STRENGTHENING HEALTH SECURITY

APEC Symposium on Strategies to Control and Prevent Antimicrobial Resistance

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Executive summary

The APEC project S HWG 04 12A to organize APEC symposium on strategies to control and prevent antimicrobial resistance (AMR) in the Asia Pacific region was successfully performed with organization of APEC symposium at Kuala Lumpur Convention Centre in Kuala Lumpur, Malaysia on 15 March 2013 with about 300 experts and participants from 14 APEC economies including Australia; Brunei Darussalam; China; Hong Kong, China; Indonesia; Japan; Korea; Malaysia; the Philippines; Singapore; Chinese Taipei; Thailand; the United States; and Viet Nam and from 3 non-APEC economies including Switzerland, Israel, and World Health Organization (WHO).

The key objective of the APEC symposium was to discuss and explore future strategies to control and prevent AMR in the Asia Pacific region. For this purpose, the APEC symposium consisted of 3 plenary lectures including 1) future strategies to control AMR in Asia; 2) global collaborations in tackling AMR; and 3) how to fix the antibiotics pipeline?; and 4 symposium sessions including 1) antibiotic stewardship in the Asian region; 2) policies and regulations to control AMR; 3) clinical and economic impact of AMR; and 4) infection control of resistant pathogens. A summary of the APEC symposium was as follows:

- AMR is a serious global issue with particular situation in Asian economies, where AMR rates are two- or three-times higher than those in the western part of the world.
- Combating AMR should be one of the top priorities among agenda of each economy in the Asian region.
- Public and healthcare professional education to increase awareness on AMR and appropriate antimicrobial use is of the utmost importance for containment of AMR in the region.
- Antibiotic stewardship should be practiced at international, national, regional, and institutional levels.
- Healthcare policy to control and monitor antibiotic use, supply, distribution, and sales in both clinical practice and food animals should be urgently prepared in the Asian region.
- Concerted effort employing a multifaceted strategy with collaboration among all relevant sectors and stakeholders is essential at national, regional, and international levels to control and prevent AMR.
- Strong leadership of APEC is essential to influence governments in APEC economies, particularly in the Asian region, for control and prevention of AMR.

Given the critical impact of AMR, APEC has been supporting the international projects to set up the future strategies to control and prevent AMR in the AP region since 2010. The first project entitled “International initiatives to control antimicrobial resistance in the Asia-Pacific region” (HWG 05/2010A) was successfully performed with development of the first international strategic action plans to control and prevent AMR in the Asian region. Based on the strategic action plans developed by the first project, the current project was to organize an international symposium to discuss and to explore strategies to control and prevent AMR in the AP region. Through all these efforts and international collaborations endorsed by APEC, our final goals are to prevent and control AMR in the Asian region and to strengthen APEC’s capacity to respond to public health threat caused by AMR in APEC economies.

1. Introduction

Despite the threats to global public health security and economic impact of antimicrobial resistance (AMR), AMR is still a neglected issue in many APEC economies, particularly developing economies in the Asian region. Effective control and prevention of AMR can be achieved only by multifaceted international collaborations based on strong national and international initiatives because AMR can spread across borders. Also, since AMR emerges due to multiple causes, future strategies to control and prevent AMR should be based on multi-sectoral collaboration including healthcare providers, infectious disease physicians, microbiologists, veterinarians, pharmacists, governmental officials related to healthcare and animal husbandry, and pharmaceutical companies from APEC economies and also external APEC stakeholders.

For this reason, APEC supported an international project entitled "International initiatives to control antimicrobial resistance in the Asia-Pacific region" (HWG 05/2010A), which was performed by Asian Pacific Foundation of Infectious Diseases (APFID) in collaboration with Korea Centers for Disease Control & Prevention (CDC) and APEC economies in 2010-2011. The previous APEC project was to develop future strategic action plans for control and prevention of AMR in the Asian region. The strategic action plans to control AMR in the Asian region developed by the project with multi-sectoral experts from APEC economies consist of six major pillars including 1) surveillance of AMR and antibiotic use to identify the problem of resistance in the region, 2) increase of awareness on AMR and 3) appropriate use of effective antibiotics to prevent the emergence of AMR, 4) hospital infection control to prevent the spread of resistance, 5) effective vaccination to prevent the occurrence of specific infections, and finally 6) relevant policies and regulations to control antibiotic use and to prevent AMR. Based on these strategic action plans, the APEC symposium sessions focused on antibiotic stewardship which is the key component of a multifaceted approach to prevent emergence of AMR, hospital infection control, policies and regulations to control AMR in both human medicine and animal husbandry, and clinical and economic impact of AMR and how to properly evaluate the economic impact of AMR.

Therefore, this symposium focused on understanding of the clinical and economic impact of AMR and discussion for effective implementation of policies and regulations to control AMR in both human medicine and animal husbandry and for future strategies to control and prevent AMR in APEC economies.

2. Objectives of the APEC symposium

The long-term goal of the APEC symposium was to control and prevent AMR in the Asia Pacific region based on strategic action plans, which were developed by previous APEC project entitled "International initiatives to control antimicrobial resistance in the Asia-Pacific region" (HWG 05/2010A) performed in 2010-2011, including increased awareness of AMR, appropriate antibiotic use, infection control, vaccination, and relevant policies and regulations.

The key objectives of the APEC symposium were

- to explore strategies to control and prevent AMR in the Asian region
- to understand clinical and economic impact of AMR
- to understand and discuss stewardship programs in the Asian region
- to discuss relevant policies and regulations to control AMR in human medicine and animal husbandry for their implementation in APEC economies

3. Program of APEC symposium

The Symposium was organized at Kuala Lumpur Convention Centre in Kuala Lumpur, Malaysia on 15 March 2013. The full program is provided as Annex 1. The APEC symposium consisted of three plenary lectures and four symposium sessions as follows:

APEC Symposium	Title
Plenary lectures	1. Future strategies to control AMR in Asia
	2. Global collaborations in tackling AMR
	3. How to fix the antibiotic pipeline
Symposium sessions	1. Antibiotic stewardship in the Asian region
	2. Policies and regulations to control AMR
	3. Clinical and economic impact of AMR
	4. Infection control or resistant pathogens

4. Plenary lectures and symposium sessions of APEC symposium

4.1. Plenary lecture 1

Future strategies to control AMR in Asia

Dr. Jae-Hoon Song
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Infectious diseases are posing growing global problem due to widespread emergence of AMR in major pathogens, which makes antimicrobials ineffective, resulting in treatment failure, prolonged illness, disability, greater risk of death and economic loss[1]. Furthermore, due to slowed development of new antimicrobials, very few antimicrobials are left to treat infections caused by multidrug-resistant (MDR) pathogens[2]. Given the enormous clinical and economic impact of AMR, World Health Organization (WHO) has identified AMR as one of the greatest threats to human health and the theme of World Health Day 2011 by WHO was AMR with a slogan entitled "Antimicrobial resistance: no action today, no cure tomorrow"[3].

AMR is not a local problem but a global issue because AMR can spread between different economies or continents. The massive increases in trade and human mobility brought about by globalization have enabled the rapid spread of infectious agents, including those that are resistant to antimicrobials[4]. Recent outbreak and international spread of New Delhi metallo-beta-lactamase-1 (NDM-1) producing *Escherichia* coli from India to many regions could be one of the best examples of transmission of AMR between economies, showing critical impact of AMR on economy and trade in addition to impact on public health[5].

While richer economies, to a large extent, are still able to rely on the latest antimicrobials to treat resistant infections, access to these life-saving drugs is often limited or totally impossible in many parts of the world, particularly developing economies in Asia. Although situation of AMR may vary by region or eonomy, it is evident that Asia is certainly a part of the world in which there are increasing concerns regarding AMR

because of a high prevalence of AMR in major bacterial pathogens and relatively poor and weak healthcare infrastructures in many economies [6, 7].

Asian initiatives to control and prevent AMR

Given the critical impact of AMR, the United States and European economies have prepared strategic action plan to combat AMR. The European strategic action plan on antibiotic resistance has been adopted by 53 economies in the region in 2011 and has 7 strategic objectives : to Strengthen inter-sectoral coordination, to Strengthen surveillance of antibiotic resistance, to Promote rational use and strengthen surveillance of antibiotic consumption, to Strengthen infection control and surveillance in health care settings, to Prevent emerging resistance in the veterinary and food sectors, to Promote innovation and research on new drugs, and to Improve awareness, patient safety, and partnership[8]. In the US, the Public Health Action Plan to Combat Antimicrobial Resistance was developed by an interagency Task Force on Antimicrobial Resistance in 2001 and has been revised in 2011[9]. The Action Plan consists of four focus areas, Surveillance, Prevention and control, Research, and Product development and each focus area has specific goals, consisting of 11 specific goals in total.

Despite many serious events of AMR, however, many economies in the Asian region do not have adequate national infrastructure and system to control and prevent the problems. Also, there have been few practical efforts to improve the preparedness for control of AMR based on international collaboration in the Asian region. It is quite obvious that the lack of awareness of critical situation of AMR prevents Asian economies from preparing comprehensive international strategies for AMR and leads to ineffective responses to AMR in the region. Therefore, future strategies should be prepared with multifaceted collaboration among all relevant stakeholders in the Asian region based on strong national initiatives. Also, the comprehensive strategies for control and prevention of AMR are urgently required in the region.

Given these situations in the Asian region, an international project entitled “International initiatives to control AMR in the Asia-Pacific region” was proposed to APEC by APFID in collaboration with Asian Network for Surveillance of Resistant Pathogens (ANSORP) with support from Korea CDC to prepare future strategic action plan to control and prevent AMR in the Asian region. Given its devastating impact on human lives and economy, the project was approved by APEC in 2010 (APEC HWG 05/2010A) and the first strategic action plan to control AMR in Asia has been prepared[10].

Strategic action plan to control AMR in Asia

The strategic action plan to control and prevent AMR in the Asian region consists of five major components. First, surveillance of AMR is the first and basic step to detect and identify the problems of resistance in the region. Second, appropriate use of effective antimicrobials is of utmost importance because antimicrobial abuse or misuse is the most critical driving force for the emergence of AMR. Third, hospital infection control is also important since it can prevent the spread of resistant clones in the hospitals and in the community. Fourth, vaccination can prevent the emergence of infectious diseases as well as can reduce the prevalence of AMR in certain bacterial pathogens, such as *Streptococcus pneumoniae*. Finally, adequate and relevant policies and regulation by governmental system for control of antimicrobial uses, prevention of counterfeit drugs, and surveillance of AMR are very crucial for successful control of AMR. Since current problems and issues of resistance and antibiotic uses vary by economy, actual implementation of the plan should be based on local situation.

- **Surveillance of AMR and antibiotic use**

- The national surveillance system of AMR should be urgently established in every economy in the Asian region that can identify the national status of AMR.
- The national surveillance systems for antimicrobial consumption both in patients and in animal husbandry should be established in each economy using the standardized methods.
- The microbiology laboratory procedures, data collection, and data reporting should be qualified and standardized.
- The international surveillance system(s) in the Asian region collecting the data about AMR in Asian economies should be established.

- **Appropriate use of effective antibiotics**

- Appropriate use of effective antibiotics is a key factor to prevent the further emergence of AMR in major pathogens, which includes the appropriate use of current antibiotics as well as the development of novel agents.
- Appropriate use of current antibiotics can be encouraged by campaigns and educational activities for general public, which could be implemented at various levels - hospital, local, regional, or national level.

- "I Care" (Initiatives to Control Antimicrobial REsistance) campaign prepared by the APFID can be utilized as a campaign program in the Asian region.
- Education of healthcare professionals should be continuously implemented. All economies are encouraged to implement antibiotic stewardship program in the healthcare setting.
- Antimicrobial use in food animals should be monitored and controlled by the regulations and guidelines.
- Healthcare policies and regulations for control of antibiotic use should be urgently established in some Asian economies.
- Development of novel antibiotics is critically required to overcome the problems of AMR. International collaboration is essential for the discovery of new antibiotics.

- **Hospital infection control**

- Hospital infection control is a basic procedure to prevent the spread of resistant clones in the hospital as well as in the community.
- Stringent and rigorous infection control procedures should be implemented in all hospitals.
- The microbiology laboratory should provide adequate diagnostic testing to identify nosocomial infections and accurate antimicrobial susceptibility testing.

- **Vaccination**

- Effective vaccination can reduce the prevalence of AMR in major bacterial pathogens.
- National and international efforts should be exerted to increase the awareness of the importance of vaccination both in general public and in healthcare professionals.

- **Policy and regulation**

- Control and prevention of AMR should be one of the top priorities among policies and agenda of each economy.
- Appropriate and relevant governmental regulations, commitment and support are essential for successful control of AMR.
- Relevant policies and regulations to control antibiotic abuse are urgently required in many Asian economies.
- Any kind of antibiotics should be purchased based on doctor's prescription and it should be regulated by law

in all economies.

- Monitoring and regulation to prevent the production and circulation of counterfeit drugs should be implemented in all economies.
- Antibiotic uses in animal husbandry should be monitored and regulated by appropriate regulations.

Conclusion

AMR is a serious healthcare threat worldwide. Comprehensive strategies should be implemented to control and prevent the emergence and the spread of AMR. Given the enormous clinical and economic impact of AMR, particularly in the Asian region, the Strategic Action Plan has been developed and it consists of five major components that are aimed to achieve effective control and prevention of AMR in the Asian region; surveillance of AMR and antibiotic use, appropriate use of effective antibiotics, hospital infection control, vaccination, and policy and regulation. This strategic action plan can provide Asian economies with the general concept and the frame of the strategies to address the growing threat of AMR in the region for the first time.

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4.2. Plenary lecture 2

Global collaborations in tackling AMR

Dr. Victor Lim
International Medical University, Malaysia

There has been a relentless increase in AMR in recent years. This resistance is seen in both gram-positive and gram-negative organisms. Unfortunately, there are few new promising antimicrobial agents in the pipeline. This is especially so for MDR Gram negative organisms. There is also good evidence to show that antibiotic overuse is a leading driver of resistance. Good antibiotic prescribing practices are therefore required to prolong the useful lives of existing agents.

Stewardship is the careful and responsible management of something entrusted to one's care. Antibiotic stewardship is a program comprising various strategies and interventions designed to preserve the usefulness of antibiotics. Antibiotic stewardship is now an important public health function as antibiotic resistance has become one of the most important clinical challenges today.

There is a crucial need for international collaboration and the political will to put in place interventions to overcome this formidable challenge. Stewardship programs should be established at international, as well as national and institutional levels. At the international level the WHO has played a key role in encouraging all economies to adopt national strategies to contain antibiotic resistance. As early as 1998 a World Health Assembly approved a resolution urging all member states to develop measures to encourage appropriate and cost-effective use of antimicrobials. In this respect the WHO published a document for a global strategy to contain AMR. This document describes a comprehensive multi-faceted strategy to be adopted by nations to counter the threat of AMR. Measures included strengthening antibiotic resistance surveillance, developing and implementing antibiotic guidelines for practitioners, improving access to and upgrading the quality of microbiological diagnostic facilities, increasing public awareness of antibiotic resistance and controlling and regulating the use of antibiotics for both medicinal and non-medicinal purposes. More recently the WHO launched its Third Global Patient Safety Challenge focusing on tackling AMR. The WHO also has a program in

AMR monitoring.

As a regional grouping, the European Union has probably achieved the most in the containment of AMR. In 2002, the ARPAC (Antibiotic Resistance; Prevention and Control Concerted Action) project was launched with funds from the European Commission. Coordinated by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 4 Study Groups were established namely; Antibiotic Policies (ESGAP), Antimicrobial Resistance Surveillance (ESGARS), Nosocomial Infections (ESGNI) and Epidemiological Markers (ESGEM). The European Centre for Disease Prevention and Control (ECDC) organizes an annual European Antibiotic Awareness Day to promote more appropriate use of antimicrobial agents among both prescribers and the public. The EU also regularly publishes resistance data through the EARS network as well as antibiotic consumption data in the region.

There have been several international collaborations in the Asian region. An initiative has been started under the auspices of APEC with the aim of preventing and control of AMR in the Asia Pacific region. The Asia Pacific Society for Clinical Microbiology and Infection organizes a forum at its biennial scientific meeting for the sharing of resistance data among its member economies. Similar initiatives are also being undertaken by WPRO (WHO Regional Office for the Western Pacific) and SEARO (WHO Regional Office for South-East Asia) of the WHO. There are also industry-driven surveillance networks targeting specific organisms. However these efforts are largely uncoordinated and there is a need for standardization of methods and reduction of duplication.

AMR clones can spread across national boundaries at alarming speeds. A recent example is that of NDM-1. It was first reported in a Swedish patient of Indian origin in April 2009. This patient had been admitted to a hospital in New Delhi, India in December 2008. By November 2010, NDM-1 cases were reported in 20 economies around the world. In many of these cases the patients have been previously hospitalized in India, Pakistan or Bangladesh.

The emergence of resistance is a crisis of global proportions. A concerted effort employing a multifaceted strategy is essential at international, national and institutional levels. As resistance can spread rapidly between economies, an Improved global surveillance with early warning systems is required. It is clear we need to work together to meet this challenge.

4.3. Plenary lecture 3

Fixing the antibiotic pipeline

Dr. David Shlaes
Anti-Infectives Consulting, the United States

Most experts who have examined the subject agree that our antibiotic development pipeline is not sufficient by a long shot. The days when there was always a new antibiotic just around the corner that would allow treatment of the latest superbug are long gone.

Fixing the antibiotic pipeline is not rocket science. The main difficulty lies in finding molecules that enter the bacterial cell, stay there and inhibit growth of the bug without being toxic to us. One thing that prevents us from overcoming this difficulty is that the number of people working on the problem has shrunk to historically low levels.

The continuing consolidation (mergers and acquisitions) within large pharmaceutical companies, plus the outright abandonment of antibiotic research by these companies has severely impacted our ability to come up with new ideas, new approaches and new molecules. In addition, the lack of experience and training of well-meaning academics in the science of drug discovery undermines current efforts in the public sector.

So how can we fix this? We can't make scientific discovery any easier. But there are three areas over which we have some control.

First and foremost we need regulatory reform. One of the reasons industry has abandoned the area has been the increasing regulatory stringency, which translates into larger clinical trials and greater development expense, and the accompanying regulatory uncertainty for antibiotics. Regulators are working on the use of small, streamlined trials to get antibiotics specifically targeting specific resistant bacteria to the market quickly to help those patients who truly need these life-saving drugs. Of course this approach may increase the safety risk to patients. Europe has been leading the way in this effort with a transparent process. The US is making great strides but this is still al behind closed doors. This leads to continued uncertainty within the industry. Finally – Asia and emerging markets have not really focused on this problem yet from a regulatory perspective.

For example, NEWDIGS does not focus on antibiotics yet.

Secondly, we need to attack the economic factors that have led industry to leave antibiotic R&D. Push incentives such as funding to support expensive stages of research and development are important. A good example is BARDA in the US and the Wellcome Trust in the UK.

The other economic factor we can control is drug pricing. We are happy to pay tens of thousands of dollars for oncology drugs that prolong life maybe a few months, while we expect to pay only a few dollars for antibiotics that can be incredibly effective in curing disease, but that are only taken for days. As a global society, we must value new antibiotics appropriately. This means that for those new drugs developed to serve a small population of patients with highly resistant infections for whom other effective options do not exist, we have to be willing to allow industry to recoup its costs and to make a small profit. Prices for such drugs could range from $2,000 to $30,000 for a course of therapy.

One area we do not think we need to fix is the market itself. There has been discussion of "pull" incentives where government would provide a guaranteed market for antibiotics active against key drug-resistant superbugs. Given the evolving dominance of emerging economies in the global antibiotic market and the high incidence of superbugs in many of these economies, we think that the market will provide enough incentive in this regard.

Finally, we need to train our academic researchers in the science of drug discovery. We support using government funds to provide such training within industry in exchange programs. Academics should be allowed, even encouraged to spend time with partner pharmaceutical companies and 'learn by doing'.

So a five point plan to fix the antibiotic pipeline –
1) regulatory reform
2) streamlined clinical trials for antibiotics against resistant superbugs
3) better antibiotic pricing policies
4) getting needed and appropriately valued new antibiotics to emerging economies
5) training for academic researchers

4.4. Symposium session 1 : Antibiotic stewardship

Antibiotic stewardship : why, what and how ?

Dr. Stephan Harbarth
Hopitaux Universitaires de Geneve, Switzerland

Facts:

Poor adherence to infection control and irrational antibiotic use promotes AMR. There is widespread misuse of antibiotic treatment and prophylaxis for surgery.

Interventions to improve antibiotic use:

Quality improvement (QI) approaches are helpful, feasible and low-cost tools (especially in resource-poor economies), in order to improve efficiency in antimicrobial drug management.

They should be based on:

- Evidence-based interventions (balanced between sound methodology and pragmatic considerations);
- Center specific strategies (education & management);
- Committed team of people (physicians, microbiologists & clinicians)
- Co-ownership of the project through involvement of relevant opinion leaders;
- Immediate feedback;

  Essential medicine programs with evidence-based standard treatment guidelines may further improve compliance and antibiotic use.

Recommendations on a local level:

- Monitoring and feedback of antibiotic prescription and antimicrobial-resistant resistance should be performed (at least within large teaching hospitals), in order to identify problem areas and perform targeted interventions

- Dissemination and implementation of priority practices based on already existing knowledge and guidelines, with local enforcement
- QI-based strategies with feedback should be more widely disseminated, published and implemented. Prominent targets for these strategies are:
  - optimize antibiotic prophylaxis (streamlining choices, admit forms & prepared packages, mailing of memos, feedback), in order to enable rational and cost-effective use of antimicrobial drugs for surgical prophylaxis;
  - reduce unnecessary and inappropriate use of empiric treatment;
  - decrease treatment duration for microbiologically proven infections.
- Reduce financial incentives and physician-industry interactions to overprescribe antibiotic agents
- Increase institutional and political commitment (regulatory pressure)

Recommendations on a national or international level:

a) Public education on preventing infection and reducing transmission

b) Provider education on diagnosis and management of common infections, antimicrobial use, containment of antibiotic resistance, disease prevention, infection control

c) Development, updating and use of essential medicines lists, clinical guidelines and treatment algorithms

d) Drug and Therapeutic Committees to ensure the safe effective use of antimicrobials

e) Restriction of availability of antimicrobials

f) Granting marketing authorization only to antimicrobials meeting international standards of quality, safety and efficacy

g) Knowledge transfer between economies: Collaboration and continued networking of people in low-resource economies. Commitment of WHO as exchange platform.

4.4. Symposium session 1 : Asian perspectives : Brief introduction of Asian programs

Legislation for promoting antibiotic stewardship program in People's Republic of China

Dr. Yonghong Xiao
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On 1 August 2012, China formally implemented the decree 'Administrative regulations for clinical use of antibacterial agents', which was issued by the Ministry of Health. This ruling defines all aspects of antibiotic use in hospitals, including antibiotic selection, procurement, prescription, use, monitoring, and legal responsibility, which was called as the ever-history strict regulation for antibiotic management in China. This event got widespread concern both in China and overseas, as this is the first formal standardized regulation regarding the administration of antibacterial drugs in the world issued by national healthcare authority. The major purpose of implementing this new regulation is to ensure that antimicrobial agents are rationally used within hospitals[1,2].

In recent years, China has carried out an extensive healthcare system reform, which is expected ultimately to provide everyone with access to basic medical care. To achieve these aims, the existed running manner of profit-orientation in public hospitals should be completely abandoned and the administration of drugs, including antimicrobial agents, should be rationalised[3]. Long-term antibiotic irrational use caused by the existed hospital running manner in China has generated severe antibiotic-resistant bacterial strains, although the healthcare authority released several technical files for promoting the rational use of antibiotics during the past 10 years, such as "principles for clinical use of antibiotics (2004)", "national formulary (2008)" and "guides for hospital drug therapeutic committee (2002)". Bacterial resistance now constitute a major problem in the healthcare system. Methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum beta-lactamase (ESBL)-producing *E. coli*, quinolone-resistant *E. coli* and carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* amounted to approximately 60% in a national survey. The rational use of antimicrobial agents and the implementation of other methods to prevent bacterial resistance worsening have

become critical[4,5].

The regulations recently introduced concerning antibiotic usage incorporate the internationally received antibiotic stewardship program, and include some administrative requirements tailored for the Chinese healthcare system[1,6]. The regulations also include specific instructions for the leaders of medical institution who are responsible for the rational administration of antimicrobial agents, for establishing an effective antibacterial drug management system, and for forming a working group composed of infectious physicians, pharmacists, microbiologists and management personnel. Medical institutions must ensure that antibiotics are classified as non-restricted, restricted or special grades. Physicians and pharmacists need to receive specialized training in the prescribing of antibiotics before being granted varying levels of prescribing privileges depending on their professional title. The healthcare authority will set administrative goals for institutions; conduct reviews of antibacterial drug prescriptions; regularly publish information regarding the usage of antibacterial drugs in hospitals; commend physicians who closely follow the regulations; and impose penalties on medical staff who violate the regulations.

The regulations also encourage medical institutions to explore other strategies to improve the rational use of antibacterial drugs, such as antibiotic diversity use, active intervention for antibiotic use, clinical guide implementation and hospital infection control. At the same time, pharmaceutical companies should implement a standardized drug promotion procedure, and stop attempting to increase drug sales for economic incentives. Medical institutions need to regularly report the use of antibacterial drugs to the healthcare authority. In order to improve the administration of antibiotics, institutions which seriously and/or persistently violate the regulations will be imposed with appropriate penalties by the authority, such as degrading the hospital level and dismissing the leaders of the institutes involved. Medical staff who seriously violate the regulations may no longer be able to prescribe antibacterial drugs, have their professional qualification revoked, or may even be legally prosecuted if their actions have serious consequences.

To promote the implementation of these regulations, the Ministry of Health in China initiated a 3-year campaign in 2011 with a special task force in antibiotic management. Through the strict implementation of these regulations and the introduction of legal penalties, the rational use of antibiotics in public medical

institutions can be quickly and efficiently enforced[7]. While these steps are suitable to reduce antibiotic use in the current Chinese healthcare system, the long-term management of these strategies requires further planning and a sustainable back-up system should be established, such as antibiotic stewardship professional, guidelines, ongoing staff training, illegal practice identifying procedure and so on Unfortunately, the antibiotic sales in social pharmacies are not within the legal jurisdiction of the regulation.

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4.4. Symposium session 1 : Asian perspectives : Brief introduction of Asian programs

Implementation of antibiotic stewardship programs in Korea

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AMR rates in major human pathogens including S. *pneumoniae*, S. *aureus*, and *Enterobacteriaceae* have rapidly increased in Korea, and antibiotic overuse and misuse had contributed to it. Multidisciplinary efforts have been made to cope with increasing AMR in Korea. The pharmaceutical policy reform was implemented for separation of prescription and dispensation of drugs in outpatient care in July 2000, and antibiotic usage in the community decreased after then. Further reduction of antibiotic overuse and misuse has been promoted through quality assessment of antibiotic usage for individual hospital by Health Insurance Review & Assessment Service. Antibiotic prescription rates for upper respiratory infections in the outpatient setting and adequacy of surgical antibiotic prophylaxis at individual hospital have been assessed and reported since 2004 and 2007, respectively. Many secondary- and tertiary-care hospitals have implemented various antibiotic stewardship programs during the past decade. According to a survey of infectious diseases specialists in 44 hospitals in 2006, 95.5% had employed restriction programs of antimicrobial prescription, and automatic stop orders were applied for certain antibiotics in 38.6%. Computerized decision support systems for antibiotic prescription have been developed at 5 hospitals and used at 11 hospitals. Strict regulations have also been implemented to reduce antibiotic usage in animal husbandry.

There is not enough public awareness on appropriate antibiotic use. Based on a questionnaire survey in 2010, 71.4% responded that antibiotics were effective for treatment of common colds, and 28.1% had experiences of taking left-over antibiotics without asking doctors. Accordingly, nationwide campaigns have been implemented by the Korean Society of Infectious Diseases, Korean Society for Chemotherapy, APFID, and the Korea CDC to increase awareness of general public and healthcare professionals since 2011.

4.4. Symposium session 1 : Asian perspectives : Brief introduction of Asian programs

Antibiotic stewardship : Where are we ? Report from Malaysia

Dr. Victor Lim
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Antibiotic stewardship is a planned program of strategies and interventions to enable us to make the most of the antibiotics we have and requires the careful and responsible management of this precious resource. Antibiotic stewardship is now an important public health function as antibiotic resistance has become one of the most important clinical challenges today. Antibiotic stewardship should be practiced at international, national and institutional levels. A national strategy should be a multifaceted approach which includes strengthening antibiotic resistance surveillance, developing and implementing antibiotic guidelines for practitioners, improving access to and upgrading the quality of microbiological diagnostic facilities, increasing public awareness of antibiotic resistance and controlling and regulating the use of antibiotics for both medicinal and non-medicinal purposes.

In Malaysia the Ministry of Health has established a fairly well defined administrative structure for the purpose of antibiotic stewardship. The National Infection and Antibiotic Control Committee is chaired by the Director General of Health. A National Antibiotic Resistance Surveillance System was established in 1990. The monitoring of antibiotic utilization is also undertaken annually through National Medicines Use surveys. Monitoring of antibiotic utilization in the Ministry of Health and selected private hospitals is focused on 4 major groups of compounds namely cephalosporins, carbapenems, quinolones and glycopeptides.

At the institutional level all government hospitals have antibiotic formularies and guidelines. However the effectiveness of antibiotic stewardship at an institution depends very much on the presence of “champions”. In the private sector doctors can use any product so long as it is registered by the Drug Control Authority and consultants operate as independent contractors in private hospitals. Professional societies also issue practice guidelines from time to time but the effectiveness of these guidelines is questionable. Some attempts have

also been made to control the use of antibiotics in agriculture.

Other measures in antibiotic stewardship would be the legislative control of prescription and sales of antibiotics for medicinal use as well as non-medicinal use and the regulation of marketing and promotional activities by pharmaceutical companies. Generally, Malaysia seems to be on the right track but we still have some way to go to ensure the participation of all the major stakeholders.

4.4. Symposium session 1 : Asian perspectives : Brief introduction of Asian programs

Antibiotic stewardship in The Republic of the Philippines

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The Republic of the Philippines like any other member economies in the world is facing its AMR problems. In order to address this problem, the government and private sector have implemented various initiatives to promote antibiotic stewardship. The government initiatives on antibiotic stewardship had focused on policies and programs while the private sector had focused on hospital-based initiatives.

The following are the most important laws, policies and issuances by the government to promote antibiotic stewardship:

- Generics Act (Republic Act 667), 1988 which reconstituted the National Formulary Committee and directed the mandatory use of the Philippine National Drug Formulary (PNDF) as the basis for procurement of drug products by the government
- Creation of the Antimicrobial Resistance Surveillance Committee (Department of Health [DOH] Department Order No. 339Js 1988) establishing the AMR surveillance program in the Department DOH
- National Health Insurance Act, 1995 (Republic Act 7875 as amended by Republic Act 9241) which require all hospitals to comply with specific standards prior to accreditation such as compliance to clinical practice guidelines, procurement of antibiotics included in the economy's National Drug Formulary, and establishment of and functionality of therapeutics and infection control committees
- Universally Accessible Cheaper and Quality Medicines Act of 2008 (Republic Act 9502) –rationalized promotional and marketing practices of drugs
- Issuances on clinical pathways for various infectious diseases such as HIV/AIDS, tuberculosis, sexually transmitted infections, tuberculosis, malaria, acute respiratory infections, diarrhea and others
- Establishment of the National Center for Pharmaceutical Access and Promotion (NCPAM) in the DOH to

implement, strategize, maximize and monitor the impact of the law on "Universally accessible cheaper and quality medicines act of 2008

In 2012, the DOH conducted various activities to put in place a more encompassing national AMR control program to be initiated by an Executive Order to be signed by the economy's president establishing a National Antimicrobial Resistance Control Program. Private sector initiatives on antibiotic stewardship came mainly from individual programs in various hospitals and initiatives from infectious disease specialty societies such as the Philippine Society for Microbiology and Infectious Diseases (PSMID) and the Pediatric Infectious Disease Society of the Philippines (PIDSP) through campaigns on antibiotic optimization and antibiotic stewardship.

4.4. Symposium session 1 : Asian perspectives : Brief introduction of Asian programs

Asian perspectives: Antibiotic stewardship in Singapore

Dr. Li Yang Hsu
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Antibiotic stewardship is an emerging field currently defined by a series of strategies and interventions aimed towards improving appropriate prescription of antibiotics in humans in all healthcare settings. The ultimate goal is the preservation of current and future antibiotics against the threat of AMR, although improving patient safety and reducing healthcare costs are important concurrent aims. In Singapore, several hospitals had implemented antibiotic stewardship independently since the last decade, but a nationally funded and centrally coordinated antibiotic stewardship program was initiated in 2011, with common key performance indicators and targets. This program is a combination of prospective-audit-and feedback systems coupled with the development of clinical decision support software that are linked to the hospitals' electronic prescribing systems. We present the successes, challenges, and results of the national antibiotic stewardship programs, as well as the lessons learned from the implementation process.

4.5. Symposium session 2 : Policies and regulations to control AMR

WHO strategies to control AMR in the Asia-Pacific Region

Dr. Hendrik Bekedam
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WHO has highlighted the importance of combating AMR at all levels by declaring it as an Organization-wide priority. As part of the World Health Day 2011, a series of policy briefs were launched, defining priority areas for action – from increased surveillance and tighter controls in the use of medicines, to calling for greater research efforts into new tools and innovations. The goal is to ensure today's patients have access to high quality, effective antimicrobials and that these are also preserved for future generations.

WHO is committed to supporting the implementation of the following six policy areas:

1. Commit to a comprehensive, financed national plan with accountability and civil society engagement
2. Strengthen surveillance and laboratory capacity
3. Ensure uninterrupted access to essential medicines of assured quality
4. Regulate and promote rational use of medicines, including in animal husbandry, and ensure proper patient care; and(4d). Reduce use of antimicrobials in food-producing animals
5. Enhance infection prevention and control
6. Foster innovations and research and development for new tools

Overview of AMR challenges

AMR is a complex, multi-dimensional and multi-factorial problem which involves various stakeholders at local, regional, national and international levels. Collaboration between human and animal health sectors has been very helpful in containing public health threats posed by avian influenza and rabies. However, this collaboration is still not systematically organized at all levels for the management of AMR, though antimicrobial use in animal husbandry in quantitative terms outweighs the use in human health and is a major contributing factor

for the development of AMR.

Drug resistance in specific diseases is being tackled effectively by some disease specific health programs, led by WHO and other partners.

- **Drug resistant Malaria**

The Global Plan for Artemisinin Resistance Containment (GPARC)[1] is a call to action for all members of the Roll Back Malaria (RBM) Partnership, to protect ACTs as an effective treatment for Plasmodium falciparum malaria. The emergency response to Artemisinin Resistance in the Greater Mekong Region is being addressed through coordination and high-level advocacy by WHO Regional Offices in South-East Asia and the Western Pacific across it Members States.

- **Drug resistant TB**

The global and regional Green Light Committees (GLC) provide technical assistance on programmatic management of drug resistant tuberculosis, promote rational use and improve access to quality assured second line anti-tuberculosis (anti-TB) drugs, under the Global Plan to Stop TB 2011-2015, which aims to have 1 million MDR-TB patients treated between that period, and 270,000 patients placed on treatment in 2015.

- **Drug resistant Influenza**

The WHO Global Influenza Surveillance and Response System (GISRS) gathers and analyses information on the appearance of novel strains of influenza virus and antiviral susceptibility. The GISRS in Western Pacific Region currently includes 21 National Influenza Centres in 15 economies and three WHO Collaborating Centres for Reference and Research on Influenza.

- **HIV drug resistance**

The WHO's Global Network (HIVResNet) provides standardized tools, training, technical assistance, laboratory quality assurance, analysis of results and recommendations for guidelines and public health action. WHO global strategy for the surveillance and monitoring of HIV drug resistance (2012)[2] summarizes a comprehensive package of HIV drug resistance surveys that should be implemented in all economies scaling-

up and maintaining populations on antiretroviral therapy (ART).

• AMR and Food Safety

The Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) supports WHO's efforts to minimize the public health impact of AMR associated with the use of antimicrobials in food animals. AGISAR updates the WHO list of critically important antimicrobials every two years; develops and disseminates harmonized protocols for monitoring antimicrobial usage and resistance in animals, food and humans, as well as support WHO capacity-building activities through training via the Global Foodborne Infections Network (GFN).

• Gonococcal resistance

The Global action plan to control the spread and impact of AMR in *Neisseria gonorrhoeae* (2012)[3] provides guidance on ways to contain the spread of AMR in *N. gonorrhoeae*, in conjunction with broader national and international strategies for the prevention and control of sexually transmitted infections. The Gonococcal Antimicrobial Surveillance Programme (GASP), started in 1992, monitors AMR surveillance in *N. gonorrhoeae*, with laboratories from 21 economies/jurisdictions (in the Asia Pacific region).

• MDR bacterial infections

Increasing number of healthcare associated infections are MDR, and found in hospitals. Unlike other disease specific programs, few organized networks/programs cover the surveillance of MDR bacterial pathogens, which are further limited geographically to few economies. The MDR bacteria that challenge comprehensive AMR surveillance include Gram positive organisms (MRSA, vancomycin intermediate and -resistant staphylococci [VISA/VRSA], vancomycin-resistant enterococci [VRE], and penicillin-resistant pneumococci), as well as Gram Negative organisms (ESBL and metalo-beta-lactamase [MBL] producing [carbapenemase-resistant] Enterobacteriaceae, MDR organisms like *P. aeruginosa, Acinetobacter* spp., *Burkholderia* spp., *Stenotrophomonas maltophilia*, etc.).

AMR surveillance

There are a number of global, regional and national networks and partners involved in AMR surveillance, but there is a lack of coordination and collaboration amongst them and the various stakeholders involved.

Data on AMR is available from limited geographical areas and there is a lot of disparity in terms of data standardization as well as lack of dissemination of the AMR data and information. Clinical samples from the health system, primarily hospitalized patients forms a large part of the surveillance data, with little data from the community. The correlation of laboratory data with epidemiological data from other sources is usually not used in the analyses. The key challenges identified under surveillance and laboratory capacity are (i) shortage of competent laboratories, (ii) poor infrastructure and data management, (iii) variation in methods, (iv) low coverage of surveillance, (v) insufficient inter-sectoral collaboration, and (vi) insufficient international collaboration.

Networks/partnerships

There are many AMR networks and partnership working towards AMR surveillance in the Asia Pacific Region as well as globally, but they vary widely in scope. Some of them include ANSORP of APFID, Action on Antibiotic Resistance (ReAct), Alliance for the Prudent Use of Antibiotics (APUA), Asia-Pacific Association of Agricultural Research Institutions (APAARI), etc. However, despite the numerous partnerships and networking efforts and initiatives, there is a need for better coordination to effectively combat AMR. WHO's work in the Asia Pacific region The Asia Pacific Strategy for Strengthening Health Laboratory Services (2010–2015) follows up on the Asia Pacific Strategy for Emerging Diseases (APSED)[4], and encourages each Member State to develop a national plan for laboratory services. The bi-regional strategy draws attention to interventions involving the introduction of legislation and policies governing the use of antimicrobial agents, to establish laboratory-based networks for the surveillance of resistance, and to ensure rational use of these drugs at all levels of health care settings.

The bi-regional National Laboratory Policy and Plan[5] provides technical support to Member States on the steps required to develop and effectively implement a National Laboratory Policy and National Laboratory Plan in accordance with the Asia Pacific Strategy for Strengthening Health Laboratory Services (2010-2015). Establishment of National Laboratory-based Surveillance of Antimicrobial Resistance[6] provides essential information on key elements of laboratory-based national surveillance program for AMR and its utilization for prevention and containment of AMR.

A cross-divisional AMR Technical Working Group (AMR-TWG), established at WHO's Regional Office for the Western Pacific in August 2010, ensures a comprehensive and coordinated approach within the overall

context of patient safety and quality improvement. Support to the Member States at the member economy level is also provided, and the recent development of a comprehensive national AMR policy with participation of stakeholders from health and agriculture sectors in Philippines is a good example of such support.

What next?

Coordination and collaboration amongst various sectors and stakeholders is the need of the hour. WHO Global taskforce on AMR is working on a global WHO framework for action to help Member States implement policies to combat AMR. In addition to zoonotic influenza and rabies, AMR is also now a part of the WHO-FAO (Food and Agriculture Organization)-OIE (World Organisation for Animal Health) tripartite partnership agenda to strengthen work at the human–animal–ecosystem interface. Economy situation analysis/assessments to understand AMR challenges in Member States as well as an advocacy strategy, along with gathering of information for evidence-informed policy making to improve antimicrobial use and reduce the spread of AMR, are also being developed. A roadmap to strengthen AMR surveillance in the western pacific region is planned following an AMR surveillance review.

WHO's role in strengthening AMR surveillance

As a chain is only as strong as its weakest link, WHO aims to standardize surveillance and introduce it in Member States with absent or limited capacity for AMR surveillance. WHO also plans to facilitate and be the convener of AMR networks globally and in the region, as well as support the dissemination of AMR data/information. WHO endorses the need for collaboration to strengthen AMR networks and standardize surveillance in Member States and is committed to re-establish/strengthen AMR surveillance systems/ networks in the Region to enable better response to risks due to emergence and spread of AMR.

WHO proposes to expand/network existing AMR networks in the Western Pacific Region supported by the introduction of an AMR surveillance focal point in Member States. WHO is ready to invest and build capacity in economies to ensure all Member States are able to respond effectively to the public health threat posed by AMR. WHO is committed to support economies combating AMR, work with existing networks, build economy's capacity and strengthen the AMR surveillance system, ensure effective dissemination of the evidence and help building bridges between sectors.

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4.5. Symposium session 2 : Policies and regulations to control AMR

How to control antibiotic abuse in the clinical practice?

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The emergence of AMR has made the appropriate use of antimicrobials an essential part of patient safety. Given the strong correlation between antimicrobial use and the selection of resistant organisms, the frequency of inappropriate antimicrobial use has been used as a surrogate marker for the high consequence but avoidable impact of AMR. The combination of effective antibiotic stewardship with a comprehensive infection control program has been shown to reduce the emergence and transmission of antimicrobial-resistant bacteria as well as limiting the ever increasing healthcare costs.

A comprehensive evidence-based stewardship program to address AMR in clinical practice includes elements from among the following recommendations based on local antibiotic use and resistance problems and on available resources that may differ, depending on the profile of the institution.

A high-level multidisciplinary antibiotic stewardship team is often the cornerstone of these programs at hospital level. It is imperative the team members are knowledgeable in and committed to the ideals and principles of antibiotic stewardship. They often comprises infectious diseases trained physicians, microbiologists and pharmacists, who are answerable to the top-level hospital administration. There are 2 core strategies, both proactive, that provide the foundation for an antibiotic stewardship program. They are prospective audit with intervention and feedback as well as formulary restriction and preauthorization.

Other components maybe considered and prioritized as supplements to the core active antibiotic stewardship strategies based on local practice and resources. These include; education activities, development of antibiotic guidelines and clinical pathways, antibiotic order forms, antibiotic stop orders as well as de-escalation or streamlining of antibiotics. Healthcare information technology in the form of electronic medical records

and computer based surveillance can facilitate good stewardship by efficient targeting of antimicrobial interventions, tracking of AMR patterns, drug utilization and identification of nosocomial infections.

Consensus building with support of administration and local providers is absolutely essential. The emphasis of collaboration must be focused on the safety and care of patients rather than that of a policing role. Numerous reports have consistently demonstrated a decrease in antimicrobial use (up to 22%–36%) and annual savings of USD 200,000–900,000, which adequately finances these programs in hospitals. Quantifying a long-term impact on resistance can be more difficult and further studies are necessary to determine the optimal processes by which goals of improved clinical outcomes and containment of resistance can be realized.

4.5. Symposium session 2 : Policies and regulations to control AMR

How to implement policies and regulations to control AMR in Chinese Taipei?

Dr. Shu-Hui Tseng
Center for Disease Control, Chinese Taipei

MDR organisms are increasingly recognized as a global public health issue. The WHO has chosen AMR as its theme for World Health Day on 7 April 2011. WHO strongly recommends that governments conduct antibiotic stewardship for containment of AMR.

Government health policies and the health care systems in which they are implemented play a crucial role in determining the efficacy of interventions to contain AMR. National commitment to understand and address the problem is prerequisite. Creating a national inter-sectoral task force (membership to include health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties) to raise awareness about AMR, organize data collection and oversee local task forces is critical.

Effective action requires the introduction and enforcement of appropriate regulations and allocation of appropriate resources for education and surveillance. Prospective audit of antibiotic use with direct interaction and feedback to the prescriber, performed by an infectious diseases physician through hospital accreditation and inspection and national health insurance payment system can effectively result in reduced inappropriate use of antimicrobials.

The combination of effective antibiotic stewardship with a comprehensive infection control program has shown to limit the emergence and transmission of antimicrobial resistant bacteria. Continuing to promote hand hygiene in health care facilities and communities and conducting a project entitled “the integrated bundle to lower the healthcare associated infections” is Chinese Taipei CDC’s top priority.

“No action today, no cure tomorrow.” Chinese Taipei CDC would make every effort to combat AMR by targeting consumers, prescribers and dispensers, veterinarians, managers of hospitals and diagnostic laboratories, patients and visitors to health care facilities, as well as national governments, the pharmaceutical industry, professional societies, and international agencies.

4.5. Symposium session 2 : Policies and regulations to control AMR

How to control antibiotic abuse in animal husbandry?

Dr. Stephen Page
Advanced Veterinary Therapeutics, Australia

The various use patterns of antibacterial agents in terrestrial livestock and aquaculture species have been described recently and include prophylaxis, metaphylaxis and treatment. Since as long ago as 1947 the subject of antibiotic abuse or misuse in as well as animals has been repeatedly described in the literature. However, there is no universally accepted definition of 'abuse' and 'misuse' and many of the current use patterns that have been described in this way reflect label instructions approved by regulatory agencies.

What is beyond debate is that there is serious and growing concern about the impact of AMR on human health especially when pandrug resistance has been identified in pathogenic Gram-negative bacteria, livestock-associated MRSA is emerging and the dearth of new antibacterial agents has been described as contributing to a 'perfect storm'.

The contribution of antibacterial use (in any and all its forms) in animals to the dire situation of increasingly untreatable infections in humans remains a subject of much discussion and a growing number of quantitative risk assessments. The potential pathways travelled by resistance determinants from animals and other sources are complex and human exposure to such sources of resistance is difficult to study. However, if it is accepted that antibacterial agents are 'societal drugs', drugs of special importance that may be used in an individual but have impacts on the entire ecosystem, then it is time for inter-professional collaboration to ensure that all uses of antibacterial agents are 'optimized'.

For as long as the subject of abuse has been on the agenda, so has the solution. Prudent use guidance and calls for action and action plans have a long history with the most recent, the Chennai Declaration,

representing a powerful reminder of how imminent crisis can focus the mind to prepare a practical and implementable approach to solve the seemingly insoluble problem.

Management of infectious disease is not a trivial exercise yet antibacterial agents remain available over-the-counter and used with no professional oversight. Clearly one of the approaches to improved antibacterial use is to ensure these societal drugs are only available on prescription.

Even if available on prescription there remain many additional important elements of appropriate or optimal use. Amongst these elements are improved diagnosis, improved prescribing behavior, refined dosage regimens that incorporate the most pertinent information from economic and mathematic models, clinical studies, and investigations of pharmacokinetic and pharmacodynamic properties. Guidelines on the selection and prudent use of antibacterial agents are benefiting from a growing evidence base. Antibiotic stewardship programs are emerging as vehicles supporting better use.

A significant problem remains the effective implementation of the action plans that have been developed and that have benefited from decades of refinement while still not widely adopted. Awareness and education of all stakeholders is clearly a critical step. The need for more veterinarians (and paraveterinarians) to provide the essential professional support necessary to ensure livestock health and welfare is a global issue present in developing and developed economies alike and must be addressed if antibacterial use is to be improved.

4.5. Symposium session 2 : Policies and regulations to control AMR

How to implement policies and regulations to control AMR in animal husbandry?

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Antimicrobials have a key role to play in protecting animal health and welfare. Protecting animals against disease contributes to the production of high quality food from healthy animals whilst minimizing the impact on the environment. The concern that the use of antimicrobials in food animal production can increase the risk of selection of antimicrobial resistant bacteria has led to international expert meeting on combating AMR. A variety of recognized international, governmental, and professional organizations have worked to develop and implement various types of risk management activities. We briefly summarize below some important activities or recommendations for effective implementation of policies and regulations to combat AMR.

Commitment for implementation of policies and regulations

National governments must commit to a comprehensive plan to implement policies and recommended measures for containment of AMR. Strong leadership and political will are required to translate knowledge and recommendations into practice. Besides, civil society representatives should be involved in the implementation of the action plan and the monitoring activities.

Strengthening the monitoring systems on antimicrobial usage and resistance

Surveillance of antimicrobial usage and resistance provides important data for the identification of resistance problems and contributing factors for the development and spread of resistance at a national and local level. A paucity of surveillance data contributes to a poor understanding of the scale of the problem and hampers an effective response to it. Moreover, AMR trends should be consistently monitored over time and across geographical areas and should be shared at the regional and global levels. Many economies conduct veterinary monitoring programs for food-borne pathogens, indicator bacteria, and animal pathogens from animals and

animal products. However, harmonization and standardization are needed to compare situations at the national and international levels.

Regulatory decisions based on risk assessment

The purpose of risk assessment is to supply the proper information to risk managers, policy makers, and other stakeholders. It is based on Codex and OIE frameworks of risk assessment with the incorporation of several adaptations and alternative approaches in response to important data gaps and the needs of risk manager. Several risk assessments have been conducted and some have contributed to regulatory policies in economies such as the United States and Australia. However, the results of risk assessment can vary in different economies or regions in the world because of differences in risk tolerance and in the respective importance given to human health over animal health. With increasing demands for evidence-based and transparent decision-making on public health, there is a lot of work to be done in the area of risk analysis including development of further methodology and training of personnel.

Strict enforcement of guidelines on prudential use of antimicrobials

The rational use of antimicrobials in real practice is essential for containing AMR. International organizations have emphasized the importance of prudential and rational use of antimicrobials in animals in order to minimize the possible impact of animal antimicrobial usage on public and animal health. A guiding principle with respect to antimicrobials use should be “as little as possible, as much as necessary” since we owe it to both present and future generations to use these agents with care and discrimination. Furthermore, the overuse and misuse of antimicrobials in animals for human consumption must be addressed by educating veterinarians and farmers and through legislative and regulatory measures. It is essential that all parties work together to ensure safe use and to minimize the development of AMR.

Reduction of antimicrobial use in animal husbandry

To tackle AMR, decreasing the use of antimicrobials is essential by minimizing infections in food animals. This can be achieved by improving hygiene, biosecurity, and health management on farms and preventing disease through the use of vaccine and other measures such as probiotics, prebiotics, or competitive exclusion products.

Communication and education

More efforts should be exerted to raise public awareness of the importance of antimicrobials in treating bacterial infection and the public health challenges of AMR. It is also essential to educate people including farmers and veterinarians on the importance and benefits of the prudent use of antimicrobials and providing relevant information about resistance.

In conclusion, interventions to reduce AMR by risk management will be able to minimize antimicrobial resistant bacteria and ensure that healthy animals enter the food chain, while allowing responsible use of antimicrobials in animals. Furthermore, a "One health" approach to antimicrobial use and resistance is essential to minimize AMR in humans and animals. To solve AMR problem, collaboration among human health, animal health, and environmental health communities is critical.

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4.6. Symposium session 3 : Clinical and economic impact of AMR

Clinical impact of AMR

Dr. Yehuda Carmeli
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AMR has been a challenging clinicians and investigators since antibiotics have been introduced into clinical practice. The development of multiple new antibiotic agents in the 70's and early 80's, has led to reduced interest in resistance, however, soon after resistance to these new agents emerged, and over the last decade MDR and extreme-drug resistance has become an increasing problem in many parts of the world.

Infections with antibiotic resistant bacteria are associated with severe clinical outcomes. Patients with infections caused by antibiotic resistant pathogens have higher mortality, morbidity, length of hospital stay and higher expenditure than similar patients with infections caused by susceptible organisms. As a rule of thumb, resistant organisms are associated with two fold higher rates of adverse outcomes as compared to susceptible strains. This is primarily related to delay in effective therapy occurring much more often with resistant organisms. However, these adverse outcomes are also related to the affected population; patients with resistant organisms are often more vulnerable patients that those with susceptible strains. In certain cases resistant organisms are also more virulent.

The impact of resistance goes beyond that, as infection with resistant organisms do not only replace susceptible strains, but often cause extra infections, i.e., patients that would have not been infected by a susceptible strain is infected by a resistant strain. The proportion of this population is difficult to estimate, however, from the societal point of view, this causes much higher burden than replacement of susceptible organisms.

AMR has also an indirect effect of great importance. When proportion of resistance reaches certain level (usually 20%), clinicians feel it is inappropriate to use the agent as empiric therapy, and the agent is lost. In the era when effective agents are scarce, such a loss can result in severe health and economic burden.

4.6. Symposium session 3 : Clinical and economic impact of AMR

Economic impact of AMR

Dr. Sara Cosgrove
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The increasing prevalence of antimicrobial-resistant pathogens has economic consequences. Several studies have been published attempting to quantify these impacts, and the majority of studies show an association between infection and/or colonization with resistant organisms and increased costs for common hospital pathogens such as *S. aureus*, enterococci, and Gram negative organisms. Interpretation of these results requires an understanding of 1) the perspective of the study (e.g. hospitals, third-party payers, patients, society), 2) how costs can be measured and 3) how to maximize the design and analysis of the study to provide the best estimates of the association between AMR and costs.

4.6. Symposium session 3 : Clinical and economic impact of AMR

Economic impact of AMR : How to evaluate?

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The emergence of antimicrobial-resistant organisms is accelerating. Antimicrobial-resistant infection (ARI) causes ineffective treatment, delayed recovery, recurrent infection, or even death, which have economic impact to patients, hospitals, and society. From a societal perspective, the economic burden incurred by ARI includes not only medical cost but also productivity cost due to morbidity or loss of life.

In evaluating economic burden attributable to ARI, it is important to measure an unbiased cost attributable to ARI. A simple comparison of costs between patients with ARI and without ARI may cause a bias. One of the causes of the bias is the existence of confounding factors which may be associated with ARI and with increased cost. To control for the effect of the confounding factors, multiple regression is often employed. Another cause of the bias is sampling error. To address the sampling bias, propensity scores, estimated by logistic regression, are used to select matched control patients for each patient with ARI. The number of drug-resistant cases is multiplied by the attributable costs for ARI to estimate the total medical cost for the entire patients.

To estimate the societal costs for excess mortality, the number of deaths attributable to ARI is multiplied by the lost productivity cost. Excess mortality attributable to ARI is estimated by logistic regression. Productivity cost is estimated based on mean wage of the age group which patients belong to. The societal costs for excess mortality need to be discounted at various rates. To estimate the societal costs for excess length of stay, additional length of stay attributable to ARI is multiplied by the daily cost for lost productivity. The attributable length of stay is also estimated by multiple regression.

4.7. Symposium session 4 : Infection control of resistant pathogens

Antibiotic stewardship and infection control : Can they contain carbapenem-resistant Enterobacteriaceae

Dr. Anucha Apisarnthanarak
Thammasat University Hospital, Thailand

Infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) is of global concern. Patients with infections from these carbapenem-resistant pathogens have limited treatment options, low treatment success, prolonged hospitalization, higher rates of mortality, and excess healthcare costs. There are significant challenges and gaps in the disease understanding of CRE for resistance mechanisms, resistance levels, infection reservoirs, and environmental ecologies. The main problem of resistance attributed to CRE is linked with acquisition of carbapenemases via mobile, transferable genetic elements, an increased rate of detection either in the hospital settings or in the community settings, and the downstream effects for healthcare delivery within, between, and beyond healthcare facilities. It is known that several factors contribute to the acquisition of carbapenem-resistant Gram-negative bacteria (CRGNB), which are perhaps most easily categorized as individual-level and facility-level factors which include modifiable risk factors (i.e., hand hygiene, contact precautions, and non-judicious antimicrobial prescribing practices and exposures) versus non-modifiable risk factors (i.e., judicious antimicrobial exposures). These factors dynamically interact and pose transmission and acquisition risks for colonization or infection by susceptible hosts. It remains controversial as to whether antibiotic stewardship plays an important role in reducing CRGNB infections. Although recommendation for control of CRGNB must include attention to judicious use of antimicrobial agents, current evidence suggested that antibiotic stewardship cannot be used as the only intervention to prevent and control the spread of CRGNB.

4.7. Symposium session 4 : Infection control of resistant pathogens

Controlling AMR in the community

Dr. Wing Hong Seto
Queen Mary Hospital, Hong Kong China

In a real sense there are more experiences in the control of AMR in the community then in the hospital. Some of these undertaking include the control of TB and penicillin resistant pneumococcus and appropriate treatment as the DOT (Direct Observational Therapy) for TB and the production of effective vaccines as for pneumococcus must certainly play a role. However important strategies for the reduction of AMR are the organizations of public campaigns and a program to reduce antibiotics usage in general practitioners (GPs). A public program linked to the World Health Day of 2011 conducted in Hong Kong China with two public surveys of over 1500 respondents. Finally a project to reduce antibiotics abuses among GPs conducted in Hong Kong China.

4.7. Symposium session 4 : Infection control of resistant pathogens

Infection control in hospitals: how much do we need active surveillance

Dr. Stephan Harbarth
Hopitaux Universitaires de Geneve, Switzerland

Several interventions and strategies that have been documented in the literature as being successful in the prevention and control of transmission of resistant pathogens have been recently reviewed. Whereas it is unclear which bundles of interventions are effective, there is a clear suggestion that multiple simultaneous interventions can be effective in reducing infections by MDR microorganisms. Among these, active surveillance cultures are the most controversial tools to improve MDR microorganism control and compliance with hand hygiene, standard and contact precautions.

Given the lack of high-quality evidence, current practices are variable: some institutions carry out active surveillance and isolation of patients, whereas other institutions do not screen systematically and isolate only patients diagnosed with infections caused by these pathogens. Moreover, existing evidence supports screening and control interventions as cost effective in decreasing transmission of MRSA and VRE in intensive care units (ICUs), but there remains skepticism on whether these measures are cost-effective or even detrimental to the quality of patient care in non-ICU settings. For instance, a recent study evaluated the impact of active screening and contact precautions on compliance with individual and composite process of care quality measures, and found that contact isolation was associated with lower adherence to the composite pneumonia process-of-care measure, whereas other composite measures were not affected.

Despite these ongoing controversies, we discussed evidence arguing in favor of active surveillance and contact precautions as the single most important measure to prevent the spread of MDR organisms, in conjunction with improved hand hygiene compliance. We first focused on sporadically occurring MDR organisms and then discussed the effectiveness of active surveillance and contact precautions in settings with hyperendemic

MDR organisms. In particular, detailed data about the added value of active surveillance strategies including targeted screening on control of nosocomial MRSA transmission were discussed. Two important studies have produced conflicting results on the implementation of active surveillance cultures and their effectiveness in MRSA control. Harbarth et al. found no reduction in the incidence of nosocomial MRSA infections among surgical patients enrolled in a single, large institution crossover cohort trial, whereas Robicsek et al. found that the use of active surveillance cultures reduced MRSA infections by nearly 70% in an observational cohort study performed in two affiliated hospitals. More recently, two important studies carried out in the United States have highlighted the difficulties in gaining sustained and reproducible results about the effectiveness of active surveillance cultures for MRSA control.

5. Feedback from experts and participants

For evaluation of the APEC symposium, experts and participants were asked to fill out the feedback form (Annex 3).

5.1. Assessment of plenary lectures and symposium session

Experts and participates were asked to rate the each plenary lecture and session of the APEC symposium on a scale of 5-1, from excellent to poor. A total of 92 experts and participants gave their feedback. Based on the feedback, overall assessment of the APEC symposium was good as follows:

	(%) Excellent →				Poor
Plenary lectures					
• Future strategies to control AMR in Asia	39	40	20	1	0
• Global collaboration in tackling AMR	32	40	24	3	0
• How to fix the antibiotics pipeline?	24	46	23	7	0
Symposium sessions					
• Antibiotic stewardship in the Asian region	34	43	23	0	0
• Policies and regulations to control AMR	28	46	26	0	0
• Clinical and economic impact of AMR	21	52	27	0	0
• Infection control of resistant pathogens	33	39	26	2	0

5.2. Topics most valuable

- Future strategies to control AMR in Asia : 24%
- Antibiotic stewardship in the Asian region : 23%
- Infection control of resistant pathogens : 22%
- Policies and regulations to control AMR : 10%
- Clinical and economic impact of AMR : 10%
- Global collaboration in tackling AMR : 6%
- How to fix the antibiotics pipeline? : 5%

5.3. Additional comments

- The plenary lectures and symposium sessions were good, informative, and well-organized.
- Strong leadership of APEC/WHO is essential to influence governments in APEC economies, particularly in the Asian region.
- AMR control should be done between human & veterinary medical sectors and the industry.
- Need to find a way to share success of outstanding program for AMR control in developed economies with resource poor settings (developing economies)
- In the future meetings, it is suggested to include anti-mycobacterial, anti-viral, and anti-malarial topics since XDR/MDR TB and drug resistant viral and malarial infections are increasing nowadays.

6. Summary of APEC symposium

The current project was aimed to improve understanding and awareness of AMR in healthcare providers, government officials, and other stakeholders in the Asian region, to discuss the clinical and economic impact of AMR, and to explore strategies and relevant policies to control AMR in the Asian region by organizing an international symposium. Therefore, the APEC symposium focused on understanding of the clinical and economic impact of AMR and discussion for effective implementation of policies and regulations to control AMR in both human medicine and animal husbandry and for future strategies to control and prevent AMR in APEC economies.

The APEC symposium has provided relevant and updated information on how we evaluate the impact of AMR and how we control this global problem with world-renowned invited speakers and international participants, which will help APEC economies prepare the future strategies to mitigate the economic and clinical impact of AMR and preparing against human security caused by AMR. Control and prevention of AMR is one of the most critical public health issues in APEC economies and combating AMR should be one of the top priorities among agenda of each economy in the Asian region since AMR is a serious global issue with particular situation in the Asian region. Therefore, concerted effort employing a multifaceted strategy with collaboration among all relevant sectors and stakeholders is essential.

Annex 1. Program of APEC symposium

APEC symposium on strategies to control & prevent antimicrobial resistance

15 March 2013

Kuala Lumpur Convention Centre, Kuala Lumpur, Malaysia

Session	Proposed Title	Speaker	Economy
Session 1 (09:00 - 11:00) : Antibiotic stewardship			
		Chairs Wing-Hong Seto	Hong Kong China
		Christopher Lee	Malaysia
Session 1-1	Antibiotic stewardship : why, what and how ?	Stephan Harbarth	Switzerland
Session 1-2	Asian perspectives : brief introduction of Asian programs		
	- China	Yonghong Xiao	China
	- Korea	Doo Ryeon Chung	Korea
	- Malaysia	Victor Lim	Malaysia
	- Philippines	Celia Carlos	Philippines
	- Singapore	Li Yang Hsu	Singapore
	Panel discussion	All speakers	
Plenary lectures (11:10 - 12:30)			
		Chair Yasmin Malik	Malaysia
Plenary lecture 1	Future strategies to control antimicrobial resistance in Asia	Jae-Hoon Song	Korea
Plenary lecture 2	Global collaborations in tackling antimicrobial resistance	Victor Lim	Malaysia
Lunch (12:40 - 14:10)			
Plenary lecture (14:20 - 15:30)			
		Chair Robin Patel	USA
Plenary lecture 3	How to fix the antibiotics pipeline?	David Shlaes	USA
Sessions (15:10 - 16:50) : simultaneous breakout sessions			
Session 2 : Policies and regulations to control resistance			
		Chairs Dennis Dixon	USA
		Yong Ho Park	Korea
Session 2-1	Strategies to control antimicrobial resistance in the AP regionfrom the viewpoint of WPRO (or WHO)	Hendrik Bekedam	WPRO
Session 2-2	How to control antibiotic abuse in the clinical practice?	Christopher Lee	Malaysia
Session 2-3	How to implement policies and regulations to controlantimicrobial resistance?	Shu-Hui Tseng	Chinese Taipei
Session 2-4	How to control antibiotic abuse in the animal husbandry?	Stephen W. Page	Australia
Session 2-5	How to implement policies and regulations to controlantimicrobial resistance in animal husbandry?	Yong Ho Park	Korea
Session 3 : Clinical and economic impact of antimicrobial resistance			
		Chair Victor Lim	Malaysia
Session 3-1	Clinical impact of antimicrobial resistance	Yehuda Carmeli	Israel
Session 3-2	Economic impact of antimicrobial resistance	Sara Cosgrove	USA
Session 3-3	Economic impact of antimicrobial resistance:How to evaluate?	Tae-Jin Lee	Korea
Session 4 : Infection control of resistant pathogens			
		Chair Jien-Wei Liu	Chinese Taipei
Session 4-1	Antibiotic stewardship and infection control : Can they contain NDM-1?	Anucha Apisarnthanarak	Thailand
Session 4-2	Controlling antibiotic resistance in the community	Wing-Hong Seto	Hong Kong China
Session 4-3	Infection control in hospitals:how much do we need active surveillance?	Stephan Harbarth	Switzerland

Annex 2. List of speakers at APEC symposium on strategies to control and prevent antimicrobial resistance on 15 March 2013 in Kuala Lumpur, Malaysia

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Annex 3. Feedback form

Asia-Pacific Economic Cooperation

APEC Symposium on strategies to control and prevent antimicrobial resistance(AMR)

15 March 2013 / Kuala Lumpur Convention Centre, Kuala Lumpur, Malaysia

FEEDBACK FORM

Your feedback is important to us and will help us to improve future meetings. Kindly complete this feedback form and return to us at the end of the meeting.

1. Please rate the following plenary lectures and sessions you have attended by circling your response on a scale from 1 to 5.

	Excellent	Very Good	Good	Satisfactory	Poor
Plenary lectures					
1. **Future strategies to control AMR in Asia**	5	4	3	2	1
2. **Global collaborations in tackling AMR**	5	4	3	2	1
3. **How to fix the antibiotics pipeline?**	5	4	3	2	1
Sessions					
1. **Antibiotic stewardship** 1. Antimicrobial stewardship: why, what and how? 2. Asia perspectives : brief introduction of Asian programs	5	4	3	2	1
2. **Policies and regulations to control resistance** 1. Strategies to control AMR in the AP region from the viewpoint of WPRO (WHO) 2. How to control antibiotic abuse in the clinical practice? 3. How to implement policies and regulations to control AMR? 4. How to control antibiotic abuse in the animal husbandry? 5. How to implement policies and regulations to control AMR in animal husbandry?	5	4	3	2	1
3. **Clinical and economic impact of AMR** 1. Clinical impact of AMR 2. Economic impact of AMR 3. Economic impact of AMR : How to evaluate?	5	4	3	2	1
4. **Infection control of resistant pathogens** 1. Antibiotic stewardship and infection control : Can they contain NDM-1? 2. Controlling AMR in the community 3. Infection control in hospitals : How much do we need active surveillance?	5	4	3	2	1

Which topic(s) did you find most valuable?

What is your overall assessment? Do you have any other comments?

Thank you for completing the feedback form !