WHO Workshop on the Containment of Antimicrobial Resistance in Europe

Report on a WHO Meeting

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<td>MRSA</td>
<td>Methicillin-Resistant <em>Staphylococcus Aureus</em></td>
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<td>ESBL</td>
<td>Extended-Spectrum Beta-Lactamase</td>
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<td>EARSS</td>
<td>European Antimicrobial Resistance Surveillance System</td>
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The appearance and spread of infective agents resistant to commonly used antimicrobials has long been recognized and continues to increase in a number of key areas. It is also known that overuse and misuse of antimicrobials contributes to the emergence of resistance and its amplification. WHO has recognized this threat and, in formulating resolutions of the World Health Assembly (WHA51.17 and WHA54.19) in 1998 and 2001, Member States agreed to address the problem.

In September 2001 WHO released a comprehensive strategy for antimicrobial resistance surveillance and containment for application at country and international levels (WHO Global Strategy for Containment of Antimicrobial Resistance). This strategy is based on the following principles:

- Reduction of disease burden and the spread of infection
- Improved access to appropriate antimicrobials
- Improved use of antimicrobials
- Appropriate regulation and legislation
- Surveillance of antimicrobial resistance
- Focused research

The implementation strategy was devised as set of 67 recommendations for interventions, predominantly at national level.

The WHO Global Strategy Implementation Workshop, held in WHO headquarters, Geneva, on 25-26 November 2002, highlighted the lack of progress in many areas of the world in implementing the recommendations of the WHO Global Strategy.

This present Workshop was convened with the objectives of:

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

The Workshop was co-organized with the Robert Koch Institute Berlin and in close collaboration with the WHO European Regional Office. The generous support of the German Ministry of Health is gratefully acknowledged, as is that of the Robert Koch Institute, Wernigerode, concerning the local organization of the meeting.

Professor W. Witte who chaired the proceedings of Day 1 welcomed the Workshop delegates. This was opened by Professor R. Kurth, who set the scene by discussing the implication of antimicrobial resistance (AMR) spread in Europe. This was followed by a range of presentations on AMR in different areas, such as the Mediterranean Region and eastern Europe, and in different settings such as hospitals and in the community. Specific topics such as methicillin-resistant Staphylococcus aureus (MRSA), diagnostic tools and antibiotic use were also dealt with. The meeting agenda is given in Appendix 1 and the participants are listed in Appendix 2.

Day 2, chaired jointly by Dr P. Jenkins and Dr B. Ganter, consisted of group work covering:

- Advocacy for AMR containment
- AMR surveillance and diagnostics
- Appropriate antibiotic use
INTRODUCTION

Antibiotic resistance was first documented nearly six decades ago and became an important issue in the 1960s when resistance plasmids and transmissibility were detected. At this time, however, progress in development and introduction of new antibiotics was still being made. This situation had changed by the beginning of the 1990s, when resistance development in particular pathogens made certain currently available antibiotics ineffective (1). Antibiotic-resistant pathogens became an important and growing threat to public health which was addressed by national agencies and international bodies such as the European Commission and especially WHO. The latter developed a Global Strategy for Containment of Antimicrobial Resistance in 2001 (2). The molecular mechanisms of resistance development have been investigated in great detail (3, 4), and there is increasing knowledge of the selective pressure exerted by antibiotic use (5). The emergence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA) in nosocomial infections had led to the establishment of a considerable number of recommendations for infection control and containment of antibiotic resistance. Surveillance data from international studies such as the European Antimicrobial Resistance Surveillance System (EARSS) revealed that success in controlling MRSA had been greatest in countries (e.g. Denmark, Finland, Netherlands [6, 7, 8]) that adhered to rigorous infection control policies, including active surveillance cultures to identify colonized patients.

We know how antibiotic resistance develops and how it is disseminated, and we know about the effectiveness of appropriate surveillance and infection control practices (9). There is also extensive literature on recommendations for antibiotic usage (10). Nevertheless, resistance development has continued for a number of bacterial pathogens which, apart from *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*, are particularly associated with nosocomial infections such as MRSA and extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae.

The aim of this Workshop is to present examples of recent resistance developments, to discuss reasons for this, and to provide recommendations for more efficient implementation of strategies for containment of resistance.
Infectious diseases still account for 45% of deaths in low-income countries, and 85% of these deaths are due to five diseases: acute respiratory infections, diarrhoeal disease, HIV/AIDS, tuberculosis and malaria. Resistance to anti-infectives not only increases the mortality and morbidity due to infectious disease but also has an important impact on the cost of health care. In the case of pneumonia, meningitis and some sexually transmitted infections, the switch from first-line to second- or third-line treatment increases drug costs by up to 90-fold. A number of studies have shown a correlation, both over time and geographically, between antimicrobial use and the spread of resistance.

The use of antimicrobials in animals destined for human consumption undoubtedly contributes to the emergence and spread of resistance. The WHO Global Principles for the Containment of Antimicrobial Resistance in Animals intended for Food called for a phasing-out of the use for growth promotion in farm animals of antimicrobials with therapeutic relevance for humans.

In September 2001 the WHO Global Strategy for Containment of Antimicrobial Resistance was issued. This included over 60 recommendations for implementation, organized into a number of priority groups, together with indicators for monitoring implementation and outcomes. Most of the responsibility for implementing interventions will fall on national governments.

National governments and health care systems can have considerable impact on limiting the emergence and development of antimicrobial resistance through the introduction of legislation and policies concerning the development, licensing, distribution and sale of antimicrobial agents. National governments also have the responsibility for coordinating surveillance networks and for directing educational efforts to improve understanding about appropriate antimicrobial use.

Countries with poor antimicrobial resistance records need to be supplied with advocacy tools that will convince governments of the importance of making antimicrobial resistance containment a national priority, that will influence prescribers to adhere to sound antimicrobial prescription practices, and that will increase public awareness of antimicrobial resistance.

The first essential action in enabling such initiatives to proceed is the creation in each country of a national intersectoral Task Force on antimicrobial resistance, composed of health care professionals, veterinarians, agriculturalists, pharmaceutical manufacturers, government, media representatives, consumers and other interested parties.
3.2 WHO European Region Strategies for Antimicrobial Resistance

Bernardus Ganter, Regional Advisor, Communicable Disease Surveillance and Response, World Health Organization, Copenhagen, Denmark

The globalization of travel and trade has brought the risk of emerging diseases close to all countries, as was the case during the SARS outbreak in 2003. Many other emerging infection outbreaks have occurred during the last 25 years and antimicrobial resistance has become a major concern. Now, 75 years after the discovery of penicillin, resistance of *Staphylococcus aureus* strains in the community can exceed 80% and in hospital strains may be over 95%.

The WHO European Region, with over 850 million inhabitants in 52 Member States, is susceptible to these global risks, including the spread of AMR strains, and surveillance and control systems vary widely in many aspects. In at least 15 countries in the eastern part of the WHO Region, budgets for public health are low and the change from centralized organization during the Soviet period and to market economies in the last 15 years has had a profound impact on both socioeconomic status and health care systems, leading to many under-funded and therefore under-performing programmes. As an example of the increased risk of infectious disease, the incidence rate for syphilis in 1999 was on average 100 times higher in eastern European countries than the yearly average in western European countries.

Tuberculosis case rates have jumped to over 100 cases per 100 000 population and multi-resistant TB has increased to over 10% of newly reported cases in some countries. Furthermore, in eastern European countries the prevalence rate of HIV increased by over 1300% between 1996 and 2001, giving rise to one of the fastest-growing HIV epidemics in the world, mainly due to intravenous drug use. As shown in data collected by the European Antimicrobial Resistance Surveillance System (EARSS), both a North-South as well as a West-East gradient of increasing *S. pneumoniae* resistance has been identified.

In the WHO European Region, several international activities have developed in recent years to face and control or even reverse the AMR trends. These include workshops organized in collaboration with WHO in Visby (1994), Verona (1997) and Copenhagen (1999), as well as the creation of European networks such as EARSS for the surveillance of AMR in bacterial pathogens and ESAC (European Surveillance of Antibiotic Consumption). ESAC has studied the use of antimicrobial drugs in the countries of the European Union, including some of the accession countries. Many other groups or networks are working directly or indirectly in similar fields at the international and national levels, including HELICS, ESSTI, ENARE and SCORE. In spite of the availability of ample evidence concerning AMR as an increasing public health problem, the findings discussed during the Verona workshop have unfortunately not led to efficient control programmes, although some countries have made considerable progress. WHO launched its Global Strategy for containing AMR in September 2001, but this has not led to the operational implementation of efficient and appropriate surveillance and control systems in all countries. There is a need in the European Region to face the challenges of implementing effective control programmes, including better definitions and standards for hospital- and community-based surveillance systems, as well as standardized indicators to measure epidemiological trends and programme progress. There is a need to improve the political awareness of the burden of diseases caused by AMR, increase public awareness and, above all, increase public funding for improved programme implementation and development. Finally there is a need to strengthen partnerships with organizations working in the same directions, including the European Commission, pharmaceutical industry, scientific networks and associations and organizations outside the health sector where antimicrobial substances are promoted.

3.3 European Commission Strategies for Antimicrobial Resistance

Stef Bronzwaer, European Commission, DG SANCO, Directorate Public Health, Luxembourg

In 2001 the European Commission presented a “Community strategy against Antimicrobial Resistance”. The strategy consists of fifteen actions in four key areas: surveillance, prevention, research and product development, and international co-operation. An important part of this strategy is the “Council Recommendation on the prudent use of antimicrobial agents in human medicine”. This Recommendation provides a detailed set of public health actions to contain antimicrobial resistance. This paper presents the eleven points of action of the strategy that are directly related to human medicine (focusing on Surveillance and Prevention), and discusses related Community activities. Through the Community strategy, the Commission has outlined a more comprehensive and pro-active approach to contain
antimicrobial resistance, working closely in partnership at the international level, in particular with WHO. In addition to legislative measures, the Commission considers antimicrobial resistance as a key priority through its public health and research programmes.

In 2002, a new programme of Community action in the field of public health (2003-2008) was adopted. This programme provides for an annual public health workplan and a funding mechanism for projects addressing priorities such as antimicrobial resistance. Over recent years emphasis has been given to surveillance initiatives, whereas the focus of future public health workplans may need to be broadened. Activities that develop principles and guidelines for good practice on the prudent use of antimicrobial agents are needed, as well as educational activities and intervention programmes to combat antimicrobial resistance.

**AMR IN EUROPE: THE SCOPE OF THE PROBLEM**

### 4.1 The Rise of MRSA in Central Europe

*Wolfgang Witte, Robert Koch Institute, Wernigerode Branch, Wernigerode, Germany*

As revealed by results from the regional studies of the Paul Ehrlich Society for Chemotherapy in central Europe, the frequency of MRSA increased from 1.7% in 1990 to 20.3% in 2001. This is mirrored by data on MRSA from systemic infections provided by EARSS. Over the same period, frequencies of MRSA remained at low levels in other European countries such as Denmark, Netherlands and Finland. The MRSA frequencies in German hospitals vary considerably throughout the country (range: <1% - 30%), indicating that there are efficient ways of controlling the spread. Increasing frequencies of MRSA are associated with dissemination of particular epidemic MRSA strains which are characterized by molecular typing patterns (Smα-macrorestriction, MLST, spa-sequence). During the past 10 years a dynamic of epidemic strains has been observed, with the older, more broadly resistant strains (e.g. ST247) becoming more rare and the newer ones (e.g. ST22, ST45) more frequent. Emergence of MRSA among the residents of nursing homes is still low (~3%). From the end of 2002 until the present, the emergence of community-acquired MRSA containing the lukS-lukF determinant (Panton-Valentine Leukocidin, particularly invasive strains) has been recorded. The majority of the 24 isolates exhibit MLST type ST80 as cMRSA from France. One isolate from chronic furunculosis corresponded to cMRSA from the USA (ST1). The results presented underline the need for more consistent implementation of efficient infection control based on active surveillance (with colonization included), associated with barrier and transmission precaution measures.

### 4.2 Antimicrobial resistance in the Mediterranean Region

*Raul Raz, Infectious Diseases Unit, Ha’Emek Medical Center, Afula, Israel*

The data presented show the antimicrobial susceptibility of some bacteraemic pathogens in three Mediterranean countries: Greece, Israel and Malta. In general, lower resistance rates in Malta, compared to Greece and Israel, are seen. In a local survey carried out in one of the Israeli medical centres, demographic and clinical characteristics of patients with bacteraemia were recorded. A slight decrease in the presence of *E. coli* and concomitant increase in *S. aureus* and Enterococci were noted. In addition, there was a decrease in the susceptibility of both *E. coli* and *S. aureus*. The originality of this survey is the presentation of bacteraemic episodes according to origin, community, hospital or long-term care facility. The susceptibility of community-acquired uropathogens in Northern Israel during nine years was also presented and showed an increase in the proportion of sensitive uropathogens to most of the antimicrobial agents used in the community. A high resistance rate of gonococci during recent years was noted, and distribution and susceptibility data of enteropathogens in Northern Israel were also described.

### 4.3 Extended spectrum beta-lactamase (ESBL)

*Sergei V. Sidorenko, Department of Microbiology of Russian Medical, Moscow, Russian Federation*

It is generally accepted that infections caused by an extended spectrum beta-lactamase (ESBL)-producing organism are associated with increased risk of treatment failure with 3rd or 4th generation
cephalosporins. The prevalence of ESBLs among clinical isolates varies from country to country and from institution to institution.

Eastern Europe is affected seriously by the emergence and spread of different ESBLs among hospital-acquired and some community-acquired pathogens. According to the data from international multicentre surveys, the prevalence of ESBL producers among Enterobacteriaceae isolated in ICUs in Poland and Russia is more than 40%. In ICUs in some Moscow hospitals, more than 90% of *Klebsiella* spp. isolates harbour ESBLs.

Molecular studies reveal that SHV-like enzymes are predominant among ESBL producers in Poland and Russia (in 60% and 70% of isolates, respectively), TEM-like enzymes in 20% and 40%, and CTX-M-like enzymes in 20% and 40%. In Russia 45% of isolates harboured 2 or 3 different enzymes simultaneously.

CTX-M enzymes are currently of particular interest, having formed a rapidly growing family of ESBLs distributed among members of the Enterobacteriaceae in eastern Europe. Among isolates from hospital-acquired infections (*E. coli*, *Klebsiella* spp., *Proteus* spp. and others) in Poland, Bulgaria, Romania and Russia, enzymes of the CTX-M-1 group are predominant, whereas CTX-M-2-like and CTX-M-9-like enzymes are detected only occasionally.

*Salmonella enterica* is another member of the Enterobacteriaceae affected by CTX-M-like enzymes in eastern Europe. *S. enterica* serovar Typhimurium isolates producing CTX-M-2-like enzymes have been implicated in sporadic diseases and outbreaks in Latvia, Russia, Hungary and Greece since 1990. The export of *S. enterica* serovar Typhimurium producing CTX-M-5 enzyme from Russia to the USA has been reported. In Moscow CTX-M-2-like enzymes were detected in more than 80% of *S. enterica* serovar Typhimurium isolates in 2003.

In conclusion, the rapid expansion of CTX-M-producing strains is now a major concern in eastern Europe and a potential threat for western Europe. Two distantly related groups of enzymes are spreading among hospital- and community-acquired pathogens. CTX-M-1-like enzymes are spreading among the members of the Enterobacteriaceae in hospital settings, and CTX-M-2-like enzymes among *S. enterica* in the community.

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**THE PRESENT STATUS OF AMR SURVEILLANCE & CONTAINMENT ACROSS EUROPE**

**5.1 Antimicrobial resistance surveillance at hospital and national levels: data for action**

*Marc J. Struelens, Service de Microbiologie, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium*

Surveillance of antimicrobial drug resistance (AMR) is an essential laboratory-based source of information to physicians and health policymakers. It can be performed at different levels, from a local programme to an international programme, and serve a number of different objectives. Key parameters in designing and operating such a surveillance system depends on its objectives and information end-users. These parameters include: definition of study population, target disease and sampling strategy, representativity of clinical samples to disease spectrum, laboratory methods including culture and susceptibility testing, definition of resistance, epidemiologic indicators used for analysis and feedback format.

A first objective of AMR surveillance is to monitor the probability of pathogens causing a particular infectious syndrome to be resistant to empirical therapy and to guide recommendations for changing empirical therapeutic schemes. This entails community-specific or hospital-specific monitoring of resistance frequency to commonly used antibiotics from clinically significant, representative samples of bacteria, usually on a yearly basis.

A second objective of local surveillance can be to detect the emergence of new patterns of resistance (including acquired low-level resistance phenotypes or determinants that may not be predictive of clinical failure) and epidemic spread of resistant clones of a particular pathogen. A third, and related objective, is to monitor the effect of interventions, such as infection control or antibiotic policy, to prevent or curb antibiotic resistance emergence and spread. For the latter two objectives, more comprehensive sampling strategy, including active surveillance cultures for detecting colonised patients, should be included in the surveillance data. Special culture and testing methods may be required to increase the specificity and
sensitivity of detection of target resistant phenotype/genotypes. Epidemiological typing is necessary to delineate clonal spread.

There is consistent evidence that cost-effective control of major healthcare-associated resistant pathogens such as methicillin-resistant *S. aureus* (MRSA) depends critically on active screening of carriers among high-risk patients and stringent application of contact barrier precautions to limit spread. Developing optimised active surveillance locally can be supported by national guidelines adapted to the healthcare setting and organisation, which differ significantly between countries. Concerted implementation of active hospital-based surveillance and isolation policies have kept MRSA incidence at very low levels for decades in Northern European countries and have likewise led to a decrease in the burden of nosocomial MRSA infections even in countries where these strains have reached endemic proportion, such as Belgium and France.

Multicentre surveillance at national and international levels can provide early warning of emerging resistance and monitoring of secular trends by region or by country. However, because laboratories use different methods and interpretative definition of resistance varies by country, passive reporting and comparison of routinely produced test results is often biased. Method and breakpoint harmonisation, such as that supported by WHO and EUCAST programmes, as well as cross-validation and laboratory proficiency testing, such as that implemented within the EARSS system, are important steps towards improving the reliability and comparability of numerator data. New, active surveillance methods must be defined and applied in a coordinated manner to monitor more accurately the disease burden and dynamics of antibiotic resistance, as well as inform local and national control policies. This includes revision of sampling procedures, implementation of advanced testing methods and selection of denominator-based incidence indicators designed to meet specific public health objectives.

Selected references:


5.2 Infection control and antibiotic policies in hospitals

*Stephan Harbarth, Division of Infectious Diseases, Infection Control Program, Geneva University Hospitals, CH-1211 Geneva 14, Switzerland*

**A. Infection control (using the example of MRSA)**

For over 30 years, methicillin-resistant *Staphylococcus aureus* (MRSA) strains have been identified as a major source of nosocomial infections and outbreaks in the healthcare environment. MRSA is recognised as a significant cause of mortality with, for example, MRSA bacteraemia resulting in higher rates of mortality than bacteraemia caused by methicillin-sensitive *S. aureus*. The prevalence of MRSA has now reached such high levels in certain parts of the world that some people may be tempted to argue that the battle is already lost. Indeed, MRSA bacteria are now so widespread throughout Europe that it has been referred to as “the EURO of infection control”. The problem can also be exacerbated by over-liberal use of antibiotics. Japan’s MRSA prevalence of >50% may be due in part to the fact that 20-30% of a Japanese physician’s income is derived from drug prescriptions, which can encourage the over-use of expensive, broad-spectrum antibiotics.

i) **Colonisation and infection**

Colonisation increases the chance of infection for the patient. Stays in intensive care, catheterisation, pressure ulcers and surgical wounds can all add to this risk. MRSA bloodstream infections are just the “tip of the iceberg”. There is an underlying reservoir of known and unknown carriers. Data from the University Hospital of Geneva (Switzerland) show a very good correlation between the number of total newly colonised and infected patients and the number of bloodstream infections.

ii) **Key parameters for controlling MRSA**
a) Improved hand hygiene and contact isolation
It is essential that hand hygiene is both improved and promoted, alongside contact isolation of carriers to prevent the spread of MRSA. The main route of MRSA transmission is physical transfer via the hands of healthcare workers or from patient to patient. Very little MRSA is transmitted via air. Alcohol-based hand rubs can take as little as 10-20 seconds to use and should therefore be considered as the chosen standard of care. Hand washing should only be used when the skin is visibly soiled. Contact isolation can also play a vital role in keeping MRSA in check. In studies from Charlottesville, USA, the risk of nosocomial transmission of MRSA was reduced 16-fold by contact isolation during an MRSA outbreak in a neonatal intensive care unit.

b) Decolonisation
Mupirocin may be used, along with antiseptic body washes, to decontaminate carriers, but this is of little use for patients with skin lesions or ulcers. The overall efficiency of decolonisation in endemic MRSA settings remains unclear.

c) Active screening
Carrier status can be difficult to recognise, as it may be prolonged, or recurrent, and varies with underlying disease. Better knowledge of the patient reservoir, however, is essential in order to take more appropriate action.

d) Control programs
Combinations of screening, hand hygiene, decolonisation and other factors have formed the basis of several successful control programs in endemic acute care institutions.

B. Antibiotic policies
Unnecessary and irrational antimicrobial use augments the risk of selecting resistant bacterial strains. Despite the liberal use of antibiotic prescription, in some patients bacterial infection is not diagnosed until they have progressed to serious conditions like septic shock. Considering this dilemma, the question arises: What can be done to improve antimicrobial management of patients with suspected bacterial infection, without harming patients and increasing the risk of adverse outcomes? In the following paragraphs, we would like to offer some tentative answers to this question:

- Appropriate antimicrobial prescribing should benefit the patient. There should be clear clinical evidence, supported by laboratory and microbiological tests. Laboratory parameters should be documented and should support the need for antimicrobial treatment. Critically ill patients should receive appropriate treatment as quickly as possible in order to decrease the risk of adverse outcomes.
- Empiric treatment should be limited to severe infections, using antibiotics directed against potential causative agents, given in optimal dosage, interval and length of treatment.
- Prophylaxis or pre-emptive treatment should be limited to selected indications only. Overuse of surgical prophylaxis is a universal tendency in many hospitals. Despite a lack of evidence of benefit from such prophylaxis for more than 24 hours following an operation, surveys revealed that many surgeons extend antibiotic use to more than 24 hours.
- Standard treatment guidelines should cover both health-care-associated and community-acquired infections, should be readily accessible, drawn up with multidisciplinary prescriber involvement, subject to peer review, evidence-based where possible and compatible with local resistance patterns.
- Treatment duration should be shortened according to recently available evidence (e.g. 8 days for ventilator-associated pneumonia). Antibiotic therapy should be streamlined at the earliest opportunity, using culture results and susceptibility testing whenever available. It is helpful for the physician to know the sensitivity patterns of organisms isolated in a hospital. Therefore, the microbiology laboratory should provide these data at least once a year. There is a great need to improve the clinical diagnostic rigour prior to treating suspected bacterial infection where, for too long, broad-spectrum antibiotics have been used as a substitute for accurate diagnosis because of their perceived safety. Sepsis parameters such as procalcitonin may help to assess the severity of infection and allow withdrawal of antimicrobial treatment at an earlier stage. Clearly, new diagnostic approaches aimed at improving detection of early sepsis are needed.
5.3 National drug use surveillance and improving antibiotic prescribing

Winfried V. Kern, Centre for Infectious Diseases and Travel Medicine, University Hospital, Freiburg, Germany

Although the relationship between antibiotic use and antibiotic resistance is complex and dynamic, there is no doubt that more intense antibiotic use will eventually lead to higher resistance that may be associated with increasing treatment failures. There is increasing evidence showing that antibiotic use in human medicine does not only vary according to patient characteristics (medical determinants) but also according to geographical location associated with different health systems, reimbursement systems, medical education, primary care structural components, cultural expectations and market characteristics (socioeconomic and cultural determinants). In European countries, striking variation in overall antibiotic consumption as well as in specific drug class use densities has now been confirmed by the European Surveillance of Antibiotic Consumption (ESAC) database. For the outpatient setting (covering ~80-90% of the total antibiotic exposure), ESAC offers national antibiotic use density estimates based on reimbursement data (thereby excluding drugs that were sold over-the-counter) for many European countries. Limited data are available so far for the hospital setting, but there has been an increasing number of successful surveillance programmes that include the hospital setting (e.g. the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme [DANMAP], the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance [STRAMA], or the more recent Medical Antibiotic Use Surveillance and Evaluation [MABUSE] network and Surveillance of Antibiotic Use and Resistance in Intensive Care [SARI] project in Germany). Given the well documented, large, medically unexplained variation in antibiotic use, an important question is whether programmes are available that are effective in reducing unnecessary antibiotic use, and, if the answer is yes, what could be the reasons for reluctance to establish such programmes in areas where they would be felt to be needed. In fact, there are many reports of successful antibiotic use reduction programmes, both in the inpatient as well as outpatient setting. The experience with national (often multifaceted) campaigns to reduce community prescribing, for example, has been favourable. In particular, prime-time TV spots may be very effective in addressing patient knowledge and expectations towards “antibiotics for flu” and may be very cost-effective in reducing antibiotic use. Such educational programmes, however, appear to require repeated efforts to exert a sustained effect, otherwise they tend to be short-lived. It should also be clear that the scope of such programmes is often beyond the medical profession. Medical doctors may not be the appropriate target for educational programmes in some settings. According to a recent finding in the course of a Canadian campaign, it was observed that nurses may initiate up to 80% of antibiotic prescriptions in continuing care centres. Since there is sufficient evidence that appropriately designed programmes will be able to reduce antibiotic use, the next question is why such programmes are not being established on a larger scale. Major issues here are cost and a lack of understanding on the side of the general public as well as the policy makers as to the aim of reducing prescribing. It is obvious that a mere reduction in antibiotic use cannot not be the primary endpoint of funded intervention programmes. A recent paper from England, for example, reported that a reduction in antibiotic prescribing for respiratory tract infections in winter periods since 1995 of 30% was associated with a ~50% increase in winter excess pneumonia mortality adjusted for influenza incidence. It must be explained and shown that excess antibiotic use reduction is the key issue, and that it can prevent “adverse outcomes” (via resistance and/or associated with drug treatment toxicity and cost). The cost issue includes some misunderstanding on the part of funding bodies that surveillance programmes (antibiotic use and resistance) alone are not enough and are not the same as, but just prerequisites for, intervention programmes.
6.1 Advocacy for AMR containment and surveillance

There is still insufficient awareness at government level of the seriousness of the AMR situation and, in many countries, the willingness to contain it is questionable. At present the pressure for action comes mainly from outside governments, and more initiatives for containment measures need to come from within ministries of health, etc.

More needs to be done by the health and scientific communities in terms of presenting the AMR issue to politicians, prescribers and the public. In view of the wealth of information on antibiotics coming from the pharmaceutical industry, more balanced information on antibiotics, taking into account the risks of worsening the AMR situation, needs to be provided to prescribers, especially those who have entered the profession relatively recently. The issue also needs a higher profile in the public eye, through articles in newspapers and magazines and clear messages on radio and television.

The most important measures that will lead to resistance containment vary from country to country. National programmes should be developed that blend with the international/EU approval to containment. In the first instance, a national Task Force and Reference Laboratory for AMR should be established.

6.2 AMR surveillance and diagnostics

a) Is there currently any effective AMR surveillance in the countries represented?

There are effective surveillance systems in all the countries represented, but they are limited either to selected regions or to particular pathogens.

- Effective AMR surveillance at national level should describe trends and provide early warning.
- Surveillance systems should be representative and sentinel based as an integrated approach, including the community, hospitals and food animals.
- For reasons of cost effectiveness, surveillance should use routine data.
- As a prerequisite, appropriate standards and external quality assurance need to be implemented and reference laboratories need to be established.

b) How is this surveillance information used nationally/internationally?

In some countries surveillance data are already used for treatment and/or prevention guidelines. More extensive use of the data should be implemented in all European countries, and there is an urgent need to improve data exchange between countries.

c) What is hindering more widespread AMR surveillance?

- There are substantial funding deficiencies.
- There are overlapping initiatives which should be streamlined, and communication between different authorities is still not optimal.
- In some countries and some institutes there is still insufficient quality control, and insufficient harmonization of antimicrobial susceptibility test (AST) methods.

d) What are the possibilities for more cost-effective AMR surveillance?

- Harmonization of AST methods and more training (EUCAST)
- Improved external quality assurance
- Improving routine AST methods, e.g., genotypic tests for resistance detection
- Maintaining and increasing the use of microbiological diagnostic data
- Stepwise development of surveillance systems based on a national priority list

e) Is AMR surveillance sufficiently implemented at hospital level, and are surveillance data efficiently used for infection control (early warning)?

- Surveillance data is used in many European countries, but the number of participating hospitals needs to be increased.
- Early warning requires targeted surveillance screening for particular pathogens and emerging resistance traits (e.g., MRSA, glycopeptide-resistant S. aureus, glycopeptide- and multiply-
f) Are current strategies and recommendations for AMR containment efficient and practicable?
Current guidelines offer a range of efficient control strategies, but they need to be adapted to the national and local epidemiological situation and to available resources.

g) What should be done in the situation of already elevated resistance development?
- Decisions have to be based on the local epidemiological situation, including the clinical impact, epidemic trends, evaluation of local intervention and resources.
- Appropriate response requires the presence of trained infection control staff in each hospital.

h) Are the currently available methods for diagnostics of AMR sufficiently sensitive and rapid?
- Detection methods are available for most resistance mechanisms, but further development is necessary with respect to time (more rapid molecular methods) and sensitivity.
- Interpretation of tests is crucial and should be based on resistance mechanisms.

6.3 Appropriate drug use

a) How to develop cost-effective models for surveillance of antimicrobial use in all areas of health care?
- Surveillance of antimicrobial use should be based on a quantitative (and not qualitative) analysis.
- Group-level data should be used, since individual patient-level data are rarely available.
- The surveillance of antimicrobial use should include the use of antimicrobial agents both for outpatients (community) and for inpatients (hospitals).
- This analysis should be performed for each country (at national level) per year and separately for outpatients (in a local area) and for inpatients (analyzes in large hospitals).
- As methodology, the WHO DDD method (including software support) should be used.
- Local feedback of the surveillance results on antibiotic use to the data-delivering partners concerning the out- and inpatients is necessary. This should also include a benchmarking of the results to show ways for a rational use of antibiotics in both hospitals and the community.

b) How to promote rational prescription of antibiotics in hospitals, primary health care and the community and gain the necessary government and professional investment to do so?
- A national task force for rational antibiotic use should be established, linked to WHO and EU recommendations.
- Financial support for surveillance of antibiotic use is necessary to ensure extensive and accurate analysis of these data.
- Evidence-based guidelines elaborated with professional societies should result from the surveillance data.
- Regulatory mechanisms regarding drug registration (approved indications) and restriction should be established.
- A very important point for rational use of antibiotics is local education and control by opinion leaders. Additionally, information and education on these aspects need to be established in all medical schools and the public.
- Regulations concerning “over the counter (OTC)” use must be enforced and stronger penalties (following EU standards) considered.
- Improved diagnostic tests are necessary to support the rational use of antibiotics (e.g., rapid tests for streptococcal pharyngitis).
- It is important to encourage the development and facilitate the reimbursal of new (rapid) diagnostic tests.
- Regulation by restriction and formularies (infectious diseases approval) in case of strong abuse is needed.
- Extended surgical antibiotic prophylaxis should not be reimbursed.

c) How to cooperate with industry to promote appropriate drug use?
- The registration process should be checked periodically. Are dosage, ecological issues and duration of antibiotic use still optimally defined?
• Partnership with the pharmaceutical industry should focus on periodical reviews of the registration process with respect to indication, optimal definitions of dosage, ecological issues and duration of therapy.
• The marketing strategies of the pharmaceutical industry at hospital level should be directed towards the infection control team and local pharmacy and not focus on direct contacts with junior doctors.
• Aggressive campaigns for promotion of particular antibiotics should be avoided.
• Decreased dependence on funding by industry and sources derived only from industry is desirable.
• A critical evaluation of “new” drugs is necessary. Are they really superior in comparison to established drugs, e.g., regarding antimicrobial efficiency and resistance to microbial resistance mechanisms, pharmacokinetic and pharmacodynamic properties, side effects, etc?
• An intensive analysis of the potential collateral damage caused by the introduction of new broad-spectrum antibiotics should be performed.

d) How to combine data from AMR surveillance and antibiotic use at hospital level?
• There is an urgent need for good studies and more research in this area.
• Standardized approaches should be introduced and used in practice.
• Currently this is only feasible in the context of surveillance networks.
CONCLUSIONS AND RECOMMENDATIONS

a) Overwhelming evidence exists that AMR is worsening in most countries. WHO has issued a Global Strategy to guide containment measures. Within the Member States of the WHO European Regional Office there is a need to develop a strategy to implement a public health approach for the control of AMR.

b) A Regional Strategy to improve both surveillance and control of AMR should be developed, and additional resources should be identified for its implementation. The development of standards and practical indicators for both process and progress should be included. An expert group should be convened to make a draft proposal.

c) A Regional expert group, composed of experts from different disciplines should be set up to advise on strategies for implementing the global objectives of improving control of AMR. This group would also advise WHO-EURO on other topics such as research needs, analysis of national programmes and progress reporting.

d) The establishment of a national AMR Task Force should be a top priority in all countries of the region. This should include public health specialists, infectious disease epidemiologists, microbiologists, clinicians, veterinarians, pharmacists, pharmacologists and representatives of the relevant ministries and associations.

e) Governments are more likely to respond to the worsening AMR situation when presented with hard facts, especially economic ones. Thus, it is essential that some data on the disease burden resulting from AMR be available. Even a few crude estimates are better than no data, e.g., the number of people who die from septic shock in intensive care units.

f) There is concern over the increasing burden of methicillin-resistance *Staphylococcus aureus* (MRSA), including community-acquired MRSA. Perhaps MRSA should be a focus for concern over AMR and be considered an emerging infectious disease. A communication strategy for MRSA would serve to increase awareness and funding around surveillance and control of MRSA specifically and AMR more generally.

g) Lack of harmonization of antimicrobial susceptibility test methods is still a problem. It should be addressed, preferably through the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

h) External quality assurance testing should be extended to cover the whole region. All reference laboratories should be tested at least once, preferably twice, per year. This could be done within the framework of the WHO/EQAS system, or by the system used by most European countries EU-RQAS, and other national QA references within European countries.

i) There is an urgent need to improve the exchange between countries of AMR surveillance data. There is also a need for an early warning system for emerging/spreading resistance traits (e.g. MRSA, glycopeptide-resistant *Staphylococcus aureus*, linezolid-resistant gram-positive pathogens).

j) Further development of diagnostic methods for AMR is an urgent necessity, particularly with respect to sensitivity and rapidity. As an example, rapid tests for streptococcal pharyngitis would greatly facilitate the rational use of antibiotics.

k) Surveillance of antimicrobial use needs to be extended, particularly in eastern European countries. This should be based on quantitative, not qualitative, analysis, and needs to cover use in both hospitals and the community. Local feedback of survey results to the providers is necessary.

l) AMR surveillance and prevention should be implemented particularly at hospital level, where prescribers, microbiologists, clinicians can work closely together on rational use of antibiotics. AMR containment should be a major priority of hospital infection control committees. In hospitals above a certain size, the inclusion in such committees of a professional microbiologist is highly desirable.
m) Measures should be taken in hospitals to ensure that pharmaceutical industry marketing strategies are directed towards the infection control team and not to junior doctors.

n) Information on the extent to which each country is implementing the WHO Global Strategy should be made available, preferably with an indication of the degree of spending on this.

o) The participants found the meeting to be extremely useful and recommended that follow-up meetings should take place on regular basis. This would of course require additional funding.

ADDITONAL RESOURCES

SCOPE & PURPOSE

WHO is activating its work with the Global Strategy for containment of Antimicrobial Resistance. The starting point for this work originated in November of 2002 with the first WHO EURO meeting on Antimicrobial Resistance. The aims of this meeting were:

- to update present activities in the European region by the invited participants
- to discuss activities that have accomplished good results at country and at regional level
- to try to make a practical plan for implementation in the WHO European region based on the workshop suggestions.

On 26-27 February 2004 a WHO meeting is to be held in Wernigerode, Germany to continue progress on the containment of Antimicrobial Resistance. The aim of this meeting is:

- to examine the situation in the European Region regarding antimicrobial use and resistance trends;
- to ascertain the specific problems of antimicrobial use and resistance in a number of eastern European countries;
- to increase awareness of the WHO Global Strategy and promoting implementation of its recommendations.

Working groups convened on each of the three objectives:

GROUP 1: ADVOCACY FOR AMR CONTAINMENT AND SURVEILLANCE- ORGANIZATIONAL APPROACHES

- Is there currently an awareness of AMR at government level and a willingness to contain it?
- How to present the AMR issue to politicians, prescribers and the general public
- How to achieve funding for AMR containment and surveillance
- What are the most important measures in each country that will lead to resistance containment?

GROUP 2: AMR SURVEILLANCE AND DIAGNOSTICS

- Is there currently any effective AMR surveillance in the countries represented?
- How is this surveillance information used nationally/internationally?
- What is hindering more widespread AMR surveillance?
- What are the possibilities for more cost-effective AMR surveillance?
- Promotion of patient-near diagnostics to improve prescribers’ decision-making?
- Is AMR surveillance sufficiently implemented at hospital level, and are surveillance data efficiently used for infection control (early warning)?
- Are current strategies and recommendations for AMR containment efficient and practicable?
- What to do in the situation of already elevated resistance development?
- Are the currently available methods for diagnostics of AMR sufficiently sensitive and rapid?

GROUP 3: APPROPRIATE DRUG USE

- How to develop cost-effective models for surveillance of antimicrobial use in all areas of health care.
- How to promote rational prescription of antibiotics in hospitals, primary health care and the community and gain the necessary government and professional investment to do so.
- How to cooperate with industry to promote appropriate drug use.
- How to combine data from AMR surveillance and antibiotic use at hospital level?
PROGRAMME OF THE MEETING

THURSDAY, FEBRUARY 26, 2004

08.30 – 09.00  Registration

STRATEGIES FOR AMR CONTAINMENT

09.00 – 09.30  Opening remarks, objectives and programmes
               R. Kurth (RKI, president) / B. Ganter (WHO, EURO)

09.30 – 09.55  The WHO Global Strategy for Containment of Antimicrobial Resistance
               P. Jenkins (WHO, HQ)

09.55 – 10.20  EURO and EU Strategies for antimicrobial resistance
               B. Ganter (WHO, EURO) / S. Bronzwaer (DG SANCO)

10.20 – 10.50  Tea/Coffee Break

AMR IN EUROPE: THE SCOPE OF THE PROBLEM

10.50 – 11.20  Rise of MRSA in central Europe
               W. Witte (RKI)

11.20 – 11.50  Antimicrobial resistance in the Mediterranean Region
               R. Raz (Afula, Israel)

11.50 – 12.20  ESBL in eastern Europe
               S. V. Sidorenko (Moscow)

12.20 – 13.50  Lunch Break

PRESENT STATUS OF AMR SURVEILLANCE AND CONTAINMENT ACROSS EUROPE

13.30 – 14.10  AMR surveillance at hospital and national levels – data for action
               M. Struelens (Brussels)

14.10 – 14.50  National drug use surveillance and improving antibiotic prescribing
               W. Kern (Freiburg)

14.50 – 15.30  Tea/Coffee Break

15.30 – 16.15  Present status and future needs for diagnostic tools across Europe
               P. Courvalin (Paris)

16.15 – 17.00  Infection control and antibiotic policies in hospitals
               S. Harbarth (Geneva)
FRIDAY, FEBRUARY 27, 2004

09.00 – 10.30 Group Work on Practical Approaches to AMR Containment. Country representatives should identify next steps to be taken given the practical limitations and constraints present within their respective countries. Country representatives are encouraged to prioritize the work groups most relevant to the situation in their own countries.

GROUP 1:
ADVOCACY FOR AMR CONTAINMENT AND SURVEILLANCE- ORGANIZATIONAL APPROACHES

GROUP 2:
AMR SURVEILLANCE AND DIAGNOSTICS

GROUP 3:
APPROPRIATE DRUG USE

10.30 – 11.00 Tea/Coffee Break

11.00 – 12.30 Presentation from Work Groups and Discussion

12.30 – 13.30 Lunch Break

13.30 – 15.00 Final Discussion and Adoption of Recommendations

15.00 – 15.30 Tea/Coffee Break

15.30 – 16.00 Conclusions, Next Steps and Closing

W. Witte (RKI), B. Ganter (WHO, EURO)
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