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Surveillance uncovers the smoking gun for resistance emergence

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ABSTRACT

Today, antibiotic resistance is becoming a major healthcare concern. As global travel increases, more antibiotic-resistant bacteria will be disseminated from one country to another, thereby imposing a problem worldwide. Since the development of resistance is an evolutionary process, constant surveillance is needed to gain insight into the problem and surveillance studies needed to document the spread of antibiotic resistance.

The basic objectives of surveillance studies in antimicrobial resistance are: to determine the level of resistance in a particular geographical area; to monitor changes in the level of resistance and make this information available to therapeutic policy-makers, as well as to detect new mechanisms of resistance for use as early warning signs; to study how such resistance develops, persists and spreads, and to monitor interventions.

Although, surveillance provides the smoking gun for emergence of antibiotic resistance, improvement of the system is necessary and may be achieved through enhanced information technology and diagnostic tools.

1. Introduction

Today, resistance against antimicrobial agents is becoming a major health care concern. Data on the extent of antibiotic resistance are obtained with surveillance studies. Do these studies uncover the smoking gun for the emergence of resistance? First reports about antibiotic resistance seldom come through international surveillance studies. Also novel mechanisms of resistance are not necessarily detected through these studies. So, what is the role of international surveillance studies in determining the extent of the problem of emergence of resistance, and are these data useful for policymakers?

Surveillance has been described as: ''the ongoing and systematic collection, analysis, and interpretation of health data in the process of describing and monitoring a health event'' [1]. Since resistance development is an evolutionary process, constant surveillance is needed to gain insight into the problem in a timely fashion. The follow up on first reports of resistance against a particular antibiotic in a specific host is an important task for antibiotic resistance surveillance. The basic objectives of surveillance studies of resistance among micro-organisms are to determine the level of resistance in a particular geographic area in order to monitor changes in the level of resistance and make this information available to therapeutic decision-makers in a time frame that maximizes appropriate antimicrobial agent prescription, to detect new mechanisms of resistance for use as early warning signs, to study how such resistance develops, persists and spreads, and to monitor interventions [2–4].

Bacteria can become resistant to antibiotics by mutations or the acquisition of appropriate genes from other micro-organisms. Once inside a new host the newly acquired DNA

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may recombine with resident DNA, thus forming new gene combinations including new transposons and plasmids. This may lead to the introduction of several resistance genes into a single mobile genetic element, which not only leads to multiresistance, but also to the increased spread of resistance genes. This is a phenomenon that increasingly worries medical microbiologists and infectious disease specialists. Surveillance studies will document the spread of antibiotic resistance. This can either be clonal spread or spread of a resistance determinant within in the species or even between species. As global travel increases more antibiotic-resistant bacteria go with travellers from one country to another. This makes antibiotic resistance a global problem. Once introduced in a country the bacteria may become established and resistance determinants transferred to other strains and even species. The world-wide trade in food products, as well as the trade in breeding animals, may also contribute to the global spread of antibiotic resistance.

2. What did we learn from surveillance studies?

2.1. Introduction

Surveillance of antibiotic resistance began soon after the first antibiotic-resistant pathogens were isolated. Since then antibiotic resistance surveillance studies have been conducted for most pathogens and much has been learned about the development and spread of antibiotic resistance.

2.2. Methicillin-resistant Staphylococcus aureus (MRSA)

One of the greatest concerns with regard to antibiotic resistance is methicillin-resistant *S. aureus* (MRSA). *S. aureus* is a classic wound pathogen, able to cause superficial or deep-seated wound infections. In hospitals, *S. aureus* is feared as the causative agent for post-operative wound infections, septicemia, etc. It is carried as a skin commensal by circa 30% of the population and can survive for long periods on dry surfaces.

When penicillin was introduced in 1944, over 95% of all *S. aureus* isolates were susceptible. This proportion has decreased to less than 10%. In the 1950s, isolates resistant to penicillin and tetracycline started becoming a major hospital problem. The introduction of β-lactamase-stable penicillins (e.g. methicillin) in the early 1960s overcame this problem, but was swiftly followed by the emergence of the first MRSA. These MRSA did not rapidly become prevalent, perhaps because another effective antimicrobial – gentamicin – was put into use. By the late 1970s, however, gentamicin-resistant MRSA had emerged and since then a series of epidemic MRSA (EMRSA) strains have evolved and spread. These strains have been consistently susceptible only to the glycopeptides vancomycin and teicoplanin. Many MRSA isolates also appear to be susceptible to fusidic acid, rifampicin, and (decreasingly) ciprofloxacin. Recently, there have been reports – first from Japan, then the USA, and most recently France – of MRSA with (intermediate) resistance to vancomycin (VISA and VRSA) [5–7].

Staff or patients colonized with MRSA pose an infection hazard to others with whom they are in contact. Topical therapy with mupirocin is, therefore, widely used to eliminate carriage. *S. aureus* isolates were universally susceptible when this compound was introduced in 1983, but low- and high-level forms of resistance have since emerged. In general, MRSA prevalence is lowest in those countries that have strictly implemented infection control policies, and highest in those that have liberal policies. The epidemiology of MRSA is changing however with the increasing appearance of community-acquired MRSA [8]. Surveillance studies made large contributions in understanding the different epidemiological behaviour of community-acquired MRSA when compared with the traditional hospital-acquired MRSA. Continued vigilance however, is not only required because of the emergence and continuous spread of community-acquired MRSA. Also the emergence of vanA-mediated vancomycin-resistant MRSA (VRSA), in the USA is an additional important reason for continued antibiotic surveillance of this major pathogen.

2.3. Enterococci

Enterococci are a part of the normal human gut bacterial flora, where they are harmless. They have low virulence, but can cause infections in patients with an impaired host defense. This is especially true for patients in specialized hospital settings, such as renal dialysis and bone marrow transplant units. If the bacteria reach normally sterile sites in a vulnerable patient, they can cause many types of clinical problems ranging from superficial infection of wounds and the urinary tract to septicemia and endocarditis. Serious infections are extremely difficult to treat because of the high degree of antibacterial resistance.

Most enterococci isolated from hospital patients in the EU are resistant to a wide range of antibiotics, including tetracyclines, macrolides, chloramphenicol, and trimethoprim. Combinations of penicillin and aminoglycosides were the mainstay of antibacterial therapy until the mid-1980s when high-level aminoglycoside resistance emerged and spread. About that time, *Enterococcus faecium* (which is inherently resistant to penicillins) also became more prevalent, which left the glycopeptides, vancomycin and teicoplanin, as the only agents to which sensitivity could be assumed. Unfortunately, glycopeptide resistance quickly emerged and has since spread to many hospitals. Today, many glycopeptide-resistant enterococci, particularly *E. faecium*, are resistant to all established antibacterial agents. This forces clinicians to use untested agents or combinations with no guarantee of success [9].

In the European veterinary sector, the glycopeptide avoparcin has been used as a growth promotor. In 1995, the glycopeptide avoparcin was banned for use in animal feed production in Denmark in order to limit the reservoir of vancomycin-resistant *E. faecium* (VRE) that may spread to and cause infection in humans. The occurrence of resistance among *E. faecium* in chickens followed the decrease in usage, whereas no significant change occurred in pigs. This was followed in 1999 and 2000 by a significant decrease in the occurrence of VRE among *E. faecium* isolates collected from pigs. The delay in pigs was due to the fact that the use of tylosin decreased significantly during 1998–1999 and resistance to tylosin is genetically linked to the vancomcyin resistance determinant [10].

Despite the reduction in vancomycin in resistance in enterococci form animal sources in Europe, vancomcyin-resistant enterococci are isolated at an increasing rate in hospitals [11]. This is a worrisome development that needs close attention.

2.4. *Streptococcus pneumoniae*

S. pneumoniae is the most important cause of community-acquired pneumonia, which may lead to bacteremia. The organism is also a frequent cause of otitis media, particularly among children, and is the second most common cause of bacterial meningitis.

In the past, *S. pneumoniae* was exquisitely susceptible to penicillin. This drug could be used in most pneumococcal infections, including meningitis where the drug delivery is difficult. Macrolides (e.g. erythromycin), tetracyclines, and co-trimoxazole were alternatives for respiratory tract infections, whereas several cephalosporins and meropenem were – and are – alternatives for meningitis. *S. pneumoniae* strains with low-level penicillin resistance started being recorded in the late 1960s and those with high-level resistance began to appear in the late 1970s. Strains with low-level resistance still respond to penicillin administered for respiratory tract infections and bacteremia, but not meningitis. Strains with high-level penicillin resistance that infect the respiratory tract may respond to high-dose penicillin, but with MICs (minimum inhibitory concentrations) of 8 mg/L now being recorded for the most resistant isolates, there is little doubt that even higher MIC-values may lead to therapeutic failure.

2.5. *Hospital-acquired gram-negative rods*

Many gram-negative rods act as opportunistic pathogens in hospitals, especially in immuno-compromised patients in whom virtually any site may be infected. *Escherichia coli* also is the most common cause of urinary tract infection (UTI) in the community. The rates of resistance vary according to the species: *E. coli* and *Proteus mirabilis* are among the least resistant, whereas *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas aeruginosa* show greater inherent or acquired resistance. Some *Acinetobacter* spp., and *Stenotrophomonas maltophilia* are resistant to all antibacterial agents, but are considered low-grade pathogens. Nevertheless, *Acinetobacter* spp. infections and colonization appears to be prevalent among injured US soldiers deployed to Afghanistan or Iraq. The majority of the isolates were multi-resistant [12]. The rates of resistance in gram-negative rods in Northern Europe are low by international standards, but higher in Southern Europe, much of Asia, and the Americas. The highest rates are often seen in the more prosperous developing countries, e.g. South-East Asia, Turkey, and Argentina. At one extreme, it is common to see 20–40% resistance to gentamicin in gram-negative rods isolated from patients in tertiary hospitals in Southern Europe.

2.6. *Salmonellae*

Salmonella enterica is one of the most common causes of human gastroenteritis worldwide. This infection is caused primarily by the improper handling and consumption of uncooked food and a large number of different food animal sources have been identified as reservoirs of this bacteria. Resistance in *Salmonellae* isolated from blood stream infections show an increase in antibiotic resistance. Susceptibilities for ampicillin, amoxicillin/clavulanic acid and tetracycline have dropped below 90%. Resistance is particluarly frequent in serovar Typhimurium [13].

2.7. *Campylobacter species*

Campylobacter coli and *Campylobacter jejuni* may cause severe food poisoning. Although antimicrobials are rarely warranted, macrolides and ciprofloxacin resistance is becoming a concern.

2.8. *Vibrio cholerae*

Vibrio cholerae is a major problem in developing countries. Antibiotic resistance was relatively uncommon before the end of the 1970s. However, a multi-resistant strain of *V. cholerae* O1 emerged in Tanzania and then Bangladesh. This was followed by reports of multi-resistant *V. cholerae* from other countries. Episodes with resistant isolates may be followed by episodes with susceptible isolates. Resistance in this species seems to follow antibiotic abuse. Resistance is mediated by a conjugative plasmid, but transposons and integrons also play an important role. One mobile element encoding resistance to trimethoprim/sulfamethoxazole, chloramphenicol and low levels of streptomycin became incorporated in isolates of the novel 0139 serotype. In addition, resistance to fluoroquinolones is increasingly observed [14].

2.9. *Other enteric pathogens*

Drug resistance, except to ampicillin, is rare in *Yersinia enterocolitica*. Intrinsic resistance to the cephalosporins, nalidixic acid, and polymyxin is common in *Listeria* spp. and high-level ciprofloxacin resistance has been found in a few UK strains isolated from humans and from food. Multiple drug resistance in *E. coli* O157 is very rare, whether these isolates are from humans, human food, or food animals. However, there has been an increase in resistance to streptomycin, sulfonamides, and tetracyclines.

Shigella spp. became increasingly resistant with the availability of new antibiotics, although differences exist in the levels of resistance between the different species. This has limited the treatment options to extended-spectrum cephalosporins, fluoroquinolones, and azithromycin, but resistance against these antibiotics have been documented among shigellae [15–17].

2.10. *Neisseria gonorrhoeae*

Gonococci show great heterogeneity and a remarkable ability to acquire DNA from other gonococci and related species. This ability permits a rapid evolution of resistance. Sulfonamides were very effective against gonorrhoea at their introduction in 1937, but were almost invariably ineffective by 1944. The development of penicillin resistance was slower, but did lead to the prescription of ever-increasing doses of the drug. This

reduction in penicillin susceptibility reflects target modification, efflux, and impermeability and has caused penicillin MICs to rise to 2 mg/L, which is close to marginal clinical resistance. This resistance is associated with moderate cross resistance to unrelated antibiotics, especially tetracycline and erythromycin. The origin of these penicillinase-producing *N. gonorrhoeae* is obscure, but they probably evolved in the Philippines in the early 1970s in an environment of uncontrolled and heavy ampicillin usage. These penicillinase-producing *N. gonorrhoeae* soon spread worldwide.

2.11. *Neisseria meningitides*

N. meningitidis is the major cause of bacterial meningitis. It is closely related to *N. gonorrhoeae*, but is less adept at acquiring resistance. This is fortunate, considering the greater severity of the disease and the difficulty of drug delivery to the site of infection. Some strains with increased resistance to penicillin, due to alterations of penicillin binding proteins (PBPs), have been reported (and are quite prevalent in some countries, e.g. Spain), but appear to respond to high doses of penicillin and remain susceptible to the cephalosporins.

2.12. *Mycobacterium tuberculosis*

Tuberculosis (TB) remains the most common bacterial cause of death from any single infectious agent in adults worldwide, mostly in the developing world. Unusual among bacterial infections, *M. tuberculosis* infections require treatment with combinations of three or four agents for at least 6 months. Monotherapy rapidly leads to resistance, because of spontaneous mutant selection. However, with the emergence of difficult to treat multi-resistant strains antibiotic surveillance has been become of even greater importance than in the past. In fact, antibiotic surveillance has already documented the spread of these strains in Russia, but also New York City [18]. Without appropriate surveillance and follow-up measures multi-resistant *M. tuberculosis* may easily become a global problem.

2.13. *Conclusion*

It can be said that all pathogens show at least some degree of resistance, whereas important nosocomial pathogens often show multiresistance. Furthermore, resistance has developed against each antibiotic available. It can be concluded that surveillance studies are an extremely valuable tool to monitor the development and spread of antibiotic resistance. Without this tool, our knowledge about antibiotic resistance would be severely limited.

3. The future of surveillance studies

3.1. *Flaws in current antibiotic resistance surveillance*

Despite these successes in monitoring the emergence of resistance there is room for improvement. This will be even more important with the appearance of, e.g. vancomycin-resistant MRSA, multi-resistant TB, carbapenem-resistant *Enterobacteriaceae*, multi-resistant *Pseudomonas* and vancomycin-resistant *E. faecium*. For many of these organisms no satisfying empirical therapy remains. So, these organisms should be closely monitored as well as the development of resistance against the newest antibiotics. This is particular urgent because no new classes of antibiotics are expected to be marketed during the next decade. International surveillance programs only give a snapshot of the actual situation, because all programs are limited in geographic area, time, number of isolates, reservoirs, often only involve large hospitals, the same isolates or data may be used for different studies, and a certain sample bias is present in every surveillance system, because different criteria are used by different physicians selecting patients for microbiological analysis [19]. Furthermore, different studies may use different breakpoints to define susceptible, intermediate resistant, and resistant isolates. The longitudinal component of these studies may also be a problem in that some centres may withdraw from a multicentre study. The problem of biased isolate inclusion is even greater for surveys of antibiotic resistance in the community. Usually, only samples from patients with persistent infections or infections refractory to treatment are referred to a central laboratory by a general physician. One can wonder then how representative these isolates are for pathogens causing community-acquired infections. As a result, it is not clear how representative hospitals and isolates are for a clear perspective on the global danger of resistance. Although longitudinal studies, that include the same hospitals and types of isolates give some indication about trends. Good-quality susceptibility data are essential to detect trends and new and rare resistance phenotypes. Unfortunately, the quality of resistance data, especially from clinical laboratories, is often questionable [20–22]. Quality control of the susceptibility data, therefore is crucial. Two main causal factors have been identified why optimal surveillance is not achieved: lack of financial resources and lack of standardised methods. Despite these problems, surveillance remains vital.

3.2. *Improved surveillance systems*

What improvements can be achieved? One approach to overcome the problems with surveillance studies would be to have all the isolates tested in a central reference laboratory. In this way each isolate could be analysed using the same methods, interpretation criteria and rigorous quality control. The logistics and cost of shipment, however, are prohibitive for such a proposal. The programme and the criteria set by the European Antimicrobial Resistance Surveillance System (EARSS) may be a useful starting point. The objective of EARSS is to amass and summarise comparable and reliable antimicrobial resistance data to benefit public health across Europe, taking into account laboratory methods as well as epidemiological principles [23]. EARSS is, however, limited by the number of micro-organisms and participating hospitals. A better approach would be to send the susceptibility data of isolates from each patient to a central center and make sure that these data are quality-controlled. In North America such an organization may become part of the CDC and in Europe part of the European Centres of Disease Control (ECDC).

Standardized methodology yielding quantitative data that enable the detection of small shifts in susceptibility would be

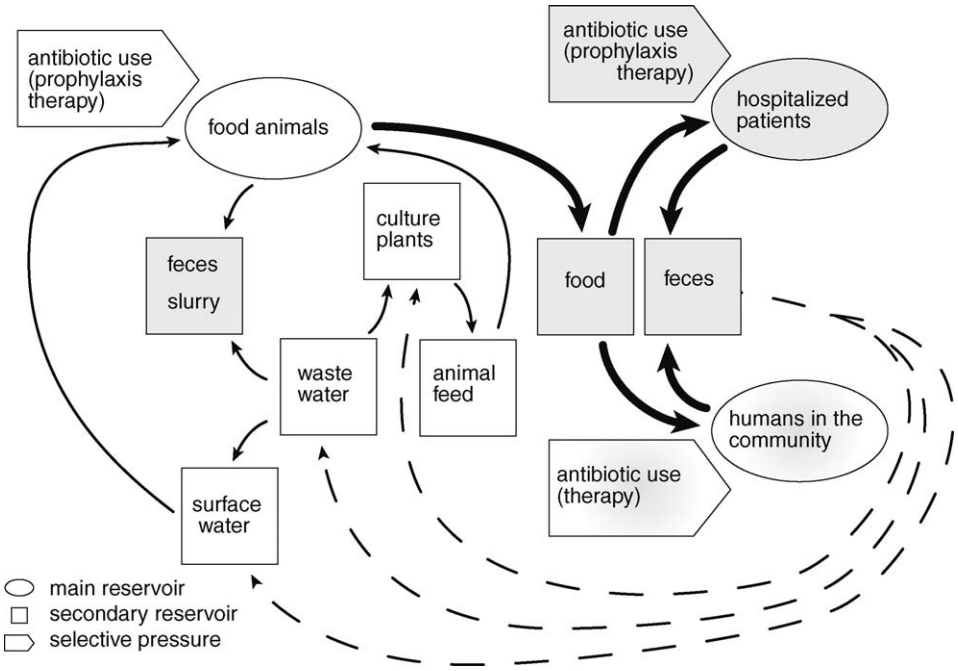

Fig. 1 – Schematic representation of the complex interaction between different reservoirs of antibiotic resistance and antibiotic pressure. Darker grey indicates increased antibiotic pressure or resistance levels. (Adapted from Witte W. Science 1998;279:996.)

ideal. This cannot be achieved in practice, however, because a number of different techniques exist for antibiotic susceptibility determinations (e.g. VITEK, Phoenix, Walkaway, disk-diffusion assays, etc.). Data obtained with these testing techniques must nevertheless be comparable, so that the results can be collated between different studies. Quality control, therefore is mandatory. Organisations that provide external quality control already exist (e.g. NEQAS, EARTHNET), but operate on a voluntary basis and with financial contributions from the participants. A much larger effort is required to monitor the performance of all laboratories providing antibiotic resistance surveillance data. Perhaps it can be based on the good example of effectively addressed quality control issues found in the EARSS programme [19,24]. Surveillance in the community and other special human reservoirs, such as nursing homes need to be addressed in dedicated surveillance programs.

The problems with antibiotic resistance are not limited to humans, but are shared to large extent with animal husbandry and food production (Fig. 1). The world-wide trade in food products, as well as the trade in breeding animals, may also contribute to the global spread of antibiotic resistance. Either directly through zoonoses with resistant bacteria or through the transfer of genes from animal adapted bacteria to human adapted strains. Ideally, the veterinary sector should follow the DANMAP/VETSTAT approach. The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) addresses the problem of antibiotic-resistant isolates in animals, food, and humans [25]. The programme has four objectives: to monitor trends in resistance among bacteria from animals, food, and humans; to monitor the consumption of antimicrobial agents in animals; to determine the association between consumption and the occurrence of resistance; to model the transmission of resistance from animals to humans. The programme examines representative isolates of human and animal pathogens, zoonotic bacteria and indicator bacteria. Animal isolates are derived from both healthy and diseased animals and the antibiotics are representative of the major classes of antibiotics. Further, antibiotic consumption data of food animals are collected according to the VETSTAT programme and are recorded for each herd.

3.3. *Future diagnostic assays and surveillance*

PCR technology is not suitable for large-scale antibiotic surveillance studies, because the wealth of different antibiotic resistance determinants. Microarray technology, which potentially allows analysis of thousands of disease markers simultaneously using microlitre sample volumes, has already entered the clinical arena, and is expected to have a growing impact on diagnostics in the future. Most experts do not expect the technology to have a major impact until at least 5–10 years from now, because of the relative immaturity of the existing devices and a lack of widespread need for analysing large numbers of targets in a single assay. The introduction of array technology may allow the simultaneous testing of hundreds of different resistance determinants. It thus will not only provide insight in the levels and spread of antibiotic resistance, but also the determinants involved. An important requirement, however, will be that the cost of these arrays is sufficiently low to allow broad implementation. It should be recognized that novel undiscovered mechanisms of resistance are not included in such arrays. There still will be a continuous need for phenotypic resistance testing as well.

Molecular diagnostics is the most rapidly growing segment of the In Vitro Diagnostics (IVD) market, and is expected to continue to be one of the highest growth segments over the next 5–7 years. The field has expanded from its initial focus on infectious disease detection to include applications, such as viral load testing, viral genotyping, pharmacogenetic testing, cancer screening and diagnosis, and genetic testing for hereditary diseases. Antibiotic resistance may well be included in these applications.

4. Conclusion

Surveillance provides the smoking gun for the emergence of antibiotic resistance, but much can be gained with improvement of the surveillance system. In particular, when routinely generated data in treating patients is quality controlled and aggregated on regional, national, and international scales. This effort may be aided by improved information technology and diagnostic tools.

REFERENCES

[1] Centers for Disease Control. Guidelines for evaluating surveillance systems. Morb Mortal Wkly Rep 1988;(S-5):1–18.
[2] Bax R, Bywater R, Cornaglia G, Goossens H, Hunter P, Isham V, et al. Surveillance of antimicrobial resistance—what, how and whither? Clin Microbiol Infect 2001;7:316–25.
[3] Felmingham D. The need for antimicrobial resistance surveillance. J Antimicrob Chemother 2002;50(Suppl.):S11–7.
[4] Annonymous. UK antimicrobial resistance strategy and action plan. Department of Health 2000.
[5] Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 1997;40:135–6.
[6] Centers for Disease Control and Prevention. *Staphylococcus aureus* with reduced susceptibility to vancomycin—United States, 1997. Morb Mortal Wkly Rep 1997; 46:765–6.
[7] Cartolano GL, Cheron M, Benabid D, Leneveu M, Boisivon A. The Association of Hospital Bacteriologists, Virologists and Hygiene Professionals. Methicillin-resistant *Staphylococcus aureus* (MRSA) with reduced susceptibility to glycopeptides (GISA) in 63 French general hospitals. Clin Microbiol Infect Dis 2004;10:448–51.
[8] Salgado CS, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. Clin Infect Dis 2003;36: 131–9.
[9] Bonten MJM, Willems R, Weinstein RA. Vancomycin-resistant enterococci: why are they here, and where do they come from? Lancet Infect Dis 2001;1:314–25.
[10] Aarestrup FM, Seyfarth AM, Emborg H-D, Pedersen K, Hendriksen RS, Bager F. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. Antimicrob Agents Chemother 2001;45:2054–9.
[11] European Antimicrobial Resistance Surveillance System. EARSS Annual Report 2003. Ongoing surveillance of *S. pneumoniae*, *S. aureus*, *E. coli*, *E. faecium*, and *E. faecalis*. RIVM, Bilthoven, The Netherlands, 2004.
[12] Davis KA, Moran KA, McAlisster CK, Gray PJ. Emerg Infect Dis 2005;11:1218–24.
[13] Stephen JM, Toleman MA, Walsh TR, Jones RN. SENTRY Program Participants Group. *Salmonella* bloodstream infections: report from the SENTRY Antimicrobial Surveillance Program (1997–2001). Int J Antimicrob Agents 2003;22:395–405.
[14] Sack DA, Sack RB, Nair GB, Siddique AK. Cholera. Lancet 2004;363:223–33.
[15] Ahmed J, Kundu M. Molecular characterization of the SHV-11 β-lactamase of *Shigella dysenteriae*. Antimicrob Agents Chemother 1999;43:2081–3.
[16] Isenbarger DW, Hoge CW, Srijan A, Pitarangsi C, Vithayasai N, Bodhidatta L, et al. Comparative antibiotic resistance of diarrheal pathogens from Vietnam and Thailand, 1996–1999. Emerg Infect Dis 2002;8:175–80.
[17] Pickering LK. Antimicrobial resistance among enteric pathogens. Semin Pediatr Infect Dis 2004;15:71–7.
[18] Espinal MA. The global situation of MDR-TB. Tuberculosis 2003;83:44–51.
[19] Kahlmeter G, Brown DFJ. Resistance surveillance studies—comparability of results and quality assurance of methods. J Antimicrob Chemother 2002;50:775–7.
[20] Richet HM, Mohammed J, McDonald LC, Jarvis WR. INSPEAR. Building communication networks: International Network for the Study and Prevention of Emerging Antimicrobial Resistance. Emerg Infect Dis 2001;7:319–22.
[21] Snell JJ, Brown DFJ. External quality assessment of antimicrobial susceptibility testing in Europe. J Antimicrob Chemother 2001;47:801–10.
[22] Tenover FC, Mohammed MJ, Stelling J, O'Brien T, Williams R. Ability of laboratories to detect emerging antimicrobial resistance: proficiency testing and quality control results from the World Health Organization's external quality assurance system for antimicrobial susceptibility testing. J Clin Microbiol 2001;39:241–50.
[23] Bronzwaer SL, Goettsch W, Olsson-Liljequist B, Wale MC, Vatopoulos AC, Sprenger MJ. European Antimicrobial Resistance Surveillance System (EARSS): objectives and organisation. Euro Surveill 1999;4:41–4.
[24] Bronzwaer S, Buchholz U, Courvalin P, Snell J, Cornaglia G, de Neeling A, et al. Comparability of antimicrobial susceptibility test results from 22 European countries and Israel: an external quality assurance exercise of the European Antimicrobial Resistance Surveillance System (EARSS) in collaboration with the United Kingdom National External Quality Assurance Scheme (UK NEQAS). J Antimicrob Chemother 2002;50:953–64.
[25] Bager F. DANMAP: monitoring antimicrobial resistance in Denmark. Int J Antimicrob Agents 2000;4:271–4.