ABR- side event during WHA66 - Tuesday 21 May 2013,

Palais des Nations, room 24

Antibiotic Resistance - a Threat to Global Health Security and the Case for Action

Written contributions

Contents

1. Asia's effort to control and prevent antimicrobial resistance

1. Antimicrobial resistance (AMR) is obviously one of the most critical healthcare problems worldwide. In particular, Asian region is the area which showed the highest prevalence rates of resistance in major bacterial pathogens. For example, high-level macrolide resistance in *Streptococcus pneumoniae* was reported to be higher than 70% among clinical isolates from Asian countries such as Korea, China, Japan, Hong Kong, Thailand and Vietnam. The prevalence rates of multidrug-resistance in *Acinetobacter* spp. were higher than 80% in Thailand, Malaysia and India. Despite the critical situation of AMR, however, it has not been recognized as an important issue in most Asian countries due to lack of awareness and limited healthcare infrastructure until recently. Antibiotics have been widely abused and misused in clinical practice and animal husbandry in most Asian countries. Resistant pathogens have extensively spread between countries not only among Asian countries but also between continents. Given the clinical and socioeconomic importance of AMR, effective and comprehensive strategies to control and prevent AMR in the Asian region are urgently required, which should be based on effective international collaboration.

2. Dr. Jae-Hoon Song of the Samsung Medical Center, Seoul, Korea has founded the **Asia Pacific Foundation for Infectious Diseases (APFID)** in 1999, which was the Asia's first international foundation for research, control and prevention of infectious diseases including AMR. APFID has been operating 4 major international programs ; Asian Network for Surveillance of Resistant Pathogens (ANSORP), Asian Bacterial Bank (ABB), International Symposium on Antimicrobial Agents and Resistance (ISAAR), and Initiatives to Control Antimicrobial Resistance (I CARE). APFID has given great efforts to serve as a core infrastructure for control and prevention of infectious diseases and AMR in the Asian region through collaborative research, technical development, exchange of ideas and information, and strategic planning for the past decade.

3. Dr. Song and physicians in Asian countries have organized the **Asian Network for Surveillance of Resistant Pathogens (ANSORP)** in 1996 for international surveillance of AMR in the Asian region. ANSORP was the first and only international study group for research collaboration on infectious diseases and AMR in the Asian region. When ANSORP was first organized in 1996, it consisted of 14 hospitals from 11 Asian countries. As of 2013, ANSORP has 120 hospitals in 14 countries or areas (Korea, China, Japan, Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, Thailand, Vietnam, and Saudi Arabia) in the Asian region for international collaboration. During the past 16 years, ANSORP has been performing multinational surveillance studies on AMR, including resistance in *Streptococcus pneumoniae*, *Staphylococcus aureus* in the community (CA-MRSA), and Gram-negative bacilli as well as major infectious diseases such as community- and hospital-acquired pneumonia in Asian countries. ANSORP data which have been

published in more than 100 papers in the international journals have first revealed the serious situation of AMR in major pathogens in Asian countries. ANSORP is the most important asset to Asian countries for evaluating current status of AMR in major pathogens through international collaboration, which will be the basis for strategic plan for control of this problem.

4. **Asian Bacterial Bank (ABB)** is the first international microbial bank of clinical pathogens in the Asian region. ABB has been collecting and storing the clinical bacterial isolates from 14 Asian countries from ANSORP studies. As of 2013, over 45,000 isolates of major bacterial pathogens with their clinical and molecular characteristics have been collected and stored. Bacterial isolates stored in the ABB have been distributed to investigators in Asia and other parts of the world upon request for their research purposes.

5. **International Symposium on Antimicrobial Agents and Resistance (ISAAR)** is an international symposium every two years to exchange ideas and up-to-date information on infectious diseases and AMR. ISAAR aims to contribute to the pivotal exchange of the most recent research on infectious diseases and AMR in the world. It emphasizes on epidemiology, mechanism of AMR, clinical impact, antimicrobial treatment, new antimicrobial agents, vaccines, guidelines of treatment and prevention, and future strategies against infectious disease threats. Since its first event in 1997, ISSAR has become the most representative international meeting on infectious diseases and AMR in the Asian region with over 2,000 worldwide participants from 50 countries.

6. **Initiatives to Control Antimicrobial REsistance (I CARE)** is an international strategy to control and prevent AMR in the Asian region. I CARE strategies consist of 6 major parts ; surveillance of AMR, increased awareness of AMR, appropriate use of antibiotics in the clinical practice and animal husbandry, effective infection control, improved vaccination, and relevant policies and regulations of antibiotics and AMR in the Asian region. Since antibiotic abuse or misuse is the major driving force for the emergence of AMR, the first and the most urgent plan is to increase the awareness of AMR and to promote the appropriate use of effective antibiotics. For this reason, the first main strategic plans of I CARE are focused on strengthening the international surveillance of AMR and introducing an international campaign program to increase the awareness of AMR in general public and healthcare professionals.

7. In addition, APFID has been collaborating with Health Working Group (HWG) of the **Asia-Pacific Economic Cooperation (APEC)** to establish the future strategies to control and prevent AMR in the AP region since 2010. The first APEC collaboration in 2010-2011 has led to the "International initiatives to control antimicrobial resistance in the Asia-Pacific region" which was the first strategic action plans to control and prevent AMR in the Asian region. APFID and ANSORP are also expecting to have

strong collaborations with WHO and its regional office for surveillance of AMR and future strategies to combat AMR in the Asian region.

8. Through all these efforts for international collaboration in Asian countries, our final goal is to prevent and control AMR in the Asian region which is considered an epicenter of AMR in the world. We hope that these efforts will build and strengthen the capacity to respond to public health threat caused by AMR in the Asian region and also other parts of the world.

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2. Australian initiatives on Antimicrobial Resistance (AMR)

Australian AMR Prevention and Containment Steering Group

1. Australia has established a new Steering Group to oversee development of a national *AMR Prevention and Containment Strategy* for Australia.

2. The Steering Group is jointly chaired by the Secretaries of the Department of Health and Ageing and the Department of Agriculture, Fisheries and Forestry. Membership also includes the Commonwealth Chief Medical Officer, and the Commonwealth Chief Veterinary Officer.

3. The Steering Group provides strengthened governance arrangements and high-level leadership and coordination of Australia's current and future efforts to prevent and contain AMR. It will also ensure that issues are identified within a congruent "one health" framework, and that there is accountability for progress and outcomes on AMR.

4. The Steering Group has agreed the overarching framework for the development of Australia's *AMR Prevention and Containment Strategy* (refer to Table 1, below). The first two priority areas being considered by the Steering Group are regulation issues and enhancing surveillance. The *Strategy* will be further developed during 2013-14, in consultation with a diverse range of stakeholders from across the human and animal health sectors, and agriculture.

National Safety and Quality Health Service Standards

5. A significant recent development in relation to antimicrobial stewardship in Australia is the implementation of Standard 3 of the National Safety and Quality Health Service (NSQHS) Standards, "Preventing and Controlling Healthcare Associated Infection".

6. From 1 January 2013, the NSQHS Standards were mandated in all Australian public and private hospitals and health service organisations. This means that over 1500 hospitals and health services will now be taking active steps to address antibiotic resistance.

7. Standard 3 ensures that health services take active steps to promote the appropriate prescribing of antimicrobials and requires that all healthcare services have an antimicrobial stewardship program in place; that the clinical workforce prescribing antimicrobials have access to current endorsed therapeutic guidelines on antibiotics; that monitoring of antimicrobial usage and resistance is undertaken and that action is taken to improve the effectiveness of antimicrobial stewardship.

8. Efforts to align antibiotic prescribing practices within hospitals with best practice guidelines are critically important in reducing the overall use of antibiotics in Australia, as well as targeting more specific application of the correct antibiotic to the specific disease or condition.

TABLE 1: Framework to inform the development of a comprehensive *AMR Prevention and Containment Strategy* for Australia

Framework Element	The Australian *AMR Prevention and Containment Strategy* will involve:
Governance	Strong central leadership and governance are paramount to the success of developing and implementing effective and sustainable systemic change.
Surveillance	An integrated national surveillance system for antibiotic resistance and antibiotic usage across the human and animal health/agriculture sectors.
Infection Prevention and Control	Develop new, strengthen existing and mandate where possible effective infection prevention and control (including antibiotic stewardship and hygiene measures) to reduce the spread of antibiotic resistant organisms in human health (across the acute, primary and community sectors) and animal health.
Regulation	To further develop and streamline the regulatory mechanisms in both the human and animal health/agriculture sectors, and to ensure that regulatory levers exist in both sectors in order to respond to emerging trends in AMR nationally and internationally.
International Engagement	Regular engagement with international organisations including the WHO/FAO/APEC (to ensure alignment with current international policies and strategies) and supporting developing countries in their efforts to prevent and respond to increasing AMR.
Communication	[Education] Conducting national education initiatives, including behaviour change campaigns and awareness programs for healthcare providers, including prescribers and dispensers, in the human and animal health and agriculture sectors and the public to promote the rational and prudent use of antibiotics and infection prevention and control.
	[Stakeholder Engagement] Active engagement of all key stakeholders on the development and implementation of the AMR containment and prevention activities to ensure a coordinated and achievable approach.
	[Partnerships] Collaboration between Governments, NGOs, professional societies and international agencies to develop partnerships and commitment to containing and preventing AMR. Partnerships will also facilitate establishing improved surveillance networks, expanding existing effective AMR programs, or the inclusion of AMR in CPD/university courses.
Research	A strategic investment in research (including inter-sectoral cooperation between industry, Government and academia) to promote innovation and research on new drugs and technology, including surveillance networks and information sharing on promising research areas; and international collaboration and data sharing to ensure efficient use of limited research funding.

3. Austrian Activities to fight against AMR

From the National Initiative to fight against AMR (NI-AMR) to the National Action Plan AMR (NAP-AMR)

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1. What was the issue you were seeking to address?

- AMR is a constant challenge that has already been addressed by WHO and the EU. Especially the **close cooperation of the human and the veterinary sector is needed** to realise the "One Health" – concept.

2. Why was it an issue?

- Although Austria has a relatively consolidated situation in comparison to other States of the European Region there are still many efforts necessary to implement effective mechanisms to prevent and control AMR.

3. How did you deal with it?

- Since 2011 there exists at the Federal Ministry of Health the **AMR-platform** where the human and the veterinary sector are continuously collaborating.
    - In 2012 the **National Initiative to fight against AMR (NI-AMR)** was launched following three principles:
        - multisectoral approach
        - embedding into international AMR-activities and
        - orientation on best practice models

In a participatory discussion process with involvement of all relevant stakeholders and experts the necessary fields of action were identified and concrete measures were defined especially to achieve progress at hygiene, prevention of infection and diagnosis of infection diseases, surveillance and antimicrobial stewardship. Not to mention, to improve the information to the human population through reporting. This matrix of measures will serves as basis for the NAP-AMR.

4. What if any challenges were encountered and how were they overcome?

- The working process was very successful due to the efficient and effective cooperation with all stakeholders and experts. We did not encounter any problems

・・WHO and ECDC also supported the Austrian MoH at the kick-off conference in April 2012 with high qualified speakers (WHO: Danilo Lo Fo Wong)

5. What impact has this action had?

In 2013 the AMR-platform will finish the **National action plan to fight against antibiotic resistance (NAP-AMR)** which finally contains concrete actions to improve patient safety and the prudent use of antibiotics in human- and veterinary sector. **Thus the "one health concept" is being implemented already in the National Action Plan.**

4. Patient Safety: Actions for integrated surveillance and monitoring microbial resistance in Brazil

1. What was the issue you were seeking to address?

The microbial resistance is not restricted to the context of human health care. It also involves questions related to the use of antimicrobials in veterinary; livestock and agriculture, which impact of their actions are as relevant as the issues facing human health. Consequently, it reinforce the need for establishment of integrated actions for its control and monitoring.

2. How did you deal with it?

With respect to initiatives in health, well-structured action was created in 2005, with the leadership of ANVISA, to support the Network Laboratories and PAHO. This is the Microbial Resistance Network - National Network of Monitoring Microbial Resistance in Health Services, whose main objective was to create and organize a network of 114 reference laboratories in Brazilian sentinel hospitals. The Microbial Resistance Network works collaboratively to reduce the emergence and spread of antimicrobial resistance on health services and the in the country, through the knowledge of the susceptibility profile of pathogens and targeting prevention and control.

In 2013, the Microbial Resistance Network is composed of 317 Public Hospitals, 946 Private Hospitals and 44 Public Health Institutes, being observed the qualitative and quantitative evolution of surveillance and monitoring of antimicrobial resistance, with update of the list of priority microorganisms and adequate instruments of notification to solve the methodological changes (sensitivity profiles).

With the purpose of advising the Board of Directors of ANVISA in developing standards and measures for monitoring, control and prevention of microbial resistance on health services in Brazil, was created in 2009, the Technical Chamber of Microbial Resistance in Health Services - CATREM, composed by 07 members and eight alternates of experts or professional health with experience in areas related to the control of Infections related to Health Assistance.

Related to the food theme, the National Health Surveillance Agency-Anvisa conducted from 2004 to 2006 a monitoring program that aimed to describe the prevalence and antimicrobial resistance of Salmonella spp. and Enterococcus spp. in 2,679 frozen chicken carcasses that were collected in the Brazilian retail market. The findings reinforce the need for continuing and strengthening the monitoring program, but with the approach of an integrated surveillance system on antimicrobial resistance. In this regard, Anvisa and Pan American Health Organization will hold a Workshop on Antimicrobial Resistance, in the end of May 2013, with participants from Ministry of Agriculture, National Health Surveillance Agency (ANVISA), WHO, PAHO / PANAFTOSA, OIE, IICA and FAO in order to improve the understanding in integrated

surveillance on antimicrobial resistance and to reach consensus on a project to implement an integrated surveillance system antimicrobial resistance in the country.

With regard to the strengthening of the use of antimicrobials in the country, ANVISA issued in 2011 a Board of Directors Resolution ANVISA nº 20 of May 5, 2011, http://bit.ly/10e7mR3, which provides for the control of medicines based on substances classified as antimicrobial, prescription use, single or in combination and applies to all dosage forms that contain in its formulation this therapeutic class.

3. What if any challenges were encountered and how were they overcome?

On 01 April 2013, the National Program of Patient Safety was launched, through the publication of Ministry of Health MS n° 529, of April 1, 2013, http://bit.ly/YsH3GJ, it also deals with the prevention of infections related to health care, especially those caused by multi resistance microorganisms. The challenge is to produce, organize and share knowledge about the risk profile of Microbial Resistance that is exposed patients and population. Also constitutes the challenge to estimate the prevalence and incidence of prescription drugs by clinical specialty.

4. What impact has this action had?

- Use of protocols for the prevention of adverse events associated with healthcare and related to prescription, use and administration of medications, including antibiotics, in health services.
- Mandatory creation of Centres of Patient Safety in health services and reporting of adverse events associated with patient care.
- Integrated surveillance on antimicrobial resistance and to reach consensus on a project to implement an integrated surveillance system antimicrobial resistance in the country.
- Act to prevent the misuse of antimicrobials.

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5. ”The Chennai Declaration”- A solution to the AMR problem in developing countries

1. Hospitals in Indian subcontinent have reported very high antimicrobial resistance rates. There is currently no functioning policy to contain antimicrobial resistance in India.

2. **“A Roadmap to Tackle the Challenge of Antimicrobial Resistance - A Joint meeting of Medical Societies in India**” was organized at Chennai on 24th August 2012. This was a historic event, the first ever meeting of medical societies in India on issue of tackling resistance, where all stake holders came under one roof.

3. The meeting was attended by representatives from most medical societies in India, eminent policy makers from both central and state governments, representatives of World Health Organization, National Accreditation Board of Hospitals, Medical Council of India, Drug Controller General of India, Indian Council of Medical Research along with well-known dignitaries in the Indian medical field. Six international experts shared action plans in their respective regions.

4. Bringing together medical societies and all other stakeholders in India is undoubtedly a huge challenge. Literally thousands of e-mails and phone calls, persuasion, persistence, moments of disappointments and discouragement and months of tireless work were necessary to realise a meeting of this magnitude.

5. **“The Chennai Declaration”** published in Indian Journal of Cancer, is the consensus evolved out of the meeting and co-authored by representatives of various medical societies. The document is based on realistic goals and objectives, with a deep understanding of the background Indian scenario.

6. The theme of the Declaration is **“a practical but not a perfect policy” for a developing country.**

7. The Declaration has looked into all major aspects of the problem, has suggested practical solutions to rationalise antibiotic usage over the counter and in hospital, strategies to step-up infection control and Microbiology laboratory facilities throughout the country and explained in detail roles responsibilities of each and every stakeholder.

8. The “Roadmap symposium”, per se received extensive coverage in news papers and magazines like “Nature”. Popular newspapers in India wrote about the “Declaration” in detail.

9. The document has also caught serious attention of high level political circles.

10. The Roadmap meeting and the Declaration has in fact changed the attitude of the medical societies and Indian authorities towards resistance issue.

11. This document has definitely made the authorities more receptive, which in fact was reflected in advertisement regarding antibiotic usage in newspapers, for the first time in Indian history.

12. Chennai Declaration efforts could mobilise medical societies and all the other stakeholders.

13. The declaration has provided an opportunity to the international community to view the problem of antimicrobial resistance in developing countries in a different perspective-sympathetic rather than critical.

14. Nine international medical journals including BMJ, Lancet ID, JAMA and CID published reviews on the document, an unprecedented approach in the modern medical academic arena. Chennai declaration is a topic of discussion in many prestigious international infectious diseases conferences.

15. Chief Medical officer of England in the annual report advised British Government to recommend Chennai declaration to all commonwealth countries.

16. Indian Ministry of Health has initiated internal consultation to explore ways of formulating an antibiotic policy incorporating Chennai declaration recommendations.

The Chennai Declaration created awareness among policy makers and the highest authorities on the need of a functioning antibiotic policy in India. This is a remarkable achievement in a country with no functioning antibiotic policy.

The declaration will surely gain much more momentum in the long run and can be the major driving force behind an antibiotic policy in India and many other developing countries.

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6. China and Sweden collaboration

Sino-Swedish Bilateral Cooperation on Management of Antibiotic Resistance

Antibiotic resistance is one of 21st century's greatest challenges to health security, with a direct effect on public health in all countries around the world, whether wealthy or poor. In a multidisciplinary bilateral cooperation China and Sweden have joined their efforts to address this challenging issue.

Antibiotic resistance costs lives, money and threatens to undermine modern basic healthcare and advanced medicine. The scale of the challenge grows as globalization and increased travel promote spread of resistance. Cooperation between countries is essential to find sustainable solutions to cope with resistance.

The ongoing Sino-Swedish bilateral cooperation stems from a Memorandum of Understanding between China and Sweden in the healthcare field from 2006 and a subsequent Plan of Action specifically emphasizing cooperation on antibiotic resistance signed by the Chinese and Swedish health ministers in 2010. The fact that China and Sweden are two such distinct countries in several aspects provides unique opportunities to design and test effective strategies to manage resistance in different contexts. China is the world's most populous nation and the situation with respect to overuse of antibiotics and antibiotic resistance is severe. Sweden on the other hand, is a small country with fairly limited antibiotic consumption and low levels of resistance. China has lately initiated radical changes in the health system within the ongoing Health Care Reform –of which several have direct implications for the rational use of antibiotics. This is a very advantageous circumstance for the potential impact of the Sino-Swedish cooperation. Strama is the Swedish strategic program against antibiotic resistance which focuses on rational antibiotic use; surveillance of antibiotic resistance and consumption; as well as infection control. The relatively favorable pattern of resistance in Sweden is interpreted as a result of long term and concerted efforts e.g. through Strama.

Ongoing subprojects within the cooperation:

- **Education**
  The emergence of antibiotic resistance is a complex problem driven by many interconnected factors. A key driver is antibiotic overuse and misuse. It is therefore important to ***make information on rational use of antibiotics common knowledge.*** One of the subprojects aims to educate the general public through interventions directed to school- and preschool children in both China and Sweden as well as residents of Green Communities in China.
- **Antibiotic use**
  Other subprojects aim to gain an insight into determinants of antibiotic use and to improve the rational use of antibiotics in the community, primary care and in hospitals. This is done through ***analysis of antibiotic prescription data*** and through exploring the ***knowledge, attitude and behavior of health care providers, rural population and policy makers.***
- **Prevalence of antibiotic resistance**
  Yet other subprojects focus on a unique mapping of the ***prevalence of extended spectrum ß-lactamase producing bacteria (ESBL) in clinical infections as well as in the normal gut flora of healthy rural residents.*** ESBL is one of the fastest increasing resistance mechanisms. We run an elevated risk to remain without effective treatments to certain infections in a close future if action to contain ESBL is not taken immediately.
- **Continuous communication on experience in antimicrobial resistance containment**
  Yearly bilateral workshops on resistance containment, ***exchange*** between the two countries on achievements and on-going work.

With the overall objective to grasp the situation and develop feasible interventions to address different aspects of the antibiotic resistance problem, the results of the cooperation may pave the way for future actions to tackle the problem of overconsumption and rising resistance in the world.

For further information on the Sino-Swedish cooperation on antibiotic resistance, please contact: Malin Grape, Swedish Institute for Communicable Disease Control, malin.grape@smi.se

The projects in the Sino-Swedish Bilateral Cooperation are carried out by prominent researchers and project leaders in China and Sweden:

Dr Xiao Yonghong, Professor, Chinese State Key Laboratory for Diagnosis and Treatment of Infectious Disease (SKLID), Zhejiang University, P.R. China

Dr Sun Qiang, Associate Professor, School of Public Health, Center For Health Management and Policy, Shandong University, P.R. China

Dr Jing Sun, Senior Researcher, National Institute of Hospital Administration, Ministry of Health, P.R China

Mr Zeng Hongying, Director of Education Department Centre for Environmental Education and Communications (CEEC), Ministry of Environmental Protection, P.R China

Dr Yu Yong, Associate Professor, the First Hospital Affiliated to the Chinese PLA General Hospital, Beijing, P.R. China

Dr Lennart E. Nilsson, Professor, Department of Clinical and Experimental Medicine, Linköping University, Sweden

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Honorary Guest Professor Shandong University

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7. Summary from India

1. Antimicrobial resistance remains a global problem which gains significance in developing countries like India. As per WHO bacterial disease burden in India remains to be the highest and antibiotic use has also been documented to be extensive. [1]

2. The primary issue concerning the medical fraternity here in India remains isolation of multi drug resistant, gram negative bacilli in tertiary care health centers particularly in the high risk patients. But it was felt that the resistance pattern seen at tertiary care centers may not be the same as in the community. So a need was felt to generate antibiotic resistance and use data from the community.

3. Community antibiotic resistance data was an issue because each time policy makers were posed the questions of development of antibiotic resistance and its misuse absence of data was a great impediment. As a result, no fund allocation could be argued for lack of evidence. Hospital based data of antibiotic resistance and use around the country is also scarce. Partial data generated by Indian Council of Medical Research (ICMR) or some private players in health care industry are available which does not represent the whole country. So, as a whole absence of data for antibiotic use and its resistance was acutely felt as missing in India.

4. It was with the help of WHO that a new methodology was tested for the first time for investigating antibiotic use and resistance in the community at three centers in India (New Delhi, Bangalore & Mumbai). Two phases of the study were successfully completed. All the three centers had almost similar findings. At Delhi center in phase 1, the methodology was successfully tested and results published [**2**]. In phase 2 interventions with stakeholders were conducted while use and resistance was also monitored simultaneously. The two phases were conducted for a period of one year each with a gap of 2 years (2004 & 2006). It was found that there was highest consumption of fluoroquinolones (J01MA) (1347DDDs/1000 population) followed by penicillin (J01C) (415 DDDs/1000 population), cephalosporin (J01DA) (381DDDs/1000 population) & macrolides, (J01FA) (336DDDs/1000 population)[3] in the community in North India. Antibiotic resistance in *E.coli* (n=1815) isolated from the community studied during the similar periods, showed highest overall resistance to 3 antimicrobials, ampicillin, naladixic acid & co-trimoxazole as 75, 73 & 59%, respectively.[2] Further resistance to even injectables like aminoglycosides represented by gentamicin was documented as 29.9% in this study.[2,3]

5. In India factors that were found to influence primary care physicians to prescribe antibiotics were diagnostic uncertainty, perceived demand and expectations from patients, practice sustainability, influence from medical companies and inadequate knowledge.[4]

6. Our primary burden of disease remains to be gram negative organisms like *Klebsiella pneumoniae, Acinetobacter* spp*. , E.coli &, Pseudomonas spp., followed by Candida tropicalis, Staph.aureus and Enterococcus spp*. in their order of isolation. The same organisms get reflected as hospital acquired infections (HAIs).

7. In a recent 10 years analysis of multi-drug resistant blood stream infections caused by *E.coli* & *Klebsiella pneumoniae* in a tertiary care hospital in North India the increase in isolation rate of both organism was found to be statistically significant (0.53 - 2.59, 0.14 -17.6 percent rate of change), respectively.[5] ESBL producing *E.coli* increased from 40% in 2002 to 61% in 2009. However, *Klebsiella pneumoniae* progressed to carbapenem resistance from 2.4 % in 2002 to 52% in 2009. In another 10 year trend analysis of antimicrobial consumption and development of resistance in non-fermenters in a tertiary care hospital in North India namely *Pseudomonas aeruginosa, Acinetobacter baumannii* were studied.[6] The overall antibiotic consumption rose from 158 to 390 DDDs/100 bed days with largest increase in the consumption of carbapenems. *Acinetobacter baumannii* resistance to 3rd generation cephalosporin, fluoroquinolones, aminoglycoside, betalactam & betalactam inhibitor combination (BL+BLI) and carbapenem documented was 88%, 86%, 80%, 80% and 74%, respectively. Similarly, in *Pseudomonas aeruginosa* resistance to 3rd generation cephalosporin, fluoroquinolones, aminoglycoside, BL-BLI combination and carbapenem was documented as 42%, 65%, 65%, 44% and 55%, respectively.[6]

8. The recent episode of NDM1 as one of the novel mechanism of resistance acquired by bacteria did see us in the eye of the storm. Thereafter, an urgent need has been felt to create a reliable data base across the country regarding the prevalence of antibiotic resistance in the community and hospitals. The Ministry of Health and Family Welfare Govt. of India is ceased with the burning issue of drug resistance, prescription auditing and hospital infection control (HIC) in the country, and has started an initiative in this direction [7]. Extensive guidelines have been made by the experts from all the fields of medicine, veterinary, agriculture and horticulture sciences involving Central Scientific and Industrial Research Organization (CSIR) as well. A schedule H1 has been created for top-end antibiotics, and drugs like cephalosporin, amikacin, carbapenems, glycopeptides and tigecycline are to be made available only at tertiary-care health facilities. While restrictions in the use of antibiotics in resource-constrained settings is an issue, therefore, cannot be viewed without balancing treatment access to poor in rural India, an issue put at the forefront by our Union Health Minister. For the first time in the current five year plan, the planning commission has allocated funds adequately to lay down the firm foundation of a network across the country to make the base-line data of antibiotic resistance & use available. A model work sheet has been developed by the expert group committee on rational antibiotic use and framing of antibiotic policy which has been web cast on the official web site of the National Centre for Diseases

Control (NCDC) earlier called as National Institute of Communicable Diseases (NICD) (http://www.scribd.com/doc/54122265/Indian-National-Policy-for-Containment-of-Antimicrobial-Resiatance-2011).

9. The challenges encountered in organizing a road map to understand antibiotic resistance and its use in our country remains to be huge due to its population and variations in life style of its people across the country. The major constraint remains balancing development of resistance to access to healthcare system. Overwhelming number of people below poverty line in rural settings due to absence of primary healthcare centers can not be denied treatment with antibiotics in the name of development of resistance.

10. However, while the above measures are being drafted by every state on advisory from central health services, it is to be understood India being a democratic country, health is a state subject and still expenditure on health sector is not impressive. Most of the health expenditure of a common man in India is out of pocket. It is very early to comment on the impact of above actions. It may be sometime before an impact of such measures can be known.

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8. The German Antimicrobial Resistance Strategy

1. Tackling Antimicrobial Resistances is of highest priority for Germany. In 2008 the German Antimicrobial Resistance Strategy (DART) was developed and published in a **joint collaboration** of the Federal Ministry of Health, the Federal Ministry of Food, Agriculture and Consumer Protection, and the Ministry of Education and Research together with further stakeholders from the health system. It consists a **human** and a **veterinary medicine part**. In the part of human medicine 10 goals and 42 actions on which Germany is focusing its efforts are defined, covering the following areas:

    I. Surveillance systems for antimicrobial resistance and antibiotic consumption
    II. Prevention and control measures for reducing antimicrobial resistances
    III. Cooperation and coordination
    IV. Research and evaluation

2. The DART strategy can be downloaded in English under: http://www.bmg.bund.de/fileadmin/dateien/Publikationen/Gesundheit/Sonstiges/DART_-_German_Antimicrobial_Resistance_Strategy.pdf

3. Successfully implemented activities are amongst others:

    - At the Robert Koch Institute an **antibiotic-resistance-surveillance-system** (ARS) has been developed and is continuously extended (https://ars.rki.de/). Currently data from more than 270 hospitals and 4.300 out-patient facilities are available in ARS. Additionally a system for antibiotic-consumption-surveillance at the Robert Koch-Institute is constructed with data on cousmption from ambulatory and stationary care. Since 2011 hospitals are legally obligated to set up an **antibiotic consumption surveillance**.
    - A **training programme for Antibiotic Stewardship** (ABS) has been developed and established (http://www.antibiotic-stewardship.de/cms/). The programme is well received among physicins and hospital pharmacists and will be continually further developed. An alumni-network has been set up in 2011 with the aim to evaluate and continually improve the prescription of antibiotics in hospitals.
    - In 2012 the **Commission for Antiinfectives, Resistance and Therapy** was appointed and set up at the Robert Koch-Institute. Main task of the Commission is to compile available guidelines on antibiotic therapy and diagnostic and when deemed necessary initiate in close collaboration with scientific societies the development of new guidelines or the update of existing guidelines.
    - According to an adaptation of the German Infection Protection Act in 2011 **guidelines by the Commission for Hospital Hygiene and Infectious Disease Prevention** at the Robert Koch-Institute and those of the newly

established Commission for Antiinfectives, Resistance and Therapy **are mandatory**. In addition the Länder authorities were legally obligated to pass regulations on infection control and prevention for medical care facilities.

- **Nationwide regional networks** on the prevention and control of antimicrobial resistance involving necessary partners from the ambulatory and stationary care sector have been established. Their aim is to agree on consistent measures in the prevention and control of resistant pathogens, to provide training on a local level and to assure high-quality care (http://www.rki.de/DE/Content/Infekt/Krankenhaushygiene/Netzwerke/Tabelle_Uebersicht.html).
- Since 2012 the German MoH is funding several **research** projects over a period of three years, focussing on the following topics: "Promotion of outcome-oriented intervention-studies", "Qualification of specialised personnel", "Promoting pilot-projects on cross-sectoral care to avoid antibiotic resistances and nosocomial infections", and "Further development of quality assurance".

4. Latest Data of the national surveillance system for antimicrobial resistances (ARS) show a slightly decreasing MRSA-ratio, confirming the joints efforts of the German Antimicrobial Resistance Strategy.
5. In 2013 an **evaluation** and further development of the strategy is taking place aiming to define necessary adjustments due to new developments in the field of antimicrobial resistance. The publication of the refined strategy is planned for June 2014.
6. Tackling antimicrobial resistance can only succeed through common, international efforts and close collaboration. Germany is interested in international partnerships and is prepared to share it's knowledge and experience in combating antimicrobial resistances.

9. Tackling Antimicrobial Resistance in Malaysia

1. In 2003 the Ministry of Health of Malaysia with the assistance of WHO prepared a national strategy for the containment of antimicrobial resistance. The measures included the establishment of Infection And Antibiotic Control Committees (IACC) at hospital, state and national levels, strengthening the antibiotic resistance surveillance system in the country, developing and implementing antibiotic guidelines for hospitals as well as primary care 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 in agriculture.

2. A National Committee on Infection and Antibiotic Control was established and this committee continues to meet twice a year. The committee is chaired by the Director General of Health and attended by all state representatives and selected technical experts. The Committee receives reports on antibiotic resistance rates, nosocomial infection prevalence rates, antibiotic utilization data on selected agents as well as reports on specific topics like nosocomial tuberculosis and accidental needlestick injuries. Initially the hospitals participating in supplying data were the major Ministry of Health hospitals and the teaching hospitals under the purview of the Ministry of Education. Over the years the number of participating hospitals have increased and now include the smaller government hospitals as well as some private hospitals. The National Committee makes policies and recommendations based on the data collected.

3. A National Surveillance of Antibiotic Resistance programme in Malaysia has been established since 1990. All participating hospitals employ a standard methodology (CLSI) as well as standard antibiotic panels. The results are collected and analysed using the WHONet software. A concomitant quality assurance programme on susceptibility testing was also established. In addition there is national monitoring of selected alert organisms namely MRSA, ESBL Klebsiella and carbapenem resistant organisms. Hospitals compile line listing of all infected or colonised patients and submit the data on a monthly basis to the Quality Assurance Division of Ministry of Health which publishes the incidence rate based on the number of new patients infected or colonised per 100 admissions. Some success has been achieved in reducing the rates of transmission and the overall prevalence in MRSA (Fig 1).

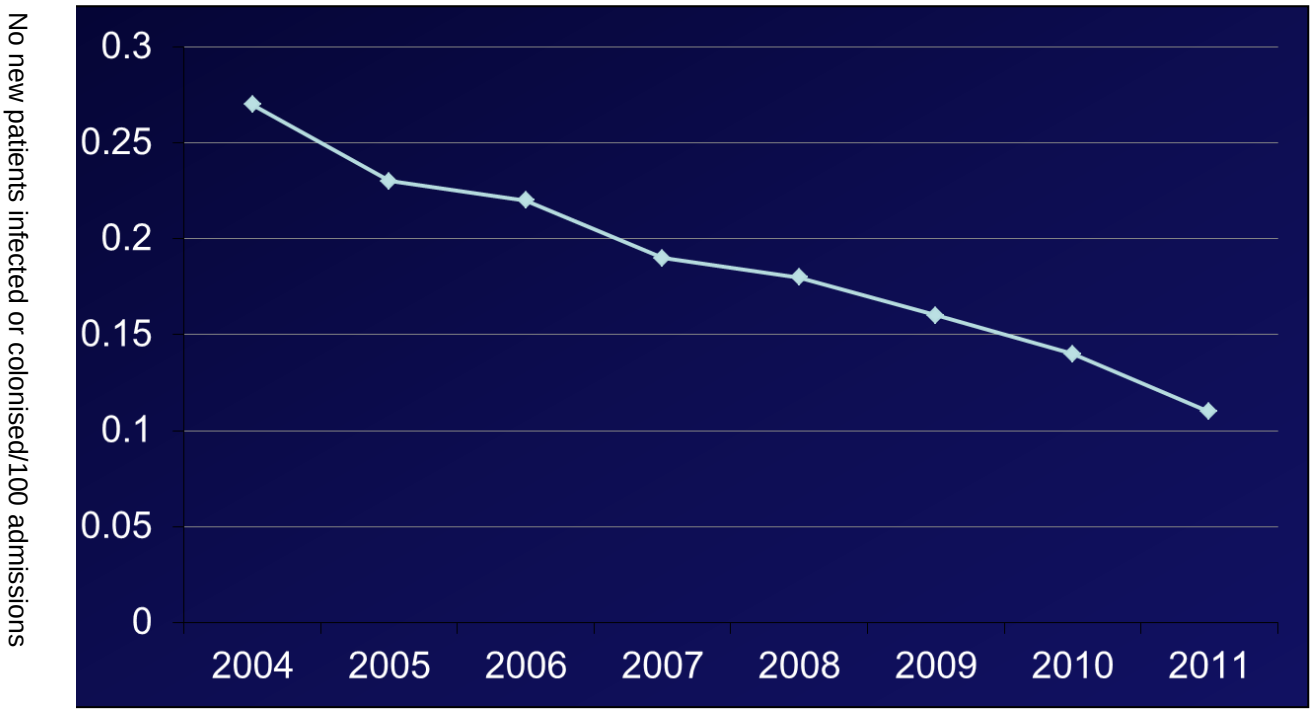

Fig 1. Incidence of MRSA in Malaysian hospitals (2004 – 2011)

5. Under the National Nosocomial Infection Surveillance Programme, prevalence studies are conducted twice a year on fixed dates. A standard definition of the various health-care associated infections is employed and universal surveillance is conducted on the defined day by all participating hospitals. The data is collected, analysed and published by the Quality Division of the Ministry of Health. In addition to the prevalence studies, incidence rates of ventilator-associated pneumonia in ICUs of major government hospitals are also routinely monitored.

6. National drug utilization studies started in 2004 and are conducted on an annual basis. Data is collected from both public and private sectors and include data from primary to tertiary care facilities. The ATC classification system is used for this purpose and the unit of measurement is expressed as daily defined doses according to WHO recommendations. In 2007 the overall antibacterial use was 9.64 DDD/1000 population/day which compared to European data is quite low.

7. Antibiotic use of selected classes of antimicrobials is also monitored in government hospitals. The classes monitored include cephalosporins, quinolones, carbapenems and glycopeptides. The data expressed as DDD/100 admissions to allow for comparison between hospitals. This data is submitted to the National Infection and

Antibiotic Control Committee where outliers are identified and remedial measures taken.

8. The Ministry of Health has a national formulary and also publishes national antibiotic guidelines on antibiotic usage in government hospitals and clinics. Individual hospitals are allowed to modify these guidelines to suit their needs. In the private sector, doctors are at liberty to use any product so long as it is registered by the Drug Control Authority. Specialists function as independent contractors in private hospitals where financing is largely through out-of-pocket payments. Control of antibiotic use is therefore difficult in the non-governmental sector.

9. Professional societies issue practice guidelines regularly but the effectiveness of these guidelines is questionable.

10. Malaysia is a participant in the Global Patient Safety Challenge on hand hygiene and antimicrobial resistance. On 16 Oct 2012 the Minister of Health launched the National Campaign on the Containment of Antimicrobial Resistance where many activities were organised over a month to increase public awareness on the issue of antimicrobial resistance. However the education of prescribers and consumers alike is still a largely uncoordinated effort. Prescriptions, dispensing and sales of antibiotics for medicinal use in Malaysia are controlled by legislation and enforcement has been quite effective. There is slower progress in regulating antibiotic use in agriculture. Marketing and promotional activities by pharmaceutical companies are still largely through self-regulation.

11. Malaysia has put in some measures to promote antibiotic stewardship but there is still a need to do more. The engagement with all major stake holders needs to be enhanced. Public awareness is still lacking and it is still difficult to involve the private health care sector.

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10. Dutch experiences and policy in the combat against antibiotic resistance

1. Development of antimicrobial resistance is an international threat. It is important to prevent health damage due to antimicrobial resistance. In the Netherlands the antimicrobial resistance is slightly increasing.

Human health care system

2. The use of antibiotics in human healthcare in the Netherlands is one of the lowest compared to other European countries. We would like to offer to share our knowledge on combating antimicrobial resistance. This can contribute to the prudent use of antibiotics in mondial healthcare.

3. In the Dutch healthcare system the responsibility for prudent use of antibiotics and prevention of transmission of infections is at the level of the healthcare professionals. This is a well working system because of the commitment of these professionals. Development of these guidelines is financially supported by the Dutch government. The guidelines are enforced by the healthcare inspectorate.
    a. The professionals develop guidelines themselves to optimize the use of antibiotics. The professionals are now working on an implementation plan for antibiotic stewardship in the Dutch health care.
    b. The professionals also develop standards for the prevention infections in hospitals.

4. Surveillance is also very important in the combat against antimicrobial resistance. This contains both the development of resistance and the usage of antibiotics in the human health care.

5. In the Netherlands it is impossible to receive antibiotics without a doctor's prescription.

Veterinary system

6. Unfortunately in the Netherlands there is a high use of antibiotics in the veterinary sector (food production animals). In the Netherlands we are working very hard to reduce this high intake. Our efforts seem to work. Last few years there was a major reduction of the veterinary use. Some antibiotics are critical for human healthcare. The Netherlands is very much in favour of preserving the use of those antibiotics for human healthcare only, and banning the veterinary use.

Development of new antibiotics

7. The Netherlands appreciate the different efforts like the work done by the European Commission to address the need for new drugs, through the Innovative Medicines Initiative as well through the 7th Framework Programme. The Netherlands life sciences sector, including our private sector, is a strong partner in these initiatives.

8. The development of new antibiotics is very important in combating the microbial challenge globally. Together we need to explore ways to influence the dynamics in product development.

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11. A UK five year antimicrobial resistance strategy

1. A wide programme of work to tackle AMR has been underway across the UK in human and animal health sectors for a number of years. The first 'UK Strategy', published in 2000, was developed in response to the recommendations contained in the Standing Medical Advisory Committee report 'Path of Least Resistance' produced in 1998. This has led to some significant changes, including improvements in antibiotic use, increased funding for drug discovery programmes and extra support for research in the field of AMR in the UK.

2. Through improvements, in part, to clinical practice and hand hygiene, MRSA bloodstream infections have been cut by 87% per cent and are now at the lowest levels since mandatory surveillance was introduced in 2001. *C. difficile* infections are at the lowest recorded since mandatory surveillance for the over 2s was introduced in 2007. However, there is much still to be done. The *Chief Medical Officer's (CMO) annual report, volume II*, published in March 2013, focused on infectious diseases as its key theme. The report set out the scale of the threat of antimicrobial resistance (AMR) and the case for further action.

3. The UK recognises the dynamic and interrelated nature of AMR requires better control in all sectors, environmental, agricultural, food production, animal health and human health. The UK Government is committed to taking an integrated approach to tackle the AMR challenge as part of the *one health agenda* at a national and international level. The Government and its key partners recognise the need to act promptly and comprehensively to minimise the implications for human and animal health and welfare and avoid a return to the pre-antibiotic era.

4. The UK strategy is due for publication in the summer and was developed with input from a wide range of experts. It sets out an approach that seeks to conserve the antibiotics we have, ensure they are used optimally in both humans and animals, reduces the risk of cross infection and overhauls arrangements for developing new antimicrobials and technologies to allow quicker diagnosis and treatment. The strategy makes it clear that everyone has a responsibility and role to play in making this happen and includes a call to action across all sectors. The approach seeks to achieve a balance between addressing national issues and tackling those challenges that require global solutions through improved collaboration.

5. A wide range of activities will be set in train across a number of organisations to address the following seven priority areas:

- optimising prescribing practice by promoting responsible prescribing and effective administration of antimicrobials,
- improving infection prevention and control practices in human and animal systems,
- raising awareness and changing behaviour activity to support better stewardship, improving public and professional knowledge and promoting changes in behaviour and practices,
- improving the evidence base through research to inform understanding of AMR, alternative treatments to new drugs as well as new or improved diagnostic tests for humans and animals,
- development of new drugs, vaccines other diagnostics and treatments by facilitating and encouraging their discovery and development,
- improving the evidence base through surveillance**,** strengthening epidemiological data and data linkage arrangements,
- strengthening UK and international collaboration by leading initiatives that aim to deliver data and technology sharing across animal and human health fields at a global level.

5. The UK strategy also recognises that we have a limited understanding of the development of AMR and resistance mechanisms and aims to improve the evidence base in a number of areas.

6. A High level Steering Group with representatives from across UK Government Departments and agencies will be convened to oversee implementation of the Strategy, develop detailed outcome measures in the following areas:
   - trends in key human "drug/bug" combinations identified to successfully control and contain resistance,
   - improvement in public and professional knowledge and understanding of antimicrobials and their appropriate use, improving quality of prescribing in primary and secondary healthcare settings compared to the position in 2012,
   - reducing the use of antibiotics in animals, in particular, the WHO defined 'Top three' CIAs in human medicine,
   - strengthened global security by development of a roadmap to tackle AMR that can be used by WHO, FAO, OIE, EU and others to assist global alignment in tackling AMR.

   It will also assess the impact of the strategy and produce an annual report on progress.

A NEW UK ANTIMICROBIAL RESISTANCE STRATEGY 2013-18

Department of Health

Background

Antimicrobials, especially antibiotics, are important and valuable agents. Without them routine medical practices such as hip replacements and cancer chemotherapy would become much riskier. The rapid emergence and international spread of multi resistant organisms combined with the lack of new therapies means there is a risk that could in future become more life threatening.

Previously we relied on fighting resistant micro organisms with drugs but this is becoming more difficult as very few new drugs are in the development pipeline, especially for Gram negative infections. Developing new therapeutic treatments takes time. It is important to act now to contain resistance. Good infection prevention and control is central to this.

Action to date

Antimicrobial resistance (AMR) is not a new problem and the UK has had a strategy and Action Plan in place since 2000[1] to tackle the issue. A wide ranging programme of work has been undertaken which has led to improvements in antibiotic prescribing. However, more needs to be done if we are to keep pace with developments in AMR.

New approach

The strategy has three key objectives:

- **slowing down the development and spread of AMR** - this will be achieved by improving our understanding of AMR, using data from surveillance and diagnostics to better effect in terms of containing transmission of infections acquired at home and abroad and promoting good clinical practice in prescribing antibiotics.
- **maintaining the efficacy of existing antimicrobials** - this will be achieved by applying stricter infection prevention and control practices, optimising prescribing practices and embedding antimicrobial stewardship programmes that ensure antibiotics are used only when needed and then in the right way, at the right dose and for the right duration.
- **supporting the development of new antimicrobials and alternative treatments** - this will be achieved by closer working with regulatory bodies, the World Health Organisation (WHO), the European Union (EU) and other partners to promote international activity to stimulate the antibiotic pipeline, encourage innovative approaches to develop diagnostics, new antibiotics and novel therapies.

The proposed new five year UK cross government AMR Strategy has been developed with the involvement of a wide range of expertise and is expected to be published in the Summer.

Monitoring results / outcome

National outcome measures will be developed to help monitor progress and assess the impact the Strategy is making in addressing AMR issues in the UK. Measures will include controlling the development of resistance by establishing the baseline and subsequent trends in key "drug/bug" combinations as determined by surveillance data.

Drug/bug combinations to be monitored in the first instance:

- Klebsiella - carbapenem (% non-susceptible to imipenem &/or meropenem)
- *E. coli* - cephalosporin (% non-susceptible to cefotaxime &/or ceftazidime)
- *E. coli* - fluoroquinolone (% non-susceptible to ciprofloxacin)*
- Pseudomonas - carbapenem (% non-susceptible to imipenem &/or meropenem)
- *N. gonorrhoeae* - ceftriaxone (% non-susceptible
- Klebsiella - cephalosporin (% non-susceptible to cefotaxime &/or ceftazidime)
- Pseudomonas - cephalosporin (% non-susceptible to ceftazidime)
- *E. coli* - gentamicin (% non-susceptible)
- *S. pneumoniae* - penicillin (% non-susceptible)

Conclusions

We cannot undo the harm that has already been done, but more can be done to minimise further harm, reduce the risk of cross infection and improve patient safety, animal health and welfare. This will require a concerted effort by all parties to eliminate poor practice, improve antibiotic prescribing and administration and develop new approaches to manage infectious disease in future.

We need to get to a point where:

- good infection prevention and control measures to help prevent disease occurring become the norm in all sectors of human and animal health rather than reliance on antibiotics,
- infections can be diagnosed quickly and the right treatment deployed,
- patients and animal keepers fully understand the importance of treatment regimens prescribed and adhere to them,
- surveillance is in place which quickly identifies new threats or changing patterns in resistance, and
- there is a sustainable supply of new, effective antimicrobials.

Going forward we need even stronger international partnerships and so that the threat of AMR is fully recognised and understood, with responsibility for reducing it shared. That is why we are keen to discuss with the World Health Organisation (WHO) and others what more can be done to tackle the issue and achieve real progress in key areas within the next few years.

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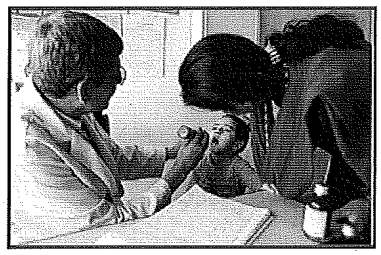
12. WHO Antimicrobial Drug Resistance

World Health Organization

Pandemic and Epidemic Diseases



WHO /Tom Pietrasik

Antimicrobial Drug Resistance

A world where infectious diseases can be prevented or treated with safe, effective and accessible medicines.

PANDEMIC AND EPIDEMIC DISEASES

Engagement and support opportunities

A growing threat worldwide

Discovery of antimicrobial medicines has saved million lives.

However, these advances are now accompanied by a **growing threat: the emergence of microorganisms resistant to our most effective medicines.**

Impacts

Numerous infectious diseases becoming **harder and sometimes impossible to treat;**

Infectious diseases are **more expensive to treat;**

Higher fatality rate from infection by drug-resistant pathogens;

New forms of resistance **rapidly spread worldwide and outpace solutions.**

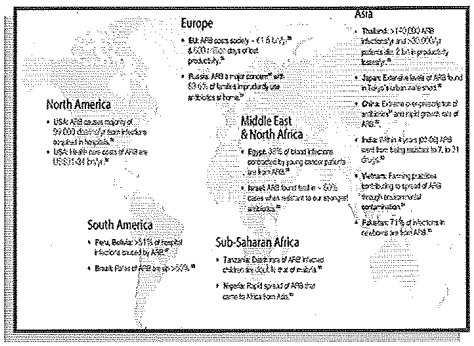
The annual cost to the US of health care–associated antibiotic-resistant infections is estimated at more than **$21 billion and at 1.5 billion €** in the European Union.

5% of tuberculosis (TB) patients have multi-drug resistant TB (MDR-TB) and the cost for 1 MDR-TB treatment equals the costs for **100 susceptible TB cases.**

Mandate and mission

- WHO will work across existing programmes and initiatives to **promote intersectoral and interagency coordination** to identify priority issues, strategies and actions.
- The AMR Team under the PED Department facilitates coordinated actions through the **WHO AMR Global Task Force**, a collaboration across headquarters and WHO Regional Offices.

Figure 1. Spread of antibiotic resistant bacteria worldwide[1]



The department of Pandemic and Epidemic Diseases (PED) develops strategies, initiatives, and mechanisms to address priority emerging and re-emerging epidemic diseases, including outbreaks, thereby reducing their impact on affected populations and limiting their international spread.

PANDEMIC AND EPIDEMIC DISEASES

Strategic Axes

I. Raising Awareness and Stakeholder Engagement

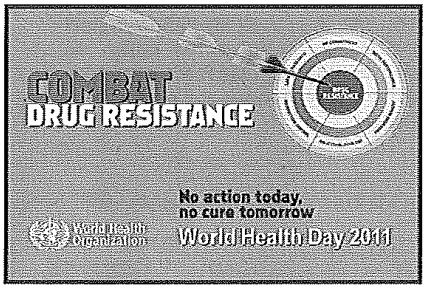
So that... public become aware AMR is a major issue and governments commit to tackle this challenge urgently.

II. National Capacity Building

So that... countries are prepared with policies, strategies and structures in place that enable knowledge-based actions and promote behavioural change.

III. Innovation, Research and Development

So that... development of new tools and knowledge is fostered to tackle AMR.



Examples of on-going activities[2]

Strategic axis I **Raising Awareness and Stakeholder Engagement**
• Launched in March 2012: "The evolving threat of antimicrobial resistance: options for action"
• Development of a communication strategy to improve awareness at multiple levels across key sectors
• Convene regional and global stakeholder consultations to increase coordination and alignment of strategies
Strategic axis II **National Capacity Building**
National stewardship and coordination
• Support country level assessment of capacities and priorities
• Support development and implementation of national AMR action plans
Coordinated systems and standards for global AMR surveillance and laboratory capacity
• Development of the WHO Global AMR report
• Development of agreed surveillance standards
• Fostering collaboration between AMR surveillance networks, including animal health sector
• Strengthening the quality of laboratory results (e.g. through systems such as EQAS)
Improved access to antimicrobials of assured quality
• Continued support for development of WHO model and national essential medicines lists
• Support to national authorities for equitable access to antimicrobials of assured quality
Improved rational use of antimicrobials for human and animal health
• Improve rational use of antimicrobials in humans and animals (e.g., concept of "critically important antibiotics" for human medicine; promote effective regulatory practices)
• Reporting on global trends of use of antimicrobials in humans
• Collaboration with animal health sector, to monitor antimicrobial use in animals
Prevention of emergence and spread of AMR in healthcare settings
• Development of standards to control spread and emergence of AMR in healthcare settings
• Development of an AMR outbreak investigation and response tool
• Development of guidance on implementation of infection prevention and control programmes
Strategic axis III **Innovation, Research and Development**
• Development of international public health research agenda for AMR
• Fostering new business models for development of new prevention, diagnostic or therapeutic tools

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[1]Source: World Economic Forum, Global Risk Report 2013 [2] As of May 2013
More information is available on the WHO website: www.who.int/druoresistance/en/index.html