Keynote Lecture 3.2

International surveillance of antimicrobial resistance: current systems and future perspective

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I. Global nature of antimicrobial resistance

Six major infectious diseases including acute respiratory infections, AIDS, diarrheal disease, malaria, tuberculosis, and measles account for more than 85% of the mortality from infectious diseases worldwide [1]. Most of these cardinal infectious diseases except measles have increasing problems in the treatment due to widespread emergence of antimicrobial resistance. The emergence and spread of multidrug-resistant microorganisms are among the most important global health threats. Community pathogens have acquired antimicrobial resistance including penicillin- or macrolide-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and multidrug-resistant enteric pathogens. Not only these community-acquired infections but also nosocomial pathogens such as methicillin- or glycopeptide-resistant *S. aureus*, glycopeptide-resistant enterococci, extended-spectrum beta-lactamase (ESBL)-producing enterobacteriaceae, and multidrug-resistant non-fermenters are also being recognized with increasing frequency around the world. Although epidemiology of antimicrobial resistance varies by countries or areas, it is evident that most major human pathogens have been increasingly resistant to almost all antimicrobial agents used in the clinical practice. It is also clearly anticipated that antimicrobial resistance will become more prevalent in most parts of the world due to regional situation such as antibiotic abuse or misuse as well as spread of resistance between regions and countries. International travel and globalization of trade and food supply could make the international spread of resistance more rapidly and effectively. There are many examples of international spread of resistant clones between countries. Global spread of the Spanish^{23F} penicillin-resistant *S. pneumoniae* has obviously contributed to rapid emergence of pneumococcal resistance in the Asian region [2]. International spread of antibiotic-resistant pathogens suggests that antimicrobial resistance should be regarded as a global problem requiring a common strategy.

II. International surveillance of antimicrobial resistance

1. General principles of surveillance

Antimicrobial resistance surveillance can be defined as ongoing and systematic collection, analysis, and interpretation of outcome-specific data essential to the planning, implementation, and evaluation of public health practice, closely integrated with timely dissemination of these data to those who need to know; the final link of the surveillance chain being the application of these data to the control and prevention of infectious diseases [3]. The objectives of antimicrobial resistance surveillance are to provide the information necessary to secure an approach to the management of communicable diseases that minimizes morbidity and mortality. The principal uses of the information from surveillance are to optimize the use of antimicrobial agents and assist in the prevention, control, and containment of antimicrobial resistance at the local, regional, and national levels. To better understand the situation and to provide an early warning of new resistant strains, surveillance of antimicrobial resistance is critical.

Surveillance activities can be performed at different levels with different goals [4]. Local information can be used in clinical management and to update treatment guidelines, educate physicians and guide infection control policies in a certain region or hospitals. National surveillance data are used to guide policies, update national formularies or lists of essential drugs and standard treatment guidelines and evaluate the cost-effectiveness of interventions. International surveillance data are used to share information on the emergence of resistance in key pathogens, analysis of the impact of resistance and of policies for control, stimulating dialogue and engaging policy makers, developing advocacy and educational programs and stimulating research.

2. Why should we perform international surveillance of resistance ?

Given the global nature of antimicrobial resistance, it is critical to collect data representing as wide and diversified a geographic and population base as possible. Moreover, it is especially important to collect data from developing countries where antibiotic abuse or misuse is more common. International surveillance of antimicrobial resistance is aimed to identify emerging resistance problems and recommend alternative solutions, monitor changing trends in resistance from a local through to an international level, track the spread of significant resistance patterns on an international scale, and generate information for design and implementation of early intervention to halt the spread of resistance. Based on these epidemiologic information, international surveillance of resistance should contribute to improve the quality of empirical antibiotic treatment in both the community and hospital, to guide the construction of antimicrobial policies and usage, to educate all those involved in the use of antimicrobial agents, to monitor prospectively the activity and usefulness of antimicrobial agents, to guide pharmaceutical industry in the development of new compounds, and to direct hospital infection control efforts [5]. International surveillance should also be utilized to raise awareness of the problems posed by antimicrobial resistance, to promote the sharing of information about resistance, to provide strategic and technical guidance on interventions to contain resistance, to assist member countries to implement these interventions, and to stimulate research to address the knowledge gaps and improve understanding of antimicrobial resistance .

3. Current international surveillance systems

Table 1 summarized representative international surveillance systems according to region, sponsoring systems, or surveillance purpose. All these international surveillance programs consist of compiling, analyzing, and disseminating data on microbial resistance to a variety of antimicrobial agents, for various target organisms and in a series of clinical settings. Some of these networks were organized by pharmaceutical industry or commercial companies. WHO is running the Antimicrobial Resistance Monitoring Program and Antimicrobial Resistance Information bank (AR-InfoBank) to aggregate information on international systems and to gather surveillance data.

A. Global surveillance system

1) INSPEAR (International Network for the Study and Prevention of Emerging Antimicrobial Resistance)

INSPEAR was begun as a collaborative effort between the Hospital Infections Program (CDC) and microbiologists and hospital epidemiologists in the United States and Europe. One hundred sixty health-care facilities in 40 countries have joined INSPEAR, with 50 % of participants in Western Europe and 29 % in Eastern Europe. Since its initiation in 1998, INSPEAR has conducted several activities essential to the implementation of the early warning system, such as assessment of the diagnosis, conduct surveillance, and control infections caused by multidrug-resistant pathogens as well as proficiency testing to ensure quality testing in laboratories participating in the program [6].

2) Alexander Project

The Alexander Project, initiated in 1992 as an international multicenter longitudinal surveillance study of antimicrobial susceptibility among common respiratory pathogens, has been generating important database on resistance in *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* [7]. The Alexander Project has initially included 15 centers in 6 countries in Europe and North America, which was expanded to include 27 countries. The Alexander Project was supported by a grant from GlaxoSmithKline.

3) SENTRY

SENTRY surveillance, supported by Bristol-Myers Squibb, is one of the most representative global surveillance projects since 1997. SENTRY is an international study covering four geographic regions : North America, South America, Europe, and Asia-Pacific. SENTRY surveillance project included 81 centers in 25 countries. SENTRY surveillance covered broad range of infection types and pathogens.

4) MYSTIC (Meropenem Yearly Susceptibility Test Information Collection)

MYSTIC program is a global multicenter susceptibility study that compares the activity of meropenem and five other antimicrobial agents against Gram-positive and Gram-negative aerobic clinical isolates [8]. Of the 46 centers contributing to this study, 29 were in Europe, 14 in the Americas and 3 in the Middle East and Asia. MYSTIC was supported by AstraZeneca.

5) PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin)

The PROTEKT study, supported by Aventis, is a longitudinal global multicenter surveillance study [9]. PROTEKT included > 100 centers in 26 countries worldwide with special focus on common respiratory pathogens. PROTEKT has also performed molecular epidemiologic studies to investigate molecular mechanism and the spread of resistance.

B. Regional (continental) surveillance system

1) EARSS (European Antimicrobial Resistance Surveillance System)

EARSS funded by the European Commission is a network of national surveillance systems aiming to collect comparable resistance data [10]. The data is collected by 800 public-health laboratories serving over 1,300 hospitals in 31 European countries. EARSS performs ongoing surveillance of antimicrobial susceptibility of seven indicator bacteria commonly causing infectious in humans ; *S. pneumoniae* , *S. aureus, E. faecalis, E. faecium, E.coli, K. pneumoniae, and P. aeruginosa* .

2) ANSORP (Asian Network for Surveillance of Resistant Pathogens)

ANSORP is the first international surveillance network of antimicrobial resistance in the Asian region. ANSORP consists of 41 centers in 13 countries in Asia and the Middle East. ANSORP is supported by the Asian-Pacific Research Foundation for Infectious Diseases (ARFID) [11]. ANSORP surveillance during the past 10 years included resistance surveillance in *S. pneumoniae*, community-acquired MRSA, VISA, enteric pathogens, other respiratory pathogens, as well as molecular mechanism and evolution of resistant pathogens in the region.

Table 1. Current internation surveillance systems

Region	System or program	Acronym	No. of countries (centers)	Launching year	Target organisms	Remark
Global	WHO Antimicrobial Resistance Information Bank	AR-InforBank		1999	Data collection	oms2.b3e.jussieu.fr/arinfobank
	Global TB surveillance		35 (200)	1994	M. tuberculosis	WHO surveillance
	International Network for the Study and Prevention of Emerging Antimicrobial Resistance	INSPEAR	40 (160)	1998	Comprehensive	www.cdc.gov/ncidod/hip/surveill/inspear
	SENTRY		25 (81)	1997-8	Comprehensive	Supported by BMS
	Alexander Project		27 (>100)	1992	RTI pathogens	Supported by GSK
	Meropenem Yearly Susceptibility Test Information Collection	MYSTIC	46	1997	Meropenem in vitro data	Supported by AstraZeneca
	The Surveillance Network	TSN	10 (200)	1994	Comprehensive	Supported by Focus Tech
	Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin	PROTEKT	26 (>100)	1999	RTI pathogens	Supported by Aventis
Europe	European Antimicrobial Resistance Surveillance System	EARSS	31 (800)	1998	7 major pathogens	www.earss.rivm.nl
	European Surveillance of Antibiotic Resistance	ESAR	4 (30)	1998	Comprehensive	www.esbic.de
	Enter-net	Enter-net		1994	GI pathogens	www2.phls.co.uk
	Euro TB	Euro TB		1996	M. tuberculosis	www.ceses.org/eurotb
	European Network for Antimicrobial Resistance and Epdemiology	ENARE		1996	Antimicrobial consumption	
Asia	Asian Network for Surveillance of Resistant Pathogens	ANSORP	13 (41)	1996	Comprehensive	ww.ansorp.org

4. Future perspective

Current international surveillance systems have limitations with regard to quality of data, sample bias, representativeness of data, limited genetic data, or timeliness & usefulness. For more effective and relevant surveillance studies, surveillance system should maintain simple and efficient structure to utilize data from the surveillance more conveniently. International surveillance systems should include qualified centers in each country or region. Surveillance programs should be specific, measurable, assessable, realistic, rapid and targeted [5]. International surveillance should be specific, well-defined, coordinated, and systematic, which can be representative. Programs should be measurable and assessable with the use of standardized methods and strict quality control procedures. International surveillance should use the standardized methods according to WHO recommendations or CLSI method for in vitro tests. International surveillance projects can be performed with adequate funding, feasible timetable, and capable participating centers. Data from the international surveillance studies should be

rapidly disseminated to the participating centers or countries to utilize them. More importantly, coordination and exchange of information between various international systems is critical to achieve basic objectives of many systems. Also, programs should be targeted with clearly identified outcomes available and address relevant and important issues.

REFERENCES

1. WHO. Global strategy for containment of antimicrobial resistance. 27 September 2000
2. Song JH and the Asian Network for Surveillance of Resistant Pathogens (ANSORP). Spread of drug-resistant *Streptococcus pneumoniae* in Asian countries. Clin Infect Dis 1999;28;1206-1211.
3. Williams RJ, Ryan MJ. Surveillance of antimicrobial resistance-an international perspective. BMJ. 1998;317:651.
4. Monnet DL. Toward multinational antimicrobial resistance surveillance systems in Europe. Int J Antimicrob Chemother. 2000;15:91-101.
5. Masterton RG. Surveillance studies ; how can they help the management of infection ? J Antimicrob Chemother. 2000;46 (T2):53-58.
6. Richet HM, Mohammed J, McDonald LC et al. Building communication networks : international network for the study and prevention of emerging antimicrobial resistance. Emerg Infect Dis. 2001; 7;319-322.
7. Felmingham D, White A, Jacobs MR et al. The Alexander Project : the benefits from a decade of surveillance. J Antimicrob Chemother. 2005; 56 (suppl 2); ii3-21.
8. Turner TJ. MYSTIC : a global overview. J Antimicrob Chemother. 2000; 46 (T 2); 9-23.
9. Felmingham D. The need for antimicrobial resistance surveillance. J Antimicrob Chemother. 2002; 50 (suppl 1); 1-7.
10. EARSS : www.earss.rivm.nl
11. ANSORP : www. ansorp.org