob Agents Chemother.* 56(3):1418-1426, 2012.
- Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, So TM, Yasin RM, Hsueh PR, Carlos CC, Hsu LY, Buntaran L, Lalitha MK, Kim MJ, Choi JY, Kim SI, Ko KS, Kang CI, Peck KR; Asian Network for Surveillance of Resistant Pathogens Study Group. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. *Am J Respir Crit Care Med.* 184(12):1409-1417, 2011.
- Singhal L, Gupta PK, Kale P, Gautam V, Ray P. Trends in antimicrobial susceptibility of *Salmonella Typhi* from North India (2001-2012). *Indian J Med Microbiol.* 32(2):149-152, 2014.
- Kang CI, Song JH. Antimicrobial resistance in Asia: current epidemiology and clinical implications. *Infect Chemother.* 45(1):22-31, 2013
- Link-Gelles R, Thomas A, Lynfield R, Petit S, Schaffner W, Harrison L, Farley MM, Aragon D, Nicols M, Kirley PD, Zansky S, Jorgensen J, Juni BA, Jackson D, Moore MR, Lipsitch M. Geographic and temporal trends in antimicrobial nonsusceptibility in *Streptococcus pneumoniae* in the post-vaccine era in the United States. *J Infect Dis.* 208(8):1266-1273, 2013.
- Wierzbowski AK, Karlowicz JA, Adam HJ, Nichol KA, Hoban DJ, Zhanel GG; Canadian Antimicrobial Resistance Alliance. Evolution and molecular characterization of macrolide-resistant *Streptococcus pneumoniae* in Canada between 1998 and 2008. *J Antimicrob Chemother.* 69(1):59-66, 2014.
- Lismond A, Carbonnelle S, Verhaegen J, Schatt P, De Bel A, Jordens P, Jacobs F, Dediste A, Verschuren F, Huang TD, Tulkens PM, Glupczynski Y, Van Bambeke F. Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium. *Int J Antimicrob Agents.* 39(3):208-216, 2012.
- Imöhl M, Reinert RR, Mutscher C, van der Linden M. Macrolide susceptibility and serotype specific macrolide resistance of invasive isolates of *Streptococcus pneumoniae* in Germany from 1992 to 2008. *BMC Microbiol.* 10:299, 2010.
- Delepierre A, Gayot A, Carpentier A. Update on counterfeit antibiotics worldwide; public health risks. *Med Mal Infect.* 42(6):247-255, 2012.
- Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, Stedtfeld RD, Hashsham SA, Tiedje JM. Diverse and abundant antibiotic resistance genes in Chinese swine farms. *Proc Natl Acad Sci USA.* 110(9):3435-3440, 2013.
- APEC guideline to tackle antimicrobial resistance in the Asia-Pacific region. Seoul, Korea: Asia Pacific Economic Cooperation (APEC), 2014.
- Song JH, Hsueh PR, Chung DR, Ko KS, Kang CI, Peck KR, Yeom JS, Kim SW, Chang HH, Kim YS, Jung SI, Son JS, So TM, Lalitha MK, Yang Y, Huang SG, Wang H, Lu Q, Carlos CC, Perera JA, Chiu CH, Liu JW, Chongthaleong A, Thamlikitkul V, Van PH; ANSORP Study Group. Spread of methicillin-resistant *Staphylococcus aureus* between the community and the hospitals in Asian countries: an ANSORP study. *J Antimicrob Chemother.* 66(5):1061-1069, 2011.
- Song JH, Lee NY, Ichiyama S, Yoshida R, Hirakata Y, Fu W, Chongthaleong A, Aswapokee N, Chiu CH, Lalitha MK, Thomas K, Perera J, Yee TT, Jamal F, Warsa UC, Vinh BX, Jacobs MR, Appelbaum PC, Pai CH. Spread of drug-resistant *Streptococcus pneumoniae* in Asian countries. *Clin Infect Dis.* 28(6):1206-1211, 1999
- Proceedings of the 1st APEC Expert Forum for "International initiatives to control antimicrobial resistance in the Asia-Pacific region". Seoul, Korea: APEC, 2011.
- Ganguly NK, Arora NK, Chandy SJ, Fairuze MN, Gill JP, Gupta U, Hossain S, Joglekar S, Joshi PC, Kakkar M, Kotwani A, Rattan A, Sudarshan H, Thomas K, Watal C, Easton A, Laxminarayan R; Global Antibiotic Resistance Partnership (GARP) - India Working Group. Rationalizing antibiotic use to limit antibiotic resistance in India. *Indian J Med Res.* 134:281-294, 2011.
- Medicines in Development for Vaccines : 2012 Report. Washington, DC, USA: Pharmaceutical Research and Manufacturers of America (PhRMA), 2012.