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Expert consultation on antimicrobial resistance

Report on a meeting

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ABBREVIATIONS

AMR	Antimicrobial Resistance
ARMed	Antimicrobial Resistance in the Mediterranean
CIA	Critically Important Agents
CISID	Centralized Information System for Infectious Diseases
CLSI	United States Clinical and Laboratory Standards Institute
Codex	Codex Alimentarius Commission
CGD	Center for Global Development
DDD	Defined Daily Dose
DG SANCO	European Union Directorate General for Health and Consumer Affairs
DOTS	Directly Observed Treatment – Short-course
DST	Drug Susceptibility Testing (for tuberculosis)
EAAD	European Antibiotic Awareness Day
EARS-Net	European Antimicrobial Resistance Surveillance Network
EARSS	European Antimicrobial Resistance Surveillance System
ECDC	European Centre for Disease Prevention and Control
ECV	Epidemiological Cut-off Values
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESAC	European Surveillance of Antimicrobial Consumption
EU	European Union
EUCAST	European Committee for Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization
MDR-TB	Multidrug-resistant tuberculosis
MRSA	Methicillin-Resistant *Staphylococcus aureus*
TB	Tuberculosis
TATFAR	Trans-Atlantic Task Force on Antimicrobial Resistance
TESSy	The European Surveillance System
WHA	World Health Assembly
WHD	World Health Day
XDR-TB	Extensively drug-resistant tuberculosis
WHAAT	WHO Hospital Antibiotic Audit Tool
WHO AGISAR	WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance

1. INTRODUCTION

Antimicrobials are the mainstay of therapy in the treatment of infectious disease, and are essential elements of modern medical practice including safe surgery, chemotherapy, organ transplantation, and prosthesis placement. Use and particularly overuse of antimicrobials decimates susceptible microbial populations permitting resistant strains to thrive, while conditions of poor sanitation in communities and poor hygiene in health care settings promotes the movement of resistant organism to new vulnerable communities locally and in many instances worldwide.

Recognizing the threat to human welfare of resistant pathogens and their drain on limited health care resources, WHO has promoted policies and activities which aim to provide effective therapeutic agents for patients today, to preserve the efficacy of antimicrobials for future generations; to decrease the need for antimicrobials through disease prevention and infection control; and to direct resources into the development of new treatment options and diagnostic tools.

An extensive series of expert consultations, consensus meetings, and reviews of existing policy documents and evidence base culminated in the publication in 2001 of the WHO Global Strategy for Containment of Antimicrobial Resistance. The document included a set of 67 prioritized recommendations targeting national governments, health care workers and pharmacists, veterinary and food production professionals, industry, researchers, media, consumers, and the general public based on the following principles:

- reduction of disease burden and the spread of infection
- improved access to appropriate antimicrobials
- improved use of antimicrobials in human, animal, and industrial applications
- appropriate regulation and legislation
- surveillance of antimicrobial resistance
- focused research.

Through resolutions passed by the World Health Assembly (WHA), WHO Member States have highlighted not only the public health threat of resistant organisms, but also the harm caused by misuse of antimicrobials by patients, prescribers, and drug dispensers.

> WHA51.17 – Emerging and other communicable diseases: antimicrobial resistance, 16 May 1998
> WHA54.14 – Global health security: epidemic alert and response, 21 May 2001
> WHA58.27 – Improving the containment of antimicrobial resistance, 25 May 2005
> WHA60.16 – Progress in the rational use of medicines, 23 May 2007
> WHA62.15 – Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, 22 May 2009

A WHO Global Strategy Implementation Workshop, including regional advisers from all six WHO regions was held in Geneva on 25–26 November 2002 to review strategies and actions by the WHO European Regional Office for implementation of the recommendations of the WHO Global Strategy.

This was followed in the WHO European Region by a WHO Workshop on the Containment of Antimicrobial Resistance in Europe on 26–27 February 2004 with the goals:

- examining the situation in the European Region regarding antimicrobial use and resistance trends;
- ascertaining specific issues of antimicrobial use and resistance in a range of eastern European WHO Member States;
- increasing awareness of the WHO Global Strategy and promoting implementation of its recommendations.

In the present meeting, international experts were invited to provide guidance to the WHO Regional Office for Europe in two areas:

- framework and priorities for the WHO Regional Strategy for Containment of Antimicrobial Resistance in Europe to be finalized by the Regional Committee in March 2011; and
- strategies, partnerships, and activities for World Health Day 2011 on antimicrobial resistance.

In the European Region, especially within the borders of the European Community, several international meetings on the subject of antimicrobial resistance were organized including workshops and conferences in Visby (1994), Verona (1997), and Copenhagen (1998, The Copenhagen Recommendations Report from the Invitational EU Conference on the Microbial Threat), as well as the creation of expert networks dealing with antimicrobial resistance such as the European Antimicrobial Resistance Surveillance System (EARSS), the European Surveillance of Antibiotic Consumption (ESAC) and others. Several of these surveillance networks have now been or are in the process of being incorporated in the European Centre for Disease Prevention and Control (ECDC). Since 2008, European Antibiotic Awareness Day (EAAD) has taken place on 18 November, with substantial materials and information made available to the general public, health care providers, national authorities, and other stakeholders.

On 6–8 September 2010, Uppsala University and ReAct (Action on Antibiotic Resistance) hosted the conference "The Global Need for Effective Antibiotics – Moving towards Concerted Action" in Uppsala, Sweden. This invitational conference built upon and deepened the discussions held at the expert meeting on "Innovative Incentives for Effective Antibacterials" organized by the Swedish EU Presidency in the fall of 2009. The event, attended by many international experts, further highlighted the need to address the emergence of antimicrobial resistance as a global priority.

Considerable progress on surveillance of antimicrobial resistance and the prudent use of antibiotics has been made within the borders of the European Union, but much less has been achieved in other Member States of the WHO European Region.

2. THE WHO REGIONAL STRATEGY TO CONTAIN AMR

2.1 Opening remarks

Zsuzsanna Jakab, Regional Director, WHO Regional Office for Europe, Copenhagen, Denmark

Antimicrobial-resistant pathogens are major causes of morbidity and mortality in Member States of the WHO European Region, and integrated multi-level coordination is required for effective action. Dr Jakab thanked the meeting participants for their assistance to WHO in the

identification of strategies and priorities to be undertaken by WHO in this area in partnership with Member States, health care providers, industry, media, researchers, patient advocacy groups, and other stakeholders.

Resistant microorganisms lead to prolonged suffering and often death in patients with pneumonia, HIV, sepsis, meningitis, health care-associated infections, typhoid fever, malaria, and sexually-transmitted infections. An estimated two thirds of the estimated global burden of disease attributable to multidrug-resistant tuberculosis (MDR-TB) is found in the WHO European Region, along with an astonishing 15 of the 25 countries with the highest rates of MDR-TB worldwide.

The purpose of this one-day meeting is to elicit input on the direction of WHO activities from experts in infectious diseases, microbiology, antimicrobial use and national medicines policy, infection control, animal health, food safety, and media communications. Two priorities for guidance defined by Dr Jakab were:

- the WHO Regional Strategy for Containment of Antimicrobial Resistance in Europe
- World Health Day 2011: antimicrobial resistance and its global spread.

The WHO Regional Strategy for Containment of Antimicrobial Resistance in Europe (hereafter referred to as the WHO Regional Strategy for AMR) will address implementation of the recommendations to WHO and Member States established in the 2005 World Health Assembly resolution WHA58.27 “Improving the containment of antimicrobial resistance”. Given recent successes in European Union member countries of surveillance activities, legislative action, and education and advocacy campaigns, the WHO Regional Strategy will prioritize the needs of non-EU member countries in order to raise awareness of antimicrobial resistance as a public health threat and generate resources and political support for action.

World Health Day 2011 will take place on 7 April 2011 and has been dedicated worldwide to the subject of antimicrobial resistance with “a special focus on the HIV/AIDS, tuberculosis and malaria and other diseases”. Issues of particular importance in the WHO Regional Strategy for AMR highlighted by Dr Jakab include MDR-TB, as mentioned earlier, infection control and health care-associated infections, and prudent use of antimicrobials. Since 2008, European Antibiotic Awareness Day (EAAD) has been coordinated by the European Centre for Disease Prevention and Control (ECDC), and Dr Jakab indicated that a review of the EAAD successes and materials would prove valuable in developing effective communications and advocacy campaigns for World Health Day 2011.

After completion of these opening remarks, Dr Jakab proposed Dr Gunnar Kahlmeter as chairperson of the meeting and Dr John Stelling as rapporteur, and these nominations were accepted by meeting participants.

2.2 The WHO Regional Strategy

Bernardus Ganter, Senior Adviser, Antimicrobial Resistance, Division of Communicable Diseases, Health Security and Environment, WHO Regional Office for Europe, Copenhagen, Denmark

The WHO Global Strategy for Containment of Antimicrobial Resistance provides a framework for prioritized actions to be undertaken by: patients and the general community, prescribers and dispensers, hospitals, professionals involved in food-animal production, national governments and health systems, pharmaceutical and diagnostic industry, and researchers. Several European Member States and their experts have been leaders worldwide over the past ten years in establishing political commitment to containment of antimicrobial surveillance, surveillance of consumption and resistance, promotion of rational drug use in hospitals and primary health care, elimination of antimicrobials as growth promoters in food-producing animals, and research.

The goal of a WHO Regional Strategy for AMR is to provide strategic directions, to build on and expand the success of existing initiatives in Europe, in particular those currently active within the borders of the European Union, and to address gaps and weaknesses of current structures and activities with special recognition of the needs of non-European Union member countries in which political commitment for antimicrobial resistance containment is lacking, coordination among relevant professions and institutions is weak, and basic laboratory, health care and IT infrastructure has room for improvement.

The Regional Strategy should be seen as an effort to strengthen health care systems, especially in those components needed to address the complex nature of antimicrobial resistance and involving many stakeholders. It will focus on a holistic and intersectoral approach and prioritizes strategic actions for implementation at different levels of the health care system including ministries of health, national institutes of health, national references centres, health care institutions, and the agricultural sector.

The draft WHO Regional Strategy for AMR consists of seven components.

- National coordination. The establishment of a national intersectoral task force to raise awareness about antimicrobial resistance, organize data collection and oversee local national activities with sufficient resources and defined responsibilities is recommended in all Member States. An effective national programme is contingent upon political commitment by all stakeholders and mechanisms for data collection and interpretation, policy development, and coordinated action including regulations, continuous education, and guidelines.

- National public health surveillance of antimicrobial resistance. A second priority is to "designate or develop reference microbiology laboratory facilities to coordinate effective epidemiologically sound surveillance of antimicrobial resistance among common pathogens in the community, hospitals and other health care facilities". This requires sufficient laboratory and epidemiological capacity at national level and regional collaboration. The ECDC-coordinated European Antimicrobial Resistance Surveillance-Network (EARS-Net) should be used as an efficient and well tested example, and the WHONET data collection software has proven critical in many countries of the Region for achieving surveillance objectives. Quality assurance and standardization of laboratory methods across the Region are needed.

- National strategies for improving antimicrobial use and surveillance of antimicrobial consumption. Improved antimicrobial use involves action directed at many levels – drug regulatory authorities, antimicrobial prescribers and dispensers, health educators, patients and their families, and the pharmaceutical industry – and includes the establishment of effective national drug authority and policy as described by the WHO Medicines Department and adherence by prescribers with Standard Treatment Guidelines and Good Prescribing Practice recommendations. Surveillance of antimicrobial use, as exemplified by the European Surveillance of Antimicrobial Consumption (ESAC) project, provides a powerful advocacy tool for raising political support for appropriate use campaigns and a valuable monitoring tool to assess progress towards goals.

- Health care-associated infections. Patients seeking assistance from the health care system enter with the assumption that they enter a safe environment. Unfortunately, the intensive use of antimicrobials in health care establishments and opportunities for transmission among patients and clinical staff do pose important risks to vulnerable populations, including the acquisition of multiresistant pathogens in life-threatening infections. The establishment of functioning infection control teams to guide and institute hygiene and other disease prevention measures is required, especially in reference and teaching hospitals. Data on antimicrobial resistance and health care-associated infections should be collected and fed into national surveillance networks.

- Antimicrobial use and resistance in food animals and agriculture. A safe food supply requires the administration of antimicrobials to animals to ensure continued good health. However, the resulting selection pressure for resistant pathogens in animal populations poses direct (via foodborne-pathogens) and indirect (via gene transfer among microbial strains) threats to human health. Good agricultural practices must therefore balance the demands of animal welfare and food safety against the risks posed to human populations. Meaningful surveillance data related to antimicrobial use practices are critical to risk assessment initiatives and to guide risk management efforts.

- Research and innovation. The ongoing selection and movement of resistant microbes can be mitigated through sustained public health action, yet not avoided. Resistant strains continue to emerge and spread, yet resources directed to new antimicrobial development are decreasing. Consequently ongoing research is required so that future generations have safe and effective agents with which to treat infected patients. Priority areas of research are: 1) improving the use of existing antimicrobials through compliance with rational use guidelines; 2) development of new technologies (e.g. rapid diagnostics to support targeted therapy decisions), new antimicrobial agents, and alternative treatment modalities; and 3) disease prevention through specific (e.g. vaccine) or nonspecific (e.g. improved hygiene and patient nutritional status) advances to decrease the need for antimicrobials.

- Partnerships, awareness, and advocacy. Containment of antimicrobial resistance requires action at many levels, yet effective partnerships are often lacking, and broad awareness is needed to reach sustained commitment for action at the highest levels. Effective educational messages and containment initiatives require thorough understanding of the local drivers of consumer, prescriber, and organizational behaviour. Collaborations among scientists, national authorities, media communications experts, and industry among many other stakeholders are the key to translating principles of good practice to

improved patient outcomes. Consumer and patient safety groups are crucial to further promote the prudent use of antibiotics and preventive measures.

3. PARTICIPANT PRESENTATIONS AND ROUNDTABLE DISCUSSION

3.1 University of Antwerp – Vaccine and Infectious Disease Institute

Herman Goossens, Department of Medical Microbiology, University Hospital Antwerp, Edegem, Belgium

The Vaccine and Infectious Disease Institute coordinates an active programme for public health surveillance of antimicrobial consumption, molecular and epidemiological research, and development of point-of-care diagnostic tests for the detection of bacterial and viral pathogens causing hospital and community infections.

An important role of the Institute relevant to the WHO Regional Strategy for AMR is their leadership in coordinating three projects for surveillance of antimicrobial consumption funded by the European Union Directorate-General for Health and Consumer Affairs (DG SANCO) and the ECDC.

- European Surveillance of Antimicrobial Consumption (ESAC). The core of ESAC surveillance is tracking national drug consumption totals measured in defined daily doses (DDDs) in hospital and community settings. (See the ESAC web site: http://www.esac.ua.ac.be.) ESAC also provides quality indicators for antimicrobial use in primary care, hospitals, and nursing homes and explores regulatory, health system, behavioural, and knowledge-based determinants of use. ESAC results documented a 37% decrease in total antimicrobial use in Belgium from 2000 through 2008, and represent a powerful advocacy resource for generating the political will to support containment campaigns.

- Hospital Point-Prevalence Study of Healthcare-Associated Infections and Antibiotic use (PPS Antibiotic Use). This web-based annual single-day survey of antimicrobial use in over 300 participating hospitals provides a detailed snapshot of therapeutic and prophylactic antimicrobial use practices, the role of diagnostic services in clinical care, and risk factors for and the management of health care-associated infections. The experience of the Point-Prevalence Study has been proposed as a model for a WHO Hospital Audit Tool (WHAAT) which could be used worldwide as a practical web-based tool for collecting standardized information from hospitals of all resource levels with relevant benchmarking and feedback on practices.

- Antibiotic Resistance and Prescribing in European Children (ARPEC). Methodologies used to survey antimicrobial use in adult populations can provide grossly misleading insights into paediatric use. For example, 1 DDD is the amount of antimicrobial one would generally prescribe for a single average-sized adult for a single day. But this same amount of drug could perhaps be used to treat one teenager for one day, or three ten-year old children, or 20 newborn infants. ARPEC is thus developing and validating robust methodologies for surveillance in paediatric populations, a population which constitutes a high proportion of total antimicrobial use in the community setting.

The European Centre for Disease Prevention and Control (ECDC) currently funds ESAC through a grant and will assume responsibility for project management of ESAC and the PPS in Stockholm from mid-2011 onwards. DG SANCO is funding ARPEC. Additional European initiatives in which the Institute is involved include Genomics to Combat Resistance against Antibiotics in Community-Acquired LRTI (lower-respiratory tract infections) in Europe (GRACE); European Lower Respiratory Tract Infection Research Centre (TRACE); changing behaviour of health care professionals and general public towards a more prudent use of antimicrobial agents (CHAMP); appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance (APRES); TheraEDGE; and InTopSens and RAPP-ID for rapid point-of-care diagnostics. In GRACE, booklets and web-based training modules for improved communication between doctors and patients for the use of C-Reactive Protein (CRP) are developed – INternet Training for antibiotic use (INTRO). These modules will be tested in four countries in Europe.

3.2 The development of the EARSS model

Hajo Grundmann, Head, Bacteriology Department, National Institute of Public Health and the Environment (RIVM), Bilthoven, Netherlands

Surveillance of antimicrobial resistance addresses the consequences of the intersection of three domains of the ecological landscape: 1) microbial world; 2) patients and communities; and 3) antimicrobial exposure. Correlating with these three domains, one may consider three levels of AMR surveillance.

- "Micro" – pathogens. Characterization of pathogen population dynamics requires the typing, tracking, and mapping of the geographical and evolutionary trajectories of evolving microbes; tracks, and is used to investigate and explain the reservoirs and origins of emerging virulence, transmissibility, resistance, biological fitness, and the abundance of human pathogens.

- "Macro" – patients. Surveillance supports clinical management of infections, including optimization of empiric therapy decisions and the use of critically essential drugs.

- "Meta" – populations. Meta-level surveillance can define the international and national scale of AMR with an aim to assess the public health burden of AMR in comparison to other public health threats. A goal is to promote the public health recognition of anti-infectives as scarce non-renewable resources, to support policy changes, and redirect research funds into new drug development.

The European Antimicrobial Resistance Surveillance System (EARSS) was established in 1999, and currently included, in 2009, over 900 participating laboratories providing care to over 1500 hospitals in 33 European countries. The EARSS and ESAC networks have collaborated closely as sister networks providing a powerful public health message to national authorities and have proved crucial in generating the political support for successful campaigns to improve antimicrobial use in many European countries. Dr Grundmann has been Director of EARSS since 2003, and through that experience has identified six conditions that he considered as having been crucial to the success of EARSS.

- Legal support. EARSS has been endorsed by the European Parliament and Council Legislation 2119/98/EC and Commission Decision 2000/96/EC.

- Economic viability. Data collected by EARSS in over 900 participating laboratories represent the results of routine microbiological examinations used for routine clinical diagnostic support for patient care decisions. Consequently, the EARSS data generation mechanism is highly sustainable as it relies on routinely available test results. Funds were thus only required for central coordination of the network, the external quality assurance programme, and costs for the annual plenary meeting and more frequent Scientific Advisory Board meetings. Funds were not provided to Member States. In 2009, EARSS was funded by the ECDC and the Dutch Ministry of Welfare and Sport at an annual cost of € 668 458.

- Partnership. EARSS has used a devolved "network-of-networks" approach to organization in which data ownership resides with the countries with coordinated national network development with standardized microbiological protocols. There has been a great deal of pride and sense of ownership by participants in the accomplishment of EARSS, which have greatly contributed to its sustainability and impact.

- Acceptability. The initial establishment and long-term sustainability of the EARSS collaboration have crucially depended on its feasibility by participating laboratories and national network coordinators. In many countries, data collections have relied on manual paper-based approaches, especially at the beginning of the EARSS collaboration. By restricting surveillance to a limited number of pathogens from blood and cerebrospinal fluid with identified key antimicrobials, the volume of data was considered reasonable by network participants. To facilitate comprehensive and more automated reported (all organisms, all specimen types, all tested antimicrobials) as well as flexible national data management capabilities, the WHONET software was promoted through bi-annual data manager training courses and technical site visits by the Boston-based WHONET team (www.whonet.org).

- Validity and comparability. The validity and comparability of results is of course a key concern. The comparability of microbiological findings was documented through use of standard protocols, annual external quality assurance exercise, and routine use of internal quality control strains. At the beginning of EARSS there were a multitude of susceptibility reference test methods including Comité de l´Antibiogramme de la Société Francaise de Microbiologie (CA-SFM) in France, Deutsches Institute for Normung eV. (DIN) in Germany, Commissie Richtlijnen Gevoeligheidsbepalingen (CRG) in the Netherlands, the Norwegian Working Group for Antibiotics (AFA), the Swedish Reference Group of Antibiotics (SRGA), the British Society for Antimicrobial Chemotherapy (BSAC) and Clinical and Laboratory Standards Institute (CLSI) in the United States. In most cases, susceptibility test results were comparable with some well-recognized exceptions. Over the course of the past ten years, all of the European systems have been standardized around EUCAST methodologies (European Committee for Antimicrobial Susceptibility Testing) reducing much of the heterogeneity among participating laboratories. Over the next few years, a move to EUCAST methods by most European countries will permit even greater confidence in the comparability of results. Regarding comparability of clinical sampling practices across Europe, it was felt that criteria for the collection of blood and CSF isolates from patients would be more comparable than for other specimen types. This may be broadly true, but exceptions were noted in some low-resource countries where resistance incidence may be underestimated

and resistance prevalence overestimated due to less frequent sampling, perhaps of patients who have failed initial therapies.

- Representativeness. Because of the enthusiasm of participants in EARSS activities and feasibility of data collection and management protocols, EARSS has been able to achieve a remarkable success in achieving high population coverage of most participating countries. With two exceptions, over 20% population coverage was achieved in all countries representing different levels of care and segments of society, and in more than half of the countries, population coverage exceeded 80%.

3.3 European surveillance of AMR. After EARSS – transition to EARS-Net

Ole Heuer, Senior Expert and EARS-Net Coordinator, Surveillance Unit, European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

The European Centre for Disease Prevention and Control (ECDC) was established by the European Commission and began operations in Stockholm in 2005 under the leadership of Director Dr Zsuzsanna Jakab prior to her current position as Regional Director of the WHO Regional Office for Europe. At the time the ECDC was established, the European Commission funded 17 infectious disease surveillance networks in European Union Member States which covered 23 infectious diseases and conditions. These networks included the European Antimicrobial Resistance Surveillance System (EARSS), coordinated by the RIVM, and the European Surveillance of Antimicrobial Consumption project, coordinated by the University of Antwerp.

Over the past five years, coordination and operation of these networks have moved gradually to the ECDC. In 2010, this included EARSS, which has been reconstituted under the new name European Antimicrobial Resistance Surveillance Network (EARS-Net). Responsibility for the European Surveillance of Antimicrobial Consumption (ESAC) similarly will move to Stockholm in 2011. A primary aim of the EARSS transition was to maintain the high success and impact of the network.

In most respects, EARS-Net has continued without changes to the technical and strategic directions of EARSS – the same surveillance protocols, quality assurance programme – run by the United Kingdom National External Quality Assurance Scheme (NEQAS, three-year contract renewed in February 2010), and most of the same country and laboratory participants. However, the non-EU countries which participated in EARSS (33 countries) are currently not included in EARS-Net (28 countries = 26 EU member countries + Norway + Iceland). These include two EU candidate countries (Croatia and Turkey), a potential candidate (Bosnia and Herzegovina), Israel, and Switzerland. Many of the countries bordering the European Union have high resistance rates, and in some cases scientists from these countries have been leaders in the identification of emerging resistance and public health threats of concern to EU Member States. The possible re-inclusion of these previous EARSS participants awaits memoranda of understanding between the European Commission and national authorities in each of the countries.

EARS-Net direction is provided by the EARS-Net Coordination Group, filling a similar role as the prior EARSS Advisory Board and at present with the same membership as that body. The EARS-Net Coordination Group seeks a balance of professionals with various backgrounds – epidemiologists/ microbiologists, male/female, east/west, high/low incidence, and large/small countries. The ECDC Terms of Reference for the Coordination Group gives the possibility to

include external members from other networks e.g. ESCMID Study Group on Antimicrobial Resistance Surveillance (ESGARS), EUCAST, ESAC, and WHO. The Secretariat is provided by the ECDC. At present, WHO headquarters and the WHO Regional Office for Europe have not taken an active role in relation to EARS-Net activities, but an active partnership was viewed as beneficial for greatest public health impact of the EARS-Net activities.

EARS-Net surveillance continues with the same 7 pathogens from routine blood and cerebrospinal fluid cultures as previously. Gram-positive organisms under surveillance are *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecium*, and *Enterococcus faecalis*. Gram-negative organisms are *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Data files are uploaded by national data managers yearly to The European Surveillance System (TESSy), an integrated portal for the collection, validation, storage, analysis, display, and reporting for all diseases under surveillance by the ECDC. EARS-Net also provides an interactive database, which permits the dynamic query of results and display in maps, tables, and graphs.

The first submission of data from participant countries to TESSy took place in June and July 2010, and went very smoothly, especially for a first year's effort. Data were received from 28 countries, and preparation of the EARS-Net Annual Report 2009 is ongoing and was expected to be released before the end of 2010.

An objective of this first year was a smooth transition for participants, and this was largely achieved. An important element of future directions is integration within the ECDC of surveillance of antimicrobial resistance (EARS-Net), antimicrobial consumption (the eventual successor to ESAC), and health care-associated infections (formerly IPSE). Looking forward to the future of EARS-Net, a few questions are particularly relevant, and were to be discussed at the annual plenary meeting in November 2010.

- What will be major public health challenges caused by AMR in Europe within the next 5–10 years?

- Are the current surveillance systems capable of providing sufficient data for risk assessment and risk management to control these hazards?

- Which changes are needed in order to ascertain such capability?

3.4 Antimicrobial resistance surveillance in Turkey

Deniz Gür, Head, Children's Hospital, Clinical Microbiology Laboratory, Hacettepe University, Ankara, Turkey

Over the past 20 years, Turkey has had an important public health and academic role in tracking emerging resistance threats, including the initial discovery and characterization of several novel resistance genes, including extended spectrum variants of OXA beta-lactamases and PER-1. Indeed a finding of great concern throughout Europe is the finding of higher rates of antimicrobial resistance in *E. coli* (one of the most common pathogens causing both hospital and community infections) than in *K. pneumoniae* (primarily a concern in hospitalized patients).

Laboratories in the country have participated in several national and international resistance surveillance programmes over the years including EARSS and Antimicrobial Resistance in the

Mediterranean (ARMed), and coordinated by public health authorities and others sponsored by the pharmaceutical industry including HİTİT-1, HİTİT-2, MYSTIC, SENTRY, ARTEMIS, PROTEKT, SOAR, and TEST. Goals of these surveillance collaborations include improved empiric therapy decisions, antimicrobial use and resistance containment strategies, monitoring the impact of interventions, and education of health care providers, the media, and the general public.

Prior to the steady growth of EARSS to include some central and eastern European countries, Turkey was not an EARSS member. Rather, it was an active participant in the sister project ARMed coordinated by Dr Michael Borġ of St. Luke's Hospital in Malta. ARMed was funded by the research funds for EU-neighbouring countries for four years, and consisted of three arms which followed the same protocols as their European counterparts: ARMed-EARSS for antimicrobial resistance, ARMed-ESAC for antimicrobial consumption, and ARMed-HARMONY for infection control. Results from ARMed can be viewed on the EARSS web site hosted by RIVM (http://www.rivm.nl/earss/armed). ARMed members included Algeria, Cyprus, Egypt, Jordan, Lebanon, Malta, Morocco, Tunisia, and Turkey. Malta, Cyprus, and Turkey subsequently joined EARSS.

For the past several years, 16 Turkish laboratories have participated in EARSS, but Turkey has been excluded for the time being from the EARS-Net data collection programme pending high-level discussions of infectious disease surveillance collaborations between the ECDC and non-EU countries. It is hoped that a successful strategy will be identified which would permit full Turkish participation in EARSS. At present, Turkey does continue to participate in the external quality assurance programme and will attend the annual plenary meeting in Stockholm in November 2011.

In 2011, the Ministry of Health directed the Refik Saydam National Hygiene Centre to establish a more comprehensive national programme for surveillance of antimicrobial resistance including 78 participating laboratories. To support this, Dr John Stelling spent a week as a consultant in Ankara providing training in WHONET and guidance in their steps at establishing a national programme through the automated or semi-automated electronic capture of existing microbiology data from laboratory diagnostic instruments and laboratory information management systems.

3.5 Antimicrobial resistance from a food safety perspective

Hilde Kruse, Regional Adviser, Food Safety, WHO Regional Office for Europe, Rome, Italy

In many countries, over half of antimicrobial agents are given to animals, not human patients, for purposes of therapy (for sick animals), prophylaxis (for animals at high risk of disease), and growth promotion (to obtain a larger food animal for a given amount of animal feed provided). The potential consequences for human health are naturally of concern to health care providers and public health authorities. The use of antimicrobials as growth promoters is of particular concern, and such practice has been banned in European Union countries since 2003.

From the perspective of food safety, risks to human health from the food chain can be characterized as one of two types.

- Direct risk. A human patient is infected with an antimicrobial-resistant pathogen transmitted via the food chain. This would include zoonotic bacteria such as *Salmonella*

and *Campylobacter* in which resistance would reflect antimicrobial use practices in animals and non-zoonotic bacteria often transmitted through the food chain including *Shigella* and *Vibrio* in which resistance is more determined by antimicrobial use in humans.

- Indirect risk. A human patient is infected with an antimicrobial-resistant pathogen which has acquired resistance genes from a resistant animal-hosted microbe via gene transfer directly, e.g. via plasmid conjugation or other mobile genetic elements, or indirectly through a series of gene transfers in human commensal strains.

Dr Kruse presented recent results highlighting the emergence of resistant strains of public health importance, including ceftiofur-resistance *Salmonella*, fluoroquinolone-resistant *Campylobacter*, and Methicillin resistant *Staphylococcus aureus* (MRSA) – especially with strain ST398 (MLST-type) among swine production professionals. A 2008 study from the European Food Safety Authority (EFSA) found that 22.8% of breeding pig holdings were MRSA positive, and a Dutch study found MRSA in 11% of meat samples.

Dr Kruse also discussed examples where the possible transfer of resistance genes may have an important public health impact including *E. coli*, as a substantial portion of resistant *E. coli* in human intestines is derived from food and water sources, and avoparcin-resistant enterococci, which have been shown capable of transferring the *vanA* gene from animal-hosted isolates to human-host strains. Turkey and China, among many other countries, have high rates of resistant *E. coli*, and it is possible that the use of antimicrobials in the production of chicken and other meat products may be a primary contributor.

Looking ahead, the use of antimicrobials in food animals will present new challenges for food safety and international trade, and will require international cooperation and holistic interdisciplinary approaches for evidence-based risk assessment and risk management. WHO has been particularly active in promoting activities, guidelines, and standards to assist basic epidemiological research and guide antimicrobial use policies, including 15 expert meetings since 1997 on the use of antimicrobials in food animals, most of them in collaboration with the Codex Alimentarius Commission (Codex), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE). The Food Safety and Zoonoses Department in WHO headquarters has established the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO AGISAR) to coordinate WHO activities and partners in this area, including recommendations for surveillance of antimicrobial resistance and use in veterinary populations and maintenance of the list of Critically Important Agents (CIA).

The European Commission has been very active in building the scientific, public policy, and industry partnerships needed to support rational antimicrobial use practices in food animals. A major concern expressed by Dr Kruse was a lack of awareness by many ministries of health and of agriculture in non-EU countries of the public health threat of poor antimicrobial use practices on human health. Raising awareness of these issues with the relevant national authorities was identified as a top priority for action in non-EU countries.

3.6 Monitoring of antimicrobial resistance in animal and food isolates

Pia Mäkelä, Zoonoses Data Collection Unit, European Food Safety Agency (EFSA), Parma, Italy

The Community Directive on monitoring of zoonoses and zoonotic agents (2003/99/EC) obliges all EU Member States to monitor and report annual data on antimicrobial resistance in *Salmonella* and *Campylobacter* isolates from animals (poultry, cattle, swine) and meat thereof. In addition surveillance of the commensals *E. coli* and *Enterococcus* isolates is recommended, though not required. Countries of the European Union as well as Norway and Switzerland report their findings to EFSA, while results from human cases of salmonellosis and campylobacteriosis are reported to the ECDC. EFSA and ECDC collaborate in the preparation of annual Community summary reports since 2004 on the food, animal, and human isolates of these organisms.

To improve the comparability of data collected from Member States, EFSA has issued harmonized specifications for monitoring and reporting of antimicrobial resistance in three areas:

- *Salmonella* in chicken, turkey, and swine isolates identified in *Salmonella* control programmes (EFSA report 2007/96, also presented in the Commission Decision 2007/407);

- *C. jejuni* and *C. coli* in broilers from flock samples (EFSA report 2007/96);

- commensal *E. coli* and enterococci from food animals in slaughterhouses, including guidance for Extended Spectrum Beta-Lactamase ESBL monitoring (EFSA report 2008/141).

These specifications address: the target population, origin of isolates, minimum number of isolates; and laboratory methods, including antimicrobials to test and susceptibility testing methods by disk diffusion or minimal inhibitory concentration (MIC) determination, and the use of epidemiological cut-off values (ECVs) for result presentation. Where EUCAST ECVs do not exist for a particular antimicrobial, EFSA has used results from this monitoring programme to propose ECVs which are used in data presentation.

Given differences in national food production practices and in the implementation of the EFSA specifications, it is recognized that data are not completely comparable across the EU Member States. Hence the focus of data interpretation is national-level analysis (especially temporal and regional trends within a country), though efforts are under way to improve standardization of sampling practices to increase comparability at the Community level.

In 2008, data was submitted from 26 countries, including quantitative (disk diffusion zone diameter and/or MIC values) from 22 of these, on isolates from the aforementioned species from chicken, turkey, swine, and cattle, and meat thereof. Data exhibited wide differences in prevalence across the European Union among all microbial species. For most organism/antimicrobial combinations, resistance has not changed significantly over the 5-year period of data collection, but with some notable exceptions, including rising fluoroquinolone resistance in *Salmonella* and *Campylobacter* isolates from some poultry species. The latest results are published in the Community summary report on antimicrobial resistance in zoonotic and indicator bacteria from animals and food in the European Union in 2008 (*EFSA Journal,* 2010, 8(7):1658; http://www.efsa.europa.eu/en/scdocs/scdoc/1658.htm).

In addition to the above-described ongoing monitoring programme, a baseline survey of MRSA in breeding pigs was conducted in 2008 in all EU Member States using EFSA-developed protocols. This survey exhibited a wide range across the EU with an overall average of 26.9% in production holdings with breeding pigs. In 8 Member States, no MRSA were found, while in one Member State prevalence was over 50%. Statistics on the movement and importation of live swine between EU Member States demonstrates a positive association between prevalence of MRSA resistance in breeding pigs and trade patterns of live animals. The MRSA baseline results are published in two reports:

- Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008 [1] – Part A: MRSA prevalence estimates. *EFSA Journal,* 2009, 7(11):1376;

- Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008 [1] – Part B: Factors associated with MRSA contamination of holdings. *EFSA Journal,* 2010, 8(6):1597.

EFSA is not collecting data on the use of antimicrobials in food animals, but this information is regarded as crucial for a fuller understanding of the food safety issues related to antimicrobial resistance. To address this need, the European Medicines Agency has established a new surveillance collaboration to establish standards and monitoring for antimicrobial use in food animal populations – European Surveillance of Veterinary Antimicrobial Consumption (ESVAC).

Report of the Task Force of Zoonoses Data Collection including a proposal for a harmonized monitoring scheme of antimicrobial resistance in *Salmonella* in fowl (*Gallus gallus*), turkeys, and pigs and *Campylobacter jejuni* and C. *coli* in broilers. *EFSA Journal*, 2007, 96,1–46 (http://www.efsa.europa.eu/en/scdocs/scdoc/96r.htm.

Report from the Task Force on Zoonoses Data Collection including guidance for harmonized monitoring and reporting of antimicrobial resistance in commensal *Escherichia coli* and *Enterococcus* spp. from food animals. *EFSA Journal*, 2008, 141: 1–44 (EFSA report 2008/141; http://www.efsa.europa.eu/en/scdocs/scdoc/141r.htm).

3.7 WHO Infection Prevention and Control in Health Care Programme

Dr Carmem Lúcia Pessoa-Silva, Project Leader, Infection Prevention and Control, Department of Global Alert and Response, World Health Organization, Geneva, Switzerland

The WHO infection prevention and control in health care programme (IPC) in the WHO Department of Global Alert and Response (GAD) has the mission:

- to assist Member States to endorse quality promotion of health care which is safe for patients, health care workers, others in the health care setting and the environment.

This includes provision of support: 1) for infection control preparedness and response to public health emergencies; and 2) for prevention of infectious disease spread through evidence-based infection control measures in health care. The global IPC team consists of the IPC unit at WHO headquarters and IPC focal points at each of the six regional offices. IPC staff coordinate messages and activities with relevant WHO departments in biosafety and laboratory biosecurity,

water safety, occupational health, Stop TB, HIV/AIDS, patient safety, Scottish Intercollegiate Guidelines Network (SIGN), blood safety, clinical procedures, and essential medicines.

In support of the World Health Assembly resolutions WHA51.17 "Improving containment of antimicrobial resistance" and WHA58.27 "Effective monitoring and control of health care-associated infections due to multiresistant pathogens", the IPC team formulated and published in March 2009 a set of key elements of a strategy for control of health care-associated infections at hospital and national levels: the core components for infection prevention and control programmes. The framework highlights the particular importance of hospitals in the selection and transmission of multiresistant organisms. The high use of antimicrobials selects for resistant organisms, and opportunity for transmission among patients, health care workers, and family members promotes further spread among vulnerable populations.

Consequently key activities in a resistance containment strategy must incorporate: 1) rational use of antimicrobials and 2) prevention of transmission, aided by the early laboratory-based detection of emerging resistant threats and confirmation, investigation, and control of outbreaks. The IPSE (Improving Patient Safety in Europe) Consensus on Standards can prove a useful assessment and monitoring tool for identifying priorities for action.

The core components defined in the IPC framework are shown below with a few specific elements of particular relevance for antimicrobial resistance containment indicated:

- organizational structure, including defined budget (includes but is not limited to a defined recognition of the scope of responsibility to prevent the emergence and spread of antimicrobial resistance);

- technical guidelines (should include rational antimicrobial use among the set of IPC guidelines);

- human resources;

- health facility environment;

- microbiology laboratory support (identification of agents and patterns of resistance);

- surveillance of disease and monitoring of practices (priorities for surveillance of infections and pathogens);

- links with public health and other services/societal bodies (coordinated action in all sectors);

- evaluation of IPC programmes.

The framework is being used to guide IPC intervention activities in 7 low-resource West African nations and one low-resource Asian one. Main barriers identified in implementation of the core components include lack of basic infrastructure, lack of epidemiological and laboratory-based surveillance capacity, and lack of local and national policies for rational antimicrobial use. Useful positive feedback from the efforts to date recognizes the step-wise, modular approach of the component framework and the availability of monitoring and evaluation tools to track progress in implementation.

3.8 EU Research on antimicrobial drug resistance

Anna Lönnroth Sjödén, Sector Emerging Infectious Diseases, Unit of Infectious Disease, European Commission Directorate-General for Research and Innovation (DG Research), Brussels, Belgium

Since 1999, the European Commission has maintained an active research agenda which addresses a wide range of basic science, clinical, epidemiological, and policy issues related to antimicrobial resistance with over € 200 million disbursed to researchers. Most of the funds have been allocated for the study of resistance in human microbial populations, but some limited funds have been used for the study of resistance in bacteria of food and animal origin.

The EU research agenda emphasizes a multidisciplinary approach in the following broad sectors:

- rational antimicrobial use;
- infection control;
- host–pathogen interactions;
- novel antimicrobial therapies, such as new use of existing compounds, novel compounds, alternative treatment strategies;
- new rapid cost-effective diagnostic tests, to determine *whether* an antimicrobial should be used, to determine *which* antimicrobial should be used, to determine whether an antimicrobial remains effective,
- validation of the sensitivity, specificity, robustness, performance or cost of diagnostic tests.

Within the Seventh EU Framework Programme for Research and Technological Development (FP7), 15 applications relevant for antimicrobial resistance studies totalling € 65 million have already been funded including: novel drug targets in gram-negative bacteria; host–pathogen interactions in *S. pneumoniae* infections; molecular epidemiology of highly virulent multidrug-resistant pathogens causing hospital and community infections; clinical evaluation of point-of-care diagnostic tests for microbe detection and identification, biomarkers, and antimicrobial susceptibility testing; and the impact of antimicrobial therapy on the prevalence of resistant bacteria in the human host. Topics included in the current call for applications address: investigator-driven clinical trials of off-patent antibiotics; multidisciplinary research on the evolution and transfer of antimicrobial resistance genes; clinical management of gram-negative multidrug-resistant infections; multi-analyte diagnostic tests; tools to control microbial biofilms; evidence-based behavioural and communication packages to respond to major epidemics. Collaborators from anywhere in the world are eligible to apply for funding. This must be done in collaboration with partners (most often three) from EU Member States or EU Associated Countries.

The Innovative Medicines Initiative (IMI) is “a unique Public-Private Partnership (PPP) between the pharmaceutical industry represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Union represented by the European

Commission" with the stated goal "to reinvigorate the biopharmaceutical sector in Europe". One area of priority funding by IMI is the development of rapid point-of-care diagnostic tests and their validation in clinical trials.

New initiatives are advancing including a Joint Programming Initiative for Research to facilitate multinational collaborations among national research programmes, and a research agenda to be defined over the next six months by the Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR). TATFAR was established in November 2009 at the EU–United States summit in Washington. From the European side, members include the ECDC, European Medicines Agency EMA, EFSA, DG SANCO, and DG Research. United States participants include the Centers for Disease Control and Prevention (CDC), US Food and Drug Administration (FDA), and National Institute of Health (NIH). A report on the identification of priority areas for trans-Atlantic collaboration is due by March 2011, and is expected to address therapeutic antimicrobial use in human and animal populations, infection control, and the development pipeline for new antimicrobial compounds.

In December 2009, the health ministers of the Member States adopted Council conclusions concerning innovative incentives for maintaining the efficacy of existing antimicrobials and the development of new ones. The conclusions comprise some measures and recommendations with regards to antimicrobial resistance, ranging from national level strategies to ensure awareness among the public and health professionals to EU-level efforts to promote public-private partnerships to facilitate research into new antimicrobials, diagnostic methods, and strategies for appropriate use of currently available agents. The Council conclusions also call upon the Commission to "within 24 months, develop a comprehensive action-plan, with concrete proposals concerning incentives to develop new effective antibiotics, including ways to secure their rational use; and ensure that these proposals take account of the economic impact on the financial sustainability of health care systems." This EU Integrated Action Plan will be very broad, and will include the TATFAR activities as one of its areas of work.

3.9 State Research Center for Applied Microbiology and Biotechnology

Dr Lyubov Domotenko, Head of Laboratory, State Research Center for Applied Microbiology and Biotechnology (SRCAMB), Obolensk, Moscow Oblast, Russian Federation

The State Research Center for Applied Microbiology and Biotechnology (SRCAMB), located in Obolensk in the Moscow region is one of the largest research-and-production complexes dealing with dangerous biological materials in the Russian Federation. SRCAMB is part of the Federal Service of Consumer Rights, Surveillance, and Human Welfare (Rospotrebnadzor).

SRCAMB conducts research in the field of epidemiology, bacteriology, and biotechnology and includes Biosafety Level 2 (BSL-2) and Biosafety Level 3 (BSL-3), and staff are well trained in research methodologies involving pathogenic microorganisms, including bacterial agents of especially dangerous infections. The animal laboratory is equipped for the management of small laboratory animals, including specific pathogen-free (SPF) animals. Areas of research include molecular mechanisms of resistance in *Mycobacterium tuberculosis* and pathogens causing hospital infections agents. The laboratory prepares strain panels of *M. tuberculosis* for distribution to laboratories in the Russian Federation for purposes of quality assurance, research, and education.

Additional areas of work include: diagnostics and therapeutics; prophylaxis, diagnosis, and therapy in cases of epidemic microbial spread; biological safety and bioterrorism response; and novel vaccines. SRCAMB produces commercial bacteriological nutrient media for commercial distribution, including the Russian AGV medium, and is developing rapid test kits for susceptibility testing of *M. tuberculosis* within an ITSC project. The laboratory will begin production of Mueller-Hinton agar for susceptibility testing to support a move towards standard European methods.

3.10 KNCV Tuberculosis Foundation and multidrug-resistant tuberculosis

Dr Peter Gondrie, Executive Director, KNCV Tuberculosis Foundation, Netherlands

The KNCV Tuberculosis Foundation was established in 1903 with the mission of "global elimination of tuberculosis through the development and implementation of effective, efficient and sustainable tuberculosis strategies". Within the Netherlands, the foundation serves as a knowledge centre for coordination and monitoring of TB expertise and the National TB Programme (NTP) supports national surveillance activities. Internationally, the KNCV Tuberculosis Foundation is active in over 40 countries providing a wide range of expertise in tuberculosis treatment and control programmes. Of the approximately 3 million patients which they track annually, over 85% have a successful clinical outcome.

By definition, classic multidrug-resistant tuberculosis (MDR-TB) is caused by strains of *M. tuberculosis* resistant to at least isoniazid and rifampicin. Primary resistance is resistance observed in strains upon initial case detection in previously untreated individuals, while secondary or acquired resistance is resistance which develops during or following the initiation of anti-mycobacterial therapy. Extensively drug-resistant tuberculosis (XDR-TB) is tuberculosis cause by MDR-TB strains (i.e. which are resistant to isoniazid and rifampicin) which are also resistant to any fluoroquinolone and at least one of any of the second-line injectable treatment agents amikacin, kanamycin, or capreomycin. Treatment of MDR-TB and XDR-TB requires longer therapy courses and is correlated with higher mortality, drug toxicity, and treatment costs.

In 2008, there were an estimated 440 000 new cases of MDR-TB, around 3.6% of all incident cases of tuberculosis. Almost 50% of these were in China and India, and there were approximately 150 000 deaths due to MDR-TB worldwide.

At present, only 114 or 193 countries (59%) report data on resistance to first-line TB agents. The highest rates of MDR-TB worldwide were seen in the WHO European Region. Among countries worldwide with existing primary MDR-TB (i.e. resistance in newly identified cases) exceeding 12%, all were within the European Region – Azerbaijan, Estonia, Kazakhstan, Latvia, Republic of Moldova, Russian Federation, Tajikistan, Ukraine, and Uzbekistan. Secondary MDR-TB (i.e. resistance in previously treated patients), an important indicator of the inadequacy of drug treatment programmes, exceeded 50% in Azerbaijan, Kazakhstan, Republic of Moldova, Russian Federation, Tajikistan, and Uzbekistan.

Within Europe, following the Berlin Declaration of 2007 in which WHO Member States agreed to TB control recommendations, the WHO Regional Office for Europe announced a 2007–2015 Plan to Stop TB in 18 High-priority Countries in the WHO European Region of which 5 are EU members and 13 non-EU countries. Recognizing the major public health threat of multidrug-resistant strains, a ministerial meeting for high multi-resistance burden countries was conducted in Beijing in April 2009, followed shortly thereafter by World Health Assembly resolution

WHA62.15 in May 2009. The development of a new action plan for 2010–2015 to fight MDR-TB and XDR-TB in the European Region was announced in June 2010.

The World Health Assembly resolution WHA62.15 urges Member States "to achieve universal access to diagnosis and treatment of MDR and XDDR TB as part of the transition to universal health coverage, thereby saving lives and protecting communities" by means of several priority actions including "strengthening mechanisms to ensure that TB medicines are sold on prescription only and that they are prescribed and dispensed by accredited public and private providers". Implementation of the WHA resolution recommendations will also required adequate attention to programmatic management of drug- resistant TB (PMDT); monitoring and evaluation; public–private mix; infection control; advocacy, communication and social mobilization (ACSM); human resource development; laboratory, drugs, targets, and quality Directly Observed Treatment – Short-course (DOTS).

Over the past many years, the major burden of disease due to MDR-TB and XDR-TB has been in patients with inadequate completion of therapy courses (i.e. secondary resistance). Containment efforts for these are focused on the provision of adequate therapy to individuals with newly diagnosed TB. It is increasingly recognized that transmission of multidrug-resistant strains in new infections (i.e. primary resistance) is overtaking medication mismanagement as the primary cause of MDR-TB and XDR-TB in many settings, a public health threat with much broader public health and management implications.

3.11 Surveillance of multidrug-resistant tuberculosis in Europe

Dr Andrei Dadu, Technical Officer, Division of Communicable Diseases, Health Security and Environment, WHO Regional Office for Europe, Copenhagen, Denmark

In 2008, twenty-seven high-resistance burden countries accounted for 85% of cases of MDR-TB globally (an estimated 400 000 cases). Of these countries, the top 15 are in the WHO European Region reflecting years of mismanagement of new cases of TB and inability to provide continued access to anti-TB drugs of high quality.

Since 2008, data management strategies have benefited from integration of the newly established web-based TESSy data management system developed by the ECDC with the existing Centralized Information System for Infectious Diseases (CISID) managed by the WHO Regional Office for Europe. At the present time, data from all 53 Member States in the Region submit their data to the common data entry point ECDC-WHO/Europe Joint Surveillance web site (http://www.ecdcwhosurveillance.org) that redirects users to the appropriate data upload site. EU and European Economic Area (EEA) countries enter data through TESSy which sends aggregate statistics to CISID, which in turn subsequently forwards surveillance reports to the TB Monitoring and Evaluation Unit in the Stop TB Department in WHO headquarters.

There is active sharing of aggregate data and reports between TESSy and CISID. The CISID/TB database includes information on all areas of TB control as defined by the Stop TB Strategy. Case-based data for EU countries are managed by TESSy and aggregated for presentation within CISID, while aggregate data for non-EU countries are managed by CISID.

Drug susceptibility testing (DST) results are stratified into new and previously-diagnosed cases. Results from some countries represent routine comprehensive ongoing surveillance, while the

focus in some countries is periodic targeted surveys. Results for EU and non-EU countries can be queried via a joint web site interface.

Recent surveillance results indicated that there were an estimated 81 000 cases of MDR-TB in Europe in 2008 representing 19.1% of all cases of tuberculosis. An estimated 21% of all new cases of tuberculosis received DST, and among this subset, 18.1% of cases were MDR-TB. These numbers would suggest that 22.7% of all MDR-TB cases in Europe are identified by diagnostic laboratories, leaving a startlingly high 77.3% of MDR-TB cases in European communities which are not detected and treated, an important public health threat to family members and other contacts of these individuals.

3.12 WHONET

Dr John Stelling, Co-Director, WHO Collaborating Centre for Surveillance of Antimicrobial Resistance, Brigham and Women's Hospital, Boston, United States

The WHO Collaborating Centre was established in 1986 at the Brigham and Women's Hospital in Boston. The Collaborating Centre provides strategic guidance and technical support to local, national, and regional surveillance programmes in partnership with WHO headquarters, regional offices, and country offices.

A primary focus of the Collaborating Centre is the development, dissemination, and support of the WHONET software. At present WHONET is used in approximately 98 WHO Member States supporting surveillance of antimicrobial resistance in over 1300 hospital, public health, food, and veterinary laboratories. Data can be entered into WHONET manually or via electronic download and standardization from existing laboratory information systems, diagnostic instruments, or desktop applications with BacLink.

Regarding the use of WHONET in the WHO European Region, the software was used by 19 of the 28 countries reporting data to EARS-Net in 2010, and WHONET was used in 5 of the remaining 9 countries, though not to support their EARS-Net participation. As far as non-EU countries are concerned, WHONET is used in Albania, Belarus, Croatia, Georgia, Israel, Kazakhstan, Republic of Moldova, Russian Federation, Serbia, Turkey, and Ukraine.

The core of a global collaboration among antimicrobial surveillance networks already exists, but requires strengthening, mentoring, promotion, and use to support action. The WHO Western Pacific Region was the first WHO region to initiate a regional surveillance collaboration. Though not active at present, many of this Region's Member States continue surveillance activities at local and national level, and a new task force for antimicrobial resistance is being established in Manila, and regional surveillance and quality assurance activities are among the priorities.

The WHO Region of the Americas network for surveillance of antimicrobial resistance has been active since 1996 in surveillance and capacity-building collaborations, including site visits, internal and external quality assurance, regional data collection, and an annual meeting and annual resistance report.

Several of the countries of the WHO Eastern Mediterranean Region participated for five years in the EU-funded ARMed project – Antimicrobial Resistance in the Mediterranean. Participants followed the same protocols as used by EARSS (antimicrobial resistance), ESAC (antimicrobial

use), and HARMONY (infection control), and resistance surveillance data were hosted on the RIVM EARSS web site. There is a desire by the network coordinator, Michael Borġ of St. Luke's Hospital in Malta, and the participating countries to reactivate this activity, though there are no funds to support this at present. A regional external quality assurance programme which includes organism identification and antimicrobial susceptibility testing is coordinated by the Central Public Health Laboratories of Oman in collaboration with the WHO Lyon Office.

The WHO Regional Office for South-East Asia has recently published the WHO-SEARO Regional Strategy on Prevention and Containment of Antimicrobial Resistance: 2010–2015 which identifies as one objective "to institute a surveillance system that captures the emergence of resistance, trends in its spread and utilization of antimicrobial agents in different settings", and has promoted laboratory capacity-building and WHONET training in some Member States in the Region.

The focus of activities in the WHO African Region is laboratory capacity-building including laboratory training courses and an external quality assurance programme run by the National Institute for Communicable Diseases in Johannesburg under the guidance of the WHO Lyon Office.

In addition to these activities, the Global Foodborne Infections Network (GFN) is also a valuable partner for laboratory training (over 70 training courses over the past 10 years), quality assurance, and surveillance activities. Though the focus is foodborne pathogens such as *Salmonella* and *Campylobacter*, much of the training incorporates common non-zoonotic pathogens such as *E. coli* and *S. aureus*. Regional Systems for Vaccine (SIREVA) is active in Latin America for surveillance of respiratory pathogens, and Gonococcal Antimicrobial Surveillance Programme (GASP) in the western Pacific and south-east Asia for *N. gonorrhoeae*.

3.13 ESCMID and EUCAST

Gunnar Kahlmeter, Head, Department of Clinical Microbiology, Central Hospital, Chairman of EUCAST, President-Elect of ESCMID, Växjö, Sweden

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is a non-profit-making organization whose mission is to improve the diagnosis, treatment, and prevention of infection-related diseases. This is achieved by promoting and supporting research, education, training, and good medical practice. Its yearly ECCMID is the largest European congress on infectious diseases with approximately 10 000 participants each year. The next meeting will be in Milan in May 2011.

ESCMID supports 18 study groups which organize European experts in various fields of clinical microbiology including the ESCMID Study Group on Antimicrobial Resistance Surveillance (ESGARS), ESCMID Study Group for Antibiotic Policies (ESGAP), European Study group on Nosocomical infections (ESGNI), ESCMID Study Group for Molecular Diagnostics – (ESGMD), ESCMID Study Group for Epidemiological Markers (ESGEM), and ESCMID Food- and Water-borne Infections Study Group (EFWISG). ESGARS has the following mission and objectives:

- to provide a uniting forum for those medical personnel and scientists actively involved in antimicrobial resistance surveillance, in order to promote a better understanding of antimicrobial resistance;

- to provide opportunity to enhance co-operation and to establish links with and between networks of resistance surveillance programmes;

- to promote awareness and facilitate the early detection of emerging antimicrobial resistance;

- to contribute to an understanding of the epidemiology of antimicrobial resistance in Europe,

- to reconcile techniques used in resistance surveillance and to investigate the diversity of European techniques;

- to provide an opportunity for training in resistance detection and surveillance;

- to improve access to European data on surveillance.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is a standing committee jointly organized by ESCMID, ECDC, and European national breakpoint committees. Over the past several years, EUCAST has steadily harmonized antimicrobial breakpoints among European national committees responsible for antimicrobial susceptibility testing methods and interpretation guidelines. European committees include CA-SFM (France), DIN (Germany), CRG (Netherlands), and NWGA (Norway), SRGA (Sweden), and BSAC (United Kingdom). EUCAST has subcommittees on antifungal susceptibility testing, susceptibility testing of anaerobes, and susceptibility test interpretative reading and expert rules.

EUCAST recommendations are based on standard and maximum antimicrobial doses used in Europe for indications approved by the European Medicines Agency (EMA, formerly the European Medicines Evaluation Agency, EMEA), and are the sole breakpoints recognized in European "Summary of Product Characteristics" (SPC) from EMA. Methodologies and breakpoints are freely available by download from the EUCAST web site, along with the rationale and data supporting decisions.

Interpretive guidelines exist for disk diffusion and MIC methods for susceptibility testing, and the primary diagnostic instrument vendors have incorporated EUCAST breakpoints into their softwares and susceptibility test panels. At the present time, Clinical and laboratory standards institute (CLSI) methods are the most commonly used in Europe, but this is changing quickly. In 2010, six European nations are using EUCAST recommendations (France, Germany, Netherlands, Norway, Sweden, and United Kingdom). It is anticipated that nine more will switch to EUCAST in 2011 (Austria, Belgium, Denmark, Estonia, Finland, Hungary, Ireland, Switzerland, and Spain), and several more are discussing a possible transition.

3.14 EC – DG SANCO initiatives against AMR

The services of DG SANCO were invited to participate but could not attend due to previous commitments. Over the past years, DG SANCO has developed a series of initiatives against antimicrobial resistance in the fields of animal welfare, public health and food safety with actions related to surveillance, prevention, international cooperation and risk management. In addition, a new DG SANCO horizontal strategy is currently being prepared and should be presented by November 2011. In this respect and in the context of the development of the

proposed WHO Regional Strategy, efficient coordination between the WHO Regional Office for Europe and DG SANCO will be key for the success of these two strategies. Further contacts should be established to discuss and foster coordination.

4. REGIONAL APPROACH TO INCREASE AMR AWARENESS IN EUROPE

4.1 European Antibiotic Awareness Day

Dominique Monnet, Senior Expert and Programme Coordinator, Antimicrobial Resistance and Healthcare-Associated Infections, Scientific Advice Unit, European Centre for Disease Prevention and Control, Stockholm, Sweden

Data generated in by EARSS and ESAC have demonstrated wide discrepancies in antimicrobial use practices in Europe and correlated differences in resistance prevalence. Data for 2008 indicate a four-fold difference in antimicrobial use between the country with the highest use (Greece) and the countries with the lowest use (Netherlands and Latvia). As an advocacy tool, such findings have fostered political support for some successful national public campaigns to promote the prudent use of antibiotics, for example in France and Belgium which have both seen significant drops in use following effective media, public awareness, and education campaigns. Steadily decreasing resistance in *S. pneumoniae* (penicillin and erythromycin resistance) and *S. pyogenes* (erythromycin resistance) has been observed in these two countries following the campaigns, probably related to more prudent use of antibiotics.

With these examples of successful national media campaigns, a report commissioned by the European Parliament recommended in 2006 the idea of a coordinated annual one-day EU-wide campaign for raising awareness about antimicrobial resistance and prudent use of antibiotics in EU Member States (http://www.europarl.europa.eu/stoa/publications/studies/stoa173_en.pdf). This came to fruition in 2008 with the first European Antibiotic Awareness Day (EAAD) on 18 November 2008 involving 32 countries (and 34 countries in 2009) and significant political support from the EU Commissioner for Health, the French EU Presidency, and Members of the European Parliament. Posters, fact sheets, television advertisements, logos, pamphlets, and media messages were developed by ECDC to address the general public (2008), primary care prescribers (2009), and hospital prescribers (2010) and made available to EU Member States through a specific web site translated in all EU languages (http://antibiotic.ecdc.europa.eu).

The hedgehog was identified as a campaign mascot, and is featured in several media messages. Each EU Member State also crafted its own activities and strategies based on nationally identified priorities and partners. Examples of national activities include television spots, adverts in cinemas and posters in many countries, armband gimmicks in Belgium, large billboards on Malta, a poster exhibition in Poland, and press conferences, media activities and interviews with infection and antimicrobial use experts in most countries. The activities and successes of the first EAAD were summarized in an article published in *Eurosurveillance* in 2009 (http://www.eurosurveillance.org/images/dynamic/EE/V14N30/art19280.pdf).

EAAD 2010 took place as usual on 18 November. The United States Centers for Disease Control and Prevention (CDC) moved the annual “Get Smart” week on appropriate antimicrobial use to coincide with EAAD, and Canada planned to coordinate a national antibiotic awareness day on the same day as EAAD.

One of the workshop participants suggested that a coordinated activity among the over 900 hospitals across Europe participating in EARS-Net (formerly EARSS) could send a powerful message to national authorities and to the general public, either as part of EAAD in any year or as part of World Health Day in 2011.

4.2 World Health Day 2011

Dr Dennis Falzon, Medical Officer, World Health Organization, Geneva, Switzerland

World Health Day is WHO's flagship annual advocacy event and provides an opportunity to engage the global community in education and action campaigns for a selected global health priority. It is celebrated each year on 7 April to commemorate the date of creation of WHO. For 2011, the subject selected is antimicrobial resistance.

A few examples of threats which impose high suffering, increased death rates, and health care costs include: tuberculosis – over 440 000 new cases of multidrug-resistant strains (MDR-TB) emerge annually and more extensively resistant strains (XDR-TB) have been reported in 59 countries; malaria – artemisinin resistance is growing and linked to ongoing use of monotherapy; HIV – expanded use of antiretroviral therapies raises selection pressure; MRSA – a major cause of morbidity and mortality in health care-associated and community soft tissues and bloodstream infection; and a newly-identified gene "NDM-1" (New Delhi metallo-beta-lactamase) conferring resistance reserve "last-line" antimicrobial agents.

The WHO Global Strategy for Containment of Antimicrobial Resistance, published in 2001, contained a series of prioritized recommendations for action by all stakeholders including national authorities, health care providers, industry, researcher, and the general public. This was followed by World Health Assembly resolutions in 2005 (WHA58.27 – Improving the containment of antimicrobials) and 2009 (WHA62.15 – Prevention and control of multidrug-resistant and extensively drug-resistant tuberculosis). Despite progress in some areas, effective and coordinated strategies for containment of resistance have not been widely implemented.

By selecting antimicrobial resistance as the focus of World Health Day (WHD) 2011, WHO seeks to focus international and national attention and commitments to prevent and contain antimicrobial resistance. The priority package for action against AMR will include:

- providing coherent commitment and accountability to prevent and contain AMR
- strengthening surveillance
- ensuring quality and regular drug supply
- regulating and promoting rational drug use
- enhancing infection control
- fostering research and development
- empowering patients and civil society.

Key audiences targeted will include ministries of health and health policy-makers, the general public and civil society, prescribers and dispensers, pharmaceutical industry, media and communications experts, and global health leaders and donors. Specific objectives are:

- to provide concise policy guidance for top priority actions – including technical background papers, policy briefs, fact sheets, and a WHD 2011 toolkit;

- to pursue innovative communication and advocacy efforts to reach key stakeholders – via web sites, posters, videos, radio, social media, and events;

- to promote further collaboration across and within stakeholder constituencies.

In addition to national authorities and professional societies and patient advocacy groups, additional international partners may include the Bill and Melinda Gates Foundation; the Center for Global Development (CGD); the Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR); groups dedicated to rational antimicrobial use such as ReAct – Action on Antibiotic Resistance, Alliance for the Prudent Use of Antibiotics (APUA), International Network for the Rational Use of Drugs (INRUD), and ISIUM; industry partners including the International Pharmaceutical Federation (FIP) and the International Federation of Pharmaceutical Manufacturers Association (IFPMA). A meeting of national drug regulators due to take place in November 2010 is an opportunity to develop coordination plans to support activities on WHD.

WHD 2011, with its focus on resistance in tuberculosis, malaria, HIV/AIDS, and other resistant bacterial infections, will require a coordinated and effective cross-cutting collaboration within WHO and its regional offices, its partnerships, especially the Stop TB Partnership and Roll Back Malaria, and probably the Global Fund and UNITAID, and across antimicrobial resistance and disease-specific surveillance and control programmes such as EARS-Net coordinated by the European Centre for Disease Prevention and Control. A possible collaboration among WHO regional offices would be a joint summary of available antimicrobial resistance data from EARS-Net and other, WHO-affiliated antimicrobial surveillance networks such as the WHO Region of the Americas regional surveillance programme or the former regional surveillance collaboration in the WHO Western Pacific Region.

5. CONCLUSIONS AND RECOMMENDATIONS

Antimicrobial resistance is a complex public health problem and what is observed now is only the tip of the iceberg. Furthermore, resistant microbes travel with people and goods and a pan-European data system for surveillance of antimicrobial resistance would track resistant threats and inform risk assessments of the public health impact of resistance.

The group of experts considered the proposed WHO Regional Strategy objectives and actions to be comprehensive, prudent, and feasible. However to accomplish achievable objectives in the medium term, the implementation of certain activities was felt to be of special urgency, especially to take best advantage of the opportunities offered by the European Antibiotic Awareness Day on 18 November 2010 and the following World Health Day on 7 April 2011.

Thus the identification of a concrete short-list of prioritized actions to be taken by the WHO Regional Office for Europe for the seven components of the Regional Strategy became an additional objective of the meeting. Given the significant political commitment, resources,

expertise, and organizational infrastructure which exist in most EU Member States, the focus of the WHO Regional Office for Europe activities will be non-EU members as well as low-resource eastern EU nations.

Strategic objective 1. National coordination

- Organize fact-finding country missions to priority countries to identify focal points and "champions" in the areas of antimicrobial use, resistance, public policy, and communication. These partners could become the core of a national intersectoral task force or working committee for coordinating activities in antimicrobial resistance surveillance and containment. These missions could adapt existing DG SANCO indicators accompanying the second report on the implementation of the Council recommendation (2002/77/EC) on the prudent use of antimicrobial agents in human medicine.

Strategic objective 2. Surveillance of antimicrobial resistance

- An "EARS-Net-like" system for non-EU countries is proposed to be coordinated through the WHO/Europe in harmonization with the standards of EARS-Net. Identify one or more national laboratories with expertise in AMR surveillance and support data collection on resistance in common bacterial pathogens such as those monitored by EARS-Net. For countries without a data management system in place, the WHONET software, available in many languages and used by many countries participating in EARS-Net, should provide a robust data management tool to support the surveillance programme. The first priority would be integration of the five non-EU countries which had previously participated in EARSS (Bosnia and Herzegovina, Croatia, Israel, Switzerland, and Turkey).

  Of note in 2009, EARSS was funded by the ECDC and the Dutch Ministry of Welfare and Sport at an annual cost of € 668 458 primarily to support the external quality assurance programme, organization of an annual plenary meeting and more frequent Scientific Advisory Board meetings, data management, and report generation.

- Institute capacity-building exercises in Member States without the needed infrastructure and expertise. This could include laboratory training workshops, site visits, and support for participation in external quality assurance schemes.

Strategic objective 3. Prudent use of antibiotics

- Identify a national focal point for the collection of quantitative data on hospital and community use of antimicrobial drugs utilizing the methods and tools established by ESAC. This will require an initial survey of possible sources of such data from national drug purchasing bodies, national insurance schemes, industry, and individual hospitals. In absence of the WHAAT auditing tool proposed in Section 4.1, explore the feasibility of recruiting hospitals from non-EU countries into the ESAC-maintained Hospital Point Prevalence Study described in Section 4.1.

Strategic objective 4. Health care-associated infections

- Strengthen adoption of the WHO Global Patient Safety Challenge recommendations for hand hygiene in the "Clean Care is Safer Care" campaign. Identify a few leading large academic and teaching hospitals and promote structured implementation of the "core components" of the IPC framework described in Section 4.7.

Strategic objective 5. Antimicrobial resistance and use in food animals and agriculture

- Build advocacy and partnerships at the national level among ministries of health, ministries of agriculture, food and animal industry bodies, professional societies, and other stakeholders for review and assessment of the use of antimicrobials in animal production and agriculture with the aim of influencing the policies and attitudes towards a more prudent use of antimicrobials in these sectors.

- Work towards implementation of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO AGISAR) recommendations for surveillance of antimicrobial resistance and use at the national level. For lowest-resource countries, the top priority is the initiation of surveillance of antimicrobial resistance in *Salmonella* from humans followed by meat products such as chicken, swine, and cattle. Capacity-building should be done in close partnership with the Global Foodborne Infections Network (GFN).

Strategic objective 6. Research and innovation

- Participate in the establishment and guidance of the research agenda established by European Commission Directorate-General for Research and Innovation and the Trans-Atlantic Task Force on Antimicrobial Resistance. Priorities include new antimicrobial development, innovations in point-of-care diagnostics, and operational research into strategies and measures to improve the use of antimicrobials in hospital and/or community settings and to decrease health care-associated infections.

- Assist Member States in the creation of national research agendas for antimicrobial resistance and facilitate applications by institutions and partnerships in Member States to DG Research, TATFAR, and other research-funding agencies.

Strategic objective 7. Partnership and patient safety

- Take advantage of European Antibiotic Awareness Day 2010, World Health Day 2011, and ECCMID 2011 (Milan) as starting points for partnerships and advocacy campaigns to raise public and national awareness of the antimicrobial resistance threat, especially in non-EU countries. This will require close collaboration between international organizations and projects, and government agencies such as WHO, ECDC, ESAC, ESCMID, FAO, and OIE, as well as nongovernmental organizations including CGD, ReAct, APUA, INRUD, and ISUM.

MDR-TB and XDR-TB

- The WHD on 7 April 2011 will focus on AMR. In the European Region, this will be an important opportunity to increase awareness of the high rates of MDR-TB (the highest in the world), as well as of the estimated 62 000 undetected cases with MDR-TB.

- The general strategy on AMR and the focus on surveillance at microbiology laboratories, as well as other aspects of containment, such as hygiene, infection control and rapid test for drug-resistant TB should provide opportunities for integrated activities on case detection and control for M/XDR-TB.

- The intersectoral national coordinating committees on the containment of AMR, which are proposed in strategic action point 1, should include a representative of the national TB control programme, especially in those countries with high burden of multidrug-resistant tuberculosis.

Annex 1

SCOPE AND PURPOSE

Antimicrobial drug resistance (AMR) is increasing and is threatening to affect the health gains obtained in the last 50 years. Failures to prevent infections during or after medical intervention increase morbidity, mortality and costs. Hospital infections and treating infections at the primary level are increasingly faced with resistance, which is driven by overuse, the use of the wrong antibiotic agents and increasingly in some parts of the WHO European Region the use of sub-quality drugs and the affordability of the right drugs. In the European Region, an estimated 80 000 cases of TB resistant to multiple anti-tuberculosis drugs are occurring each year. Prevention and control of AMR is complex and should involve many sectors of society, the government, agencies, universities, the private sector, the agricultural and pharmaceutical industry and the patient. The WHO global strategy on AMR of 2002 has not been implemented in many countries and the need for a regional adaptation remains. Recognizing the need to address the problem of AMR the next World Health Day (WHD), on 7 April 2011, will be dedicated to make multiple stakeholders aware of the emerging threat of AMR. This will allow for a renewed effort to introduce a regional strategy on AMR in 2011.

The first meeting of AMR experts in the WHO Regional Office for Europe will review how the WHD can be best used to reach a broad public of stakeholders, adding to ongoing activities and contribute to a regional strategy on AMR.

Objectives of the meeting:

1. review the main components of a regional strategy taking into account the work already under way especially in the EU, the WHO strategy of 2002 and the WHA-related resolutions;

2. review of the main stakeholders involved in surveillance, prevention and control of antimicrobial resistance in the European Region;

3. review the main messages, target audience and best communication methods for an awareness campaign on WHD 2011;

4. harmonize the awareness campaign on the WHD with other events in the Region;

5. discuss follow-up activities.

Annex 2

PROGRAMME

Opening

Election of Chairperson and Rapporteur

Adoption of programme

Background on Regional Strategy for AMR in the WHO European Region

Roundtable discussion, presentation by participants, conclusions

Introduction to a regional approach to increase awareness of AMR in the WHO European Region

Briefing by ECDC on EAAD

Briefing by WHO headquarters on WHD 7 April 2011

Briefing by TB programme on World TB day 2011

Discussion and conclusions

Follow-up

Closure

Annex 3

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