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Fighting antibiotic resistance in Sweden – past, present and future

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Kampf gegen Antibiotikaresistenzen in Schweden – einst, jetzt und in Zukunft

Zusammenfassung. Mit dem vermehrten Auftreten von Pneumokokken mit eingeschränkter Empfindlichkeit gegenüber Penicillin und von Methicillin-resistentem *Staphylococcus aureus* wurden in Schweden Forderungen laut, durch zielgerichtete Maßnahmen einem Überschreiten kritischer Schwellenwerte der Resistenzraten vorzubeugen. Anfangs der 1990er Jahre fand sich Schweden aufgrund niedriger Antibiotika-Resistenzraten und eines geringen Antibiotikaverbrauchs in einer sehr günstigen Ausgangssituation. Eine Durchsicht der bisherigen schwedischen Erfahrungen im Lichte neuer und zukünftiger Herausforderungen war das Ziel der vorliegenden Arbeit. Daten zur Resistenzsituation in Schweden, zu Antibiotikaverbrauch, Meldungen anzeigepflichtiger Erkrankungen, Ausbruchskontrolle und Notfallpläne sowie einschlägige wissenschaftlicher Publikationen wurden ausgewertet. In Schweden ist durch gut etablierte mikrobiologische Diagnostiklaboratorien und durch die Möglichkeit, klinische Proben ohne finanzielle Restriktionen zum kulturellen Erregernachweis einsenden zu können, der Aufbau von Resistenz-Surveillancesystemen erleichtert. Antibiotikaverbrauchsdaten können für den Humanbereich seit über 20 Jahren problemlos erhoben werden. Gesetzliche Vorgaben erlaubten die Bildung intersektoraler Gruppen, sogenannter Strama (Swedish Strategic Programme Against Antibiotic Resistance)-Gruppen, zur Resistenzüberwachung auch in den Bereichen Veterinärmedizin und Lebensmittelproduktion auf regionaler Basis. Als Schwachstelle für die Surveillance von Antibiotikaresistenzen wurden unzureichende Datenverarbeitungssysteme ausgemacht. Die Grundstruktur eines dezentralisierten Überwachungssystems hat dazu geführt, dass sich sowohl geplante Maßnahmen als auch konkrete Vorgaben regional sehr unterschiedlich entwickelt haben. Die Tatsache, dass es Schweden bislang gelungen ist, die Problematik der antimikrobiellen Resistenz weitgehend zu beherrschen, kann mit der engen Kooperation zwischen Humanbereich und Vetrinärmedizin und den – mit Unterstützung der Regierung – bereits frühzeitig gesetzten Maßnahmen erklärt werden. Durch laufende Überarbeitung der einschlägigen Gesetze und der Surveillance-Systeme wird derzeit versucht, dem rezenten Anstieg von Breitspektrumbetalaktamasen-bildenden Keimen in Schweden und dem dadurch bedingten Anstieg des Antibiotikaverbrauchs entgegen zu wirken.

Summary. Sweden has been in the favorable situation of having limited antibiotic resistance and low antibiotic consumption. When pneumococci with reduced susceptibility to penicillin and methicillin-resistant *Staphylococcus aureus* emerged during the 1990s, professionals and relevant authorities called for extensive action plans to avoid the critical threshold levels of resistance experienced in other countries. The purpose of this paper is to examine Swedish experiences in light of new and future challenges by reviewing Swedish data on antibiotic resistance and antibiotic use, notifications, outbreak control, action plans and scientific papers. The tradition of liberal performance of clinical cultures, together with well functioning diagnostic laboratories, has formed a basis for close collaboration and development of surveillance within quality assurement programs. For more than 20 years the pharmacy monopoly in Sweden has made it possible to collect well defined data on antibiotic sales at the county level with almost 100% coverage. Multisectorial collaboration was set up in regional Strama (Swedish Strategic Programme Against Antibiotic Resistance) groups. Large diagnosis-prescribing surveys have been undertaken, and the concept of basic hygiene precautions was introduced, together with extensive programs for early case finding. However, surveillance has been hampered by inadequate IT systems and some difficulties in collecting relevant data on antibiotic sales at the national level. Also, a decentralized system with 21 counties and regions has resulted in divergence of action plans and rules. The containment of antibiotic resistance thus far may be explained by the early response in human and veterinary medicine and close multisectorial collaboration, supported by the government, before problems got out of hand. Nevertheless, rapidly growing problems with bacteria that produce extended beta-lactamases have recently emerged and antibiotic sales have started to increase again. The outcome of ongoing revision of legislation and surveillance will have great impact on the future possibilities of limiting antibiotic resistance in Sweden.

Key words: Antibiotic, resistance, consumption, surveillance, Strama.

Introduction

The increased use of antibiotics during the 1980s and detection and spread of several multiresistant pneumococcal clones in the early 1990s made the medical profession and authorities aware of an emerging problem with antibiotic resistance in Sweden. Strama (Swedish Strategic Programme Against Antibiotic Resistance) is a professional network that was initiated in 1994 and came into action in 1995 [1]. In 2000, the National Board of Health and Welfare in close collaboration with Strama prepared a national action plan to contain antibiotic resistance in Sweden [2]. The plan emphasized the need for adequate surveillance of resistance and antibiotic use and the importance of intersectorial collaboration, including veterinarian, food-related and environmental issues, in order to contain resistance. As existing legislation on patient safety, quality assurance (QA) etc. seemed not to put antibiotic resistance and healthcare-associated infections sufficiently into focus, the action plan was transferred into a governmental bill "Strategy to prevent antibiotic resistance and healthcare-associated infections" [3], which was passed in 2006. Systems for monitoring antibiotic resistance and antibiotic consumption in human medicine are under revision at present, and national strategies for computerized medical records and registration of healthcare-associated infections are being developed. On the veterinarian side, a restrictive antibiotic policy was adopted by the farmers association, and in the early 1980s the National Veterinary Institute (NVI) started to collect sales data on antibiotic use in veterinary medicine. Use of antibiotics as growth promotors was banned in Sweden already 1986, a policy that was later adopted by the EU. This has been followed by several recommendations and policies among sectors of veterinary medicine, which among many things has also led to a great reduction in group treatment.

Sweden is a sparsely populated country of about nine million people. A national healthcare insurance provides cover to all inhabitants and includes healthcare and drugs to a certain limit. Twenty-one county councils have the main responsibility for healthcare, mostly supplied by public providers. Healthcare in each county is organized into primary and secondary care; tertiary care is provided at eight regional university hospitals. The County Department for Communicable Disease Control (CDCDC) is the authority responsible for the prevention of communicable diseases, including antibiotic resistance and healthcare-related infections in each county. The healthcare sector, public and private, is regulated by the National Board of Health and Welfare. The Swedish Institute for Infectious Disease Control (SMI) is an expert authority, although without legislative power. The institute performs and coordinates surveillance of communicable diseases and resistance at the national level and has laboratory facilities for epidemiological typing and the diagnosis and characterization of uncommon pathogens. All (approximately 900) pharmacies belong to a state-owned company, Apoteket AB (the National Corporation of Swedish Pharmacies).

Strama was formalized in 2006 and appointed as a governmental body with a remit to facilitate coordination of the work against antibiotic resistance. The overall aim of Strama is to preserve the effectiveness of antibacterial agents for the treatment of bacterial infections in humans and animals. Today Strama is composed of a national steering group, a coordinating national Strama secretariat, and regional Strama groups in each county. The steering group includes a broad representation of professional organizations and authorities. Each county has at least one multidisciplinary Strama group that includes specialists in microbiology, infectious diseases, general practice and a pharmacist. These groups, usually led by the CDCDC, follow and feed back data on antibiotic use and resistance at the local level (hospital/ward, general practice/practitioner etc.) and develop locally adapted guidelines. The regional Strama groups work in close collaboration with the regional drug and therapeutics committees. Following an initial focus on outpatient care, Strama has continuously expanded and today is active in many fields; for example, in primary care, hospital care, intensive care, nursing homes and day-care centers. An increasing number of the regional Strama groups receive a specific mandate and financing from their county council. A report of Strama's activities in its first 10 years was published recently [4]. After a long collaboration between human and veterinary medicine on issues related to the containment of antibiotic resistance, the importance of a specific working group addressing issues related to veterinary medicine and the food chain was highlighted when the governmental bill was passed 2006. As a result, a corresponding body, Strama VL, is currently being organized by the NVI. In addition to the work in Strama, zoonotic issues related to antibiotic resistance are also discussed on a regular basis in the Zoonoses Council.

In Sweden, infectious disease is a specialty in its own right, with separate clinics and single and isolation rooms. Most intensive care units (ICUs) and many other highly specialized units are visited by a consultant in infectious disease on a regular basis. All public hospitals (and many municipalities) have a contract with an infection control team, even if the team is not located within each hospital. Alcohol hand-rub (rather than soap hand-washing) has been recommended in Swedish hospitals since the 1970s. During a large outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) in Gothenburg (see below) it was recognized that implementation of barrier precautions when new carriers of MRSA were identified was regularly too late to be able to curtail the outbreak. Instead, the uniform use of basic hygiene precautions was introduced [5]. In short, these rules apply to all staff, including physicians, and should be used for all patients, regardless of what is known about their infective status. The precautions include banning private clothes at work and banning the wearing of finger rings, wrist jewellery and watches. A dress code with short sleeves for all healthcare workers was introduced, and an alcohol hand-rub before and after every patient and the use of a gown at every close patient contact was recommended. Furthermore, early case finding through screening of patients with risk factors and contact tracing for early identification of exposed contacts was considered crucial and also cost effective [6]. Thus, screening for multiresistant bacteria, particularly in patients returning from hospitals abroad, is one of the cornerstones in the Swedish strategy. The annual number of registered screening samples for multiresistant bacteria has increased more than ten-fold, from about 30,000 in 2001 to more than 300,000 in 2006.

Antibiotic resistance

The vast amount of data on antibiotic resistance in Sweden is based on voluntary reporting of results from routine investigations of clinical samples in approximately 30 clinical microbiology laboratories. Antibiotic susceptibility testing methods have been standardized through collaboration between the laboratories and SRGA-M (Swedish Reference Group of Antibiotics – subcommittee on Methodology, www.srga.org). The disk diffusion method has been used as the routine method for susceptibility testing in clinical samples; however, this sometimes needs to be followed by methods for detecting genes that encode for resistance, by MIC determination using broth- or agar-dilution or with Etest, or by other methods for enzyme detection. Phenotypic methods (disk diffusion or MIC) are performed on a basic medium for antibiotic sensitivity testing: ISA (IsoSensitest Agar) from Oxoid Ltd, UK. For this medium and the corresponding antibiotic paper disks, interpretive criteria for SIR categorization (Sensitive, Intermediate and Resistant, respectively) are regularly updated and provided by SRGA-M. Species-specific susceptibility breakpoints are used. Validation of susceptibility testing by histogram analysis and external control by testing strains from foreign laboratories are performed annually; internal control is performed daily or weekly.

Infections or colonization with the following antibiotic-resistant pathogens are notifiable under the Communicable Disease Act: penicillin-resistant pneumococci (PRP; MIC for penicillin G ≥0.5 mg/l) since 1996, MRSA and vancomycin-resistant *E. faecalis* and *E. faecium* (VRE) since 2000, and Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs) since 2007. Data on notified numbers and incidences of these pathogens are continuously updated at national and county level on SMI's web site [www.smittskyddsinstitutet.se/in-english/].

Since 1994 all laboratories have taken part in an annual resistance surveillance and quality control (RSQC) program in which they are asked to collect quantitative data (zone diameters) for defined antibiotics in 100 consecutive clinical isolates of a number of bacterial species. *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this program every year, and on one or several occasions *Escherichia coli*, *Enterococcus faecalis* / *E. faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* spp. and *Enterobacter* spp. have also been included in these surveys. The number of antibiotics tested for each pathogen has varied between four and six. Since 2002 data from the laboratories have been collected on a web-based interactive database (ResNet). Three-fourths of the laboratories (covering about 75% of the population) contribute data on defined invasive isolates to EARSS (European Antimicrobial Resistance Surveillance System). Thus, resistance among clinical isolates of common pathogens can be followed annually at national level. There is no general feedback of aggregated results to the clinics but each regional Strama group has access to local and national data on resistance through their local laboratory if agreed.

Results from surveillance of antibiotic resistance and consumption in human medicine have been published annually in SWEDRES [http://strama.se/dyn//,33,18,20.html] since 2001. (SWEDRES is the source of original data in this paper unless stated otherwise.) Since 2002, SWEDRES has been a joint publication with the corresponding veterinary report SVARM [www.sva.se/sv/navigera/tjanster_produkter/Trycksaker/SVARM/].

Streptococcus pneumoniae

The problem of PRP was limited in Sweden for many years, with national incidences of reduced sensitivity to penicillin (PNSP; MIC >0.12 mg/l) well below 5%. However, in the early 1990s this rate increased in southern Sweden to 8–15%. Based on this observation and with the experience of rapidly increasing resistance rates in other countries, a national expert committee was formed, recommendations were developed and "The South Swedish Pneumococcal Intervention Project" was started in 1995 [7]. Particular attention was drawn to transmission of PRP (MIC >0.5 mg/l) among small children, and mandatory notification of PRP according to the Communicable Disease Act was introduced in 1996. When new cases were found, families, day-care groups and staff were sampled. Pre-school children who were carriers were sampled weekly and excluded from day-care groups until negative. Their parents were able to stay at home with full reimbursement from the social security system if day-care could not be arranged in any other way. In parallel, activities were carried out in order to reduce antibiotic consumption, in particular in treatment of upper respiratory tract infections (RTIs). As an example of this, in some counties check-ups free of charge were offered to children who did not get antibiotics on their first visit. In addition, Strama was founded, working for rational evidence-based use of antibiotics. It was later shown that much of the increase in pneumococcal resistance was related to a specific international clone belonging to serotype 9V [8]. The annual incidence of notified PRP has declined from 10.1 per 100,000 population in 1997 to between 6 and 8 per 100,000 since 2000, though some of this decrease may be partly explained by a decreased incidence of cultures. The majority of PRP cases were found in nasopharyngeal cultures in the age group 0–4 years. The proportion of PNSP in invasive isolates has varied between 2.5% and 5.0% during the last five years. There has been a trend of increasing resistance against all four antibiotics (erythromycin, trimethoprim/sulfamethoxazole, tetracycline, penicillin V) tested on *S. pneumoniae* in the RSQC program since 1994. Multiresistance (resistance to penicillin and at least two more antibiotics) has been common among PRP.

Staphylococcus aureus

Between 1997 and 2001 an outbreak of an endemic strain of MRSA (EMRSA-15) occurred at Sahlgrenska University Hospital in Gothenburg and affected a total of 146 patients in 35 wards and units. The outbreak was successfully terminated through aggressive measures of infection control and a massive sampling program. Although costs were high, they were calculated to be cost-effective [5, 6]. After the experiences of this outbreak and with the increasing problem of MRSA in many other parts of the country, MRSA was made notifiable in 2000. Annual reports of notified MRSA cases are shown in Fig. 1. About 40% of notified cases are identified during investigations of clinical symptoms but a majority of the cases are asymptomatic and found through contact tracing or in screening programs. In the past two years MRSA acquired in the community has been more common than healthcare-associated MRSA, at least among domestically acquired cases. The rate of MRSA among invasive isolates of *S. aureus* is still below 1%, as reported to EARSS. The rate among *S. aureus* isolated from wound infections tested within the RSQC program has been slowly increasing but in 2006 was still only 0.5%. MRSA isolates from almost all newly identified patients have been sent to SMI for molecular typing since 2000; in 2006 pulse-field gel electrophoresis (PFGE) was replaced by spa typing. Isolates identical or related to internationally recognized strains are still dominating. The prevalence of MRSA with PVL toxin is increasing, with PVL-positive isolates of PFGE-type SE03-5 (spa-type t008) showing the most rapid increase. This PFGE pattern is identical to that of USA300, an MRSA type internationally reported to be rapidly spreading in the community.

A fluoroquinolone-resistant strain of MRSA belonging to spa type t032 was detected in pets (dogs) for the first time in 2006–07 [9]. Investigation showed that 18% of the veterinary staff were carriers of MRSA [10], which is now included among other zoonotic diseases in Sweden. MRSA has not yet been identified in pigs or healthy dogs in screening coordinated by the veterinary institute [9].

The clonal outbreak of EMRSA-15 in western Sweden in the 1990s and the increasing incidence of reports of multiclonal MRSA in the late 1990s and early 2000s prompted infection control units and CDCDCs to develop regional action plans. These focused on early case finding (contact tracing, screening), care in single rooms for known or highly suspected cases and general practice of "basic hygiene precautions". In addition, patients and carriers had to follow rules such as informing healthcare staff of their MRSA carrier status when re-entering hospitals. Use of this "search and contain" approach has enabled several smaller clonal outbreaks of MRSA to be controlled in hospitals and long-term care facilities. For management in individual patients it can generally be said that priority has been given to control of risk factors (skin lesions etc.) rather than eradication therapy. A small decrease in the number of domestic cases of MRSA reported to be healthcare-associated was observed in 2006–07.

During 1999 a high prevalence of *S. aureus* resistant to fusidic acid was noted among patients with impetigo bullosa. Fingerprinting of isolates showed that all belonged to a clone that could be traced back to 1995, had been spread all over Sweden by 1999, and was also reported from Norway [11, 12]. A coinciding increase in the use of topical fusidic acid was noticed in the predominantly affected age group, <12 years at the time. Because of this emerging problem, the Swedish Medical Products Agency (www.mpa.se) and Strama organized a national expert meeting in 2002 to discuss therapy and measures to control impetigo. It was recommended that topical fusidic acid should not be used for the treatment of impetigo in Sweden. This led to a significant reduction in the use of topical fusidic acid and a decline in the proportion of *S. aureus* resistant to it [11].

Vancomycin-resistant enterococci (VRE)

VRE are still very rare in Sweden: during the period 2000-07 the annual number of reported cases has varied between 18 and 53. Minor local outbreaks in four counties were responsible for the majority of previous cases, but a larger outbreak with more than 100 identified cases has now been ongoing for the past six months. In a national point-prevalence survey in 1997–98, covering 841 patients in 27 hospitals, only nine patients (1.1%), all in the same hospital, carried VRE of type van-B [13]. In total, not more than 10 cases of invasive VRE have been reported to EARSS in the period 2001–06.

Other streptococci

Data from the RSQC program and from a sample of invasive isolates of *S. pyogenes* from nine laboratories in 2006 showed similar patterns, with 1–2% macrolide/clindamycin resistance and 11–14% tetracycline resis-

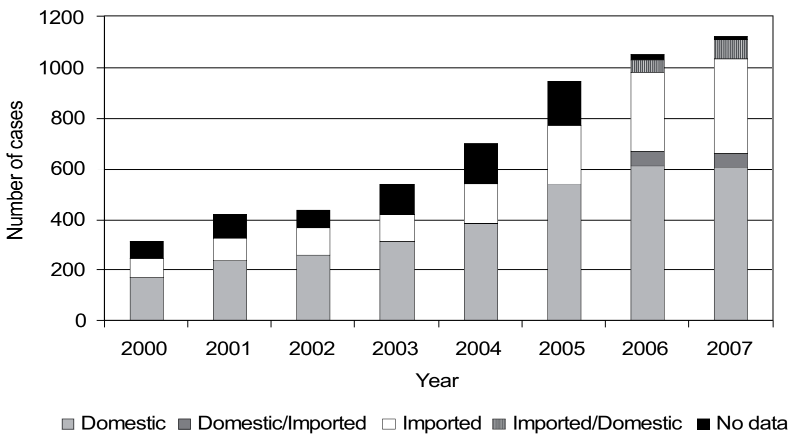

Fig. 1. Annual number of notified cases of methicillin-resistant *Staphylococcus aureus* (MRSA) in Sweden according to geographic place of acquisition. Domestic/imported and imported/domestic means two possible alternatives given in that order

tance. Among invasive isolates of *S. agalactiae*, 4.4% were resistant to macrolides.

ESBL in Enterobacteriaceae

Several minor outbreaks of *E. coli* with ESBL have been reported [14] and a major clonal outbreak of ESBL-producing *K. pneumoniae* has been ongoing in Uppsala county since 2005. The level of resistance to third generation cephalosporins among blood isolates of *E. coli* has increased to 1.4%, and in the majority of these the resistance was caused by plasmid-mediated ESBLs of type CTX-M. This resistance was often accompanied by resistance to many other antibiotics, such as aminoglycosides and fluoroquinolones. Approximately 2% of *K. pneumoniae* were cephalosporin resistant and ESBL-producing according to monitoring in the RSQC program and EARSS.

ESBL-producing Enterobacteriaceae were made notifiable by laboratories in February 2007, therefore no clinical epidemiological information is yet available. In the first 11 months, 2099 cases were notified, corresponding to 27 per 100,000 inhabitants. The most commonly reported species were *E. coli*, accounting for 77% of all cases, followed by *K. pneumoniae* in 12%. Figure 2 shows that the klebsiella cases, mainly from the outbreak in Uppsala, occurred chiefly among the elderly, whereas *E. coli* was also in the younger cases. Among the notified cases, 70% were diagnosed in urinary cultures and 13% in fecal samples, the latter known to be screening samples. A minimum of 100 patients were diagnosed in blood cultures, indicating severe infections. The rapidly growing ESBL problem prompted Strama to gather together experts, authorities and professional organizations to develop a national action plan [15]. The goal is to limit the proportion of ESBL-producing *E. coli* and Klebsiella spp. in blood isolates to a maximum of 1% and to ensure that ESBL-producing bacteria do not affect current recommendations for empiric treatment of lower urinary tract infections (UTIs) in women. The following main areas are addressed: laboratory methods (primary diagnosis and reporting, logistics and responsibility for typing), documentation (specific ICD-10 code for antibiotic resistance, tools for contact tracing), development of local strategic plans (including an empowered steering-group, guidelines for patient care, mobilization of single rooms during outbreaks, antibiotic policies), recommendations for patient care (definitions of risk factors, information exchange) and antibiotic strategies.

Escherichia coli

Between 1997 and 2006, ampicillin resistance among *E. coli* in urinary cultures increased from 17% to 26% and trimethoprim resistance from 8% to 18%, according to the RSQC program. Resistance to fluoroquinolones has increased every year and in 2006 was 11% in urine and 9% in blood isolates. This has led to revised recommendations on treating uncomplicated lower UTI in women: fluoroquinolones should not be used at all, trimethoprim has moved from a first- to a second-line alternative, and pivmecillinam and nitrofurantoin are recommended first-line alternatives [16].

Resistance in other Gram-negative bacteria

According to the RSQC program and EARSS, fluoroquinolone resistance in *K. pneumoniae* has varied between 8% and 13%. The prevalence of carbapenem resistance in *P. aeruginosa* was approximately 5% and fluoroquinolone resistance around 10%. Multiresistant Gram-negatives are rare but have occasionally been reported, sometimes in small outbreaks and usually in relation to hospital care abroad [17–19]. Since the first metallobeta-lactamase (MBL)-positive isolate was identified in Sweden in 2003, a total of only 17 such isolates have been identified in the Scandinavian countries Sweden, Norway and Denmark up to 2007: these were 11 *P. aeruginosa* strains and six *K. pneumoniae* strains. In contrast to the earlier situation, MBL isolates are now being

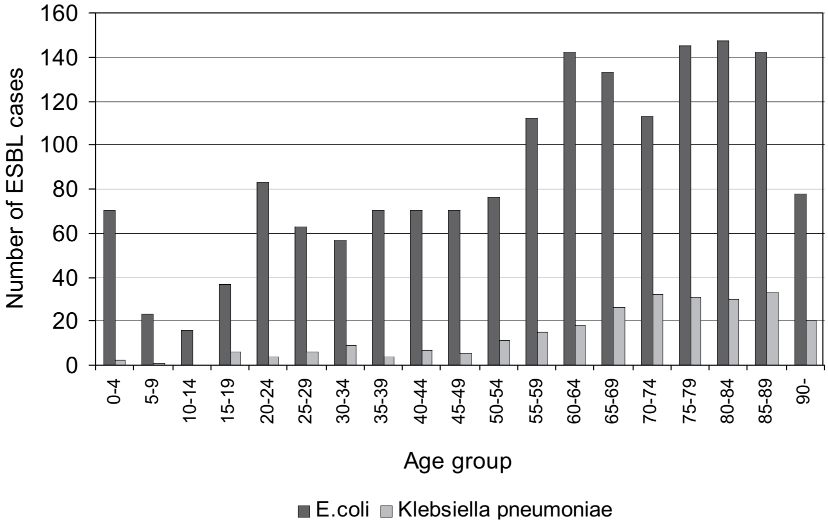

Fig. 2. Number of notified patients with *E. coli* and *Klebsiella* spp. producing ESBL (extended spectrum beta-lactamases) in Sweden in 2007 (Feb–Dec)

identified in patients in whom travel or hospitalization outside Scandinavia during the past twelve months has been precluded [20].

Antibiotic consumption and antibiotic use

Data on antibiotic sales in outpatient care have been delivered to each county council by Apoteket AB since 1974; sales data for hospital care have been available since 1988. There is no formal responsibility for aggregation and analysis of antibiotic sales at national level, a responsibility that Strama has undertaken. Data are delivered according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by WHO. Between 1974 and 1995, information on outpatient prescriptions was based on statistical samples of dispensed prescriptions; however, since 1996 all prescriptions dispensed by pharmacies have been included and, since 1999, ApoDos (individually packed doses of drugs often dispensed to the elderly) data also. In addition, the system produces statistics on sales for each hospital department and on national and county sales to hospitals. Sales are expressed as cash value, number of packages and number of defined daily doses (DDDs). After an initial study on antibiotic consumption and methods of surveillance in Europe [21], Sweden has participated and delivered annual data to ESAC (European Surveillance of Antimicrobial Consumption).

Since July 2005, the Swedish National Board of Health and Welfare has supplied an individually based register of all drugs prescribed in outpatient care. The data give information on the number of individuals treated with at least one course of antibiotics during a specific period of time, i.e. number of patients per 1000 inhabitants and year. It is also possible to follow the number of purchases per person.

Each Strama group or local drug committee is provided with data on antibiotic use by their local pharmacist. At the local level it is also possible to look at each prescriber and each workplace.

Antibiotic consumption

About 90% of the total consumption of antibiotics in Sweden is in outpatient care. After a steady decrease from a maximum of about 19 DDDs/1000 inhabitants per day in the 1990s to fewer than 13 DDDs/1000 per day in 2004, use has increased annually again and was 13.9 DDDs/1000 per day in 2007 (methenamine excluded). Further analysis has shown that since 2004 the increase mainly corresponds to an increased consumption of penicillin among children under 4 years of age. Figure 3 shows that penicillins (J01CE) and tetracyclines (J01AA) were the most widely used antibiotic classes in outpatient care in 1995–2007.

Considerable differences are found when comparing Swedish counties. For example, in 2006, children in Stockholm received more than twice as much antibiotic for RTIs as children in Jämtland county (646 and 301 prescriptions/1000 inhabitants respectively). The reasons for these differences are unknown: in a study comparing children in municipalities with low rates of antibiotic prescription versus those living in municipalities with high rates, the difference could not be explained by differences

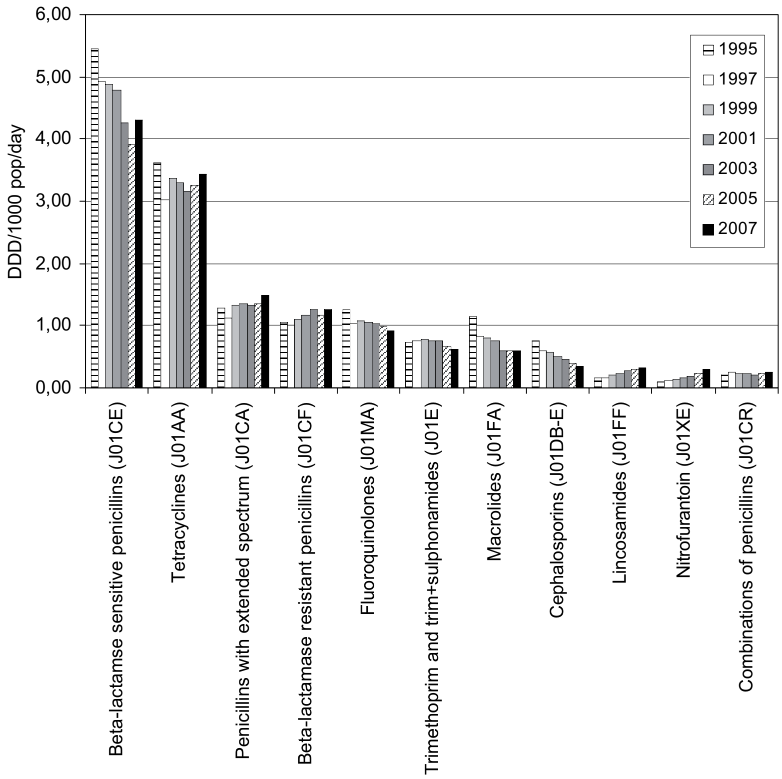

Fig. 3. Consumption of antibiotics in Sweden, outpatient care 1995–2007

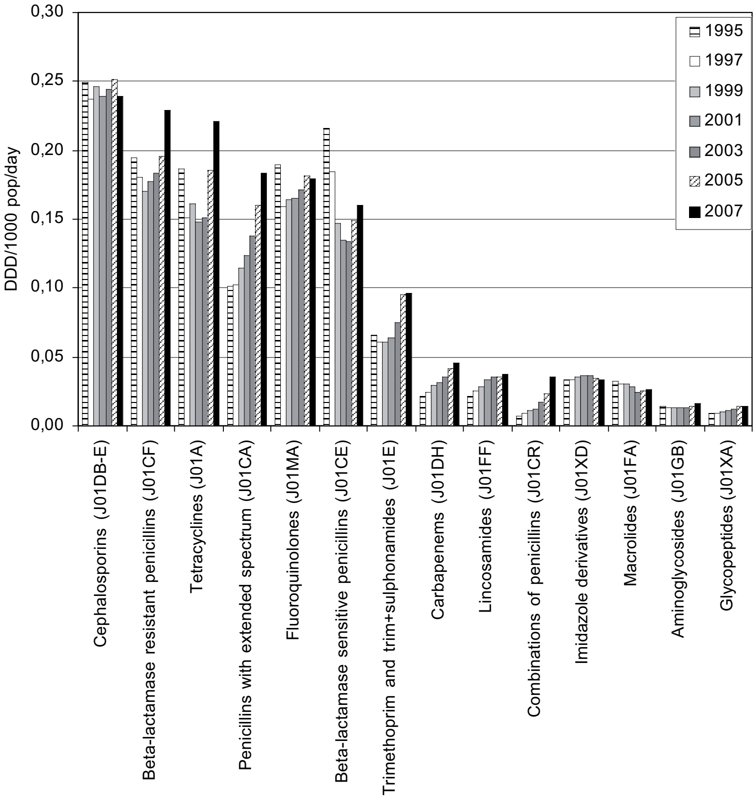

Fig. 4. Consumption of antibiotics in Swedish hospital care 1995–2007

in reported infectious symptoms, differences in socioeconomic factors, use of day-care, concern about infectious illness in the family, or physician consultations [22].

According to the National Board of Health and Welfare's drug registry 2,198,164 persons (24% of the population) purchased at least one course of antibiotics during the year July 2005–June 2006, with women making 58% of the purchases and men 42%. Treatment with antibiotics was most common in the age groups 3–6 years and 80 years or older. In the latter age group, 1.2% of the men and 1.9% of the women received more than 10 courses of antibiotics during one year.

The use of antibiotics (methenamine excluded) in Swedish hospital care is increasing slowly but steadily, while at the same time the mean duration of medical care and the number of hospital beds are decreasing. In 2006 the use of antibiotics increased by 5% in terms of DDDs/1000 inhabitants per day and the increase was seen in all classes of antibiotics used in hospitals. Those most commonly used were the cephalosporins.

Antibiotic use

The Medical Products Agency has arranged several meetings in association with expert organizations such as Strama with the aim of developing treatment guidelines for infections commonly seen in primary care. Thus, guidelines were developed for the treatment of acute otitis media in 2000, for acute pharyngotonsillitis and impetigo in 2002, for acute sinusitis in 2005, and for UTIs in women in 2006. New guidelines for lower RTIs are under way and will be released 2008. In addition, guidelines for surgical prophylaxis were developed 1999.

A survey system for diagnosis and therapy in outpatient care was started in 1978 but ended in 2002 because feedback failed to work properly and participation was low. Strama then initiated several large surveys to evaluate the quality of antibiotic prescribing in primary care [23–27]. These have pointed to a high rate of antibiotic prescribing in acute otitis media, acute pharyngotonsillitis and acute bronchitis, indicating that the new guidelines on treatment of acute otitis media and acute pharyngotonsillitis have not yet been fully implemented. The third and most recent survey in 2005, covering almost seven counties and 7498 infectious episodes, showed that fluoroquinolones were still being used to a great extent for the non-recommended indication of lower UTI in women and that tetracyclines were commonly used for acute bronchitis, a diagnosis for which the use of antibiotics has been questioned.

In a detailed survey of prescription patterns in Norrbotten county the local pattern was compared with targets set by the Swedish association for general practitioners. Among diagnoses that were prescribed antibiotics, the proportion prescribed penicillin V was: pharyngotonsillitis 81% (target >90%), acute media otitis ages 2–16 years 78% (target >90%) and "RTI" 54% (target 80%), showing that there is still room for improvement [28].

Another study based on the National Board of Health and Welfare's drug registry showed that the proportion of tetracyclines among antibiotics used for RTIs is too high in relation to the recommendations for penicillin V [29].

In 2006, 7.6% of all women in Sweden received at least one course of an antibiotic, mostly used for UTIs. Figure 5 illustrates consumption of antibiotics for treating UTI in women and shows that pivmecillinam and nitrofurantoin, the recommended first-line drugs, are increasing while trimethoprim and fluoroquinolones are decreasing. New guidelines published in 2007 are currently being implemented and compliance is being monitored by measuring an index of the proportion of prescriptions of fluoroquinolones and that of a combination of pivmecillinam, nitrofurantoin and trimethoprim. While doing this, through the National Board of Health and Welfare's drug registry, it was found that the proportion of fluoroquinolones varied between the counties from 19% to around 30% [29]. The reason for the magnitude of this variation is not known.

Antibiotic use in hospitals was surveyed in nationwide point-prevalence studies (PPS) in 2003, 2005 and 2006. In the 2006 survey, the studied population approximated 77% of all admitted patients in Swedish hospitals during one day [30], and before the survey all doctors received a leaflet by mail highlighting desired changes based on data from the first two studies. The aims of shortening peri-operative prophylaxis and reducing the use of fluoroquinolones in treatment of community-acquired cystitis in women were achieved. However, the aim of replacing cephalosporins with the recommended first-line use of penicillin in the treatment of community-acquired pneumonia failed.

Although statistics of antibiotics sales showed a decrease for the population as a whole in Sweden during the period 1993–2002, sales increased for the population 80 years of age and older. In the Swedish Antibiotic Nursing home Trial (SANT) in 58 nursing homes with 3002 residents in 15 counties, 84% of 889 recorded infectious episodes considered to require a physician's opinion by the responsible nurse were treated with antibiotics. For the major indication, lower UTI in women, half the cases were not treated according to the recommendations. The main concerns were duration of treatment and overprescribing of fluoroquinolones and that many of the antibiotics were issued without the physician actually seeing the patient [31].

Examples of national and regional projects

Intensive care

In 1999 an ICU-Strama project was started with the aim of raising awareness and establishing best practice among physicians with regard to antibiotic resistance, antibiotic use and infection control in Swedish ICUs. Antibiotic resistance data from 14 ICUs participating in the program from 1999 to 2003 showed that 0–1.8% of *S. aureus* were MRSA. Correspondingly, presumptive ESBL phenotypes were found in 2.4–4.6% of *E. coli*. Cefotaxime resistance was found in 2.6–4.9% of *Klebsiella* spp. Rates of resistance among *Enterobacter* spp to cefotaxime (20–33%) and among *P. aeruginosa* to imipenem (reduced susceptibility (I or R), 22–33%) and ciprofloxacin (5–21%) showed no time trend [32, 33]. Since 2005 ICU-Strama has participated in CARE-ICU, an EU-funded work package within the IPSE project.

A county-based intervention to reduce trimethoprim resistance

Antibiotic resistance in bacteria can be associated with a biological fitness cost, therefore it was assumed that reduction of antibiotic use may be followed by a reduction in resistance rates. In a county-wide intervention in Kronoberg, where trimethoprim resistance in *E. coli* had increased from 7% (1990) to 11% (2004), all physicians (n = 564) were persuaded, through personal visits and by mail, to replace trimethoprim and trimethoprim-sulfamethoxazole by pivmecillinam, nitrofurantoin or ciprofloxacin. A two-year 85% decrease in the use

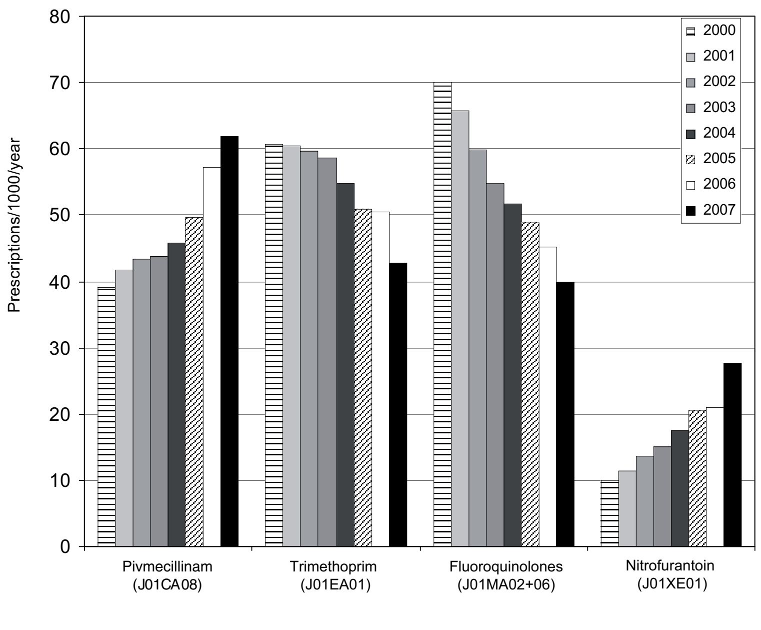

Fig. 5. Antibiotics mostly used against UTIs, women aged 18 or older, outpatient care, prescriptions/1000 patients per year

of trimethoprim did not, however, result in a clinically useful change in resistance rates. Whether an increase in fluoroquinolone resistance was related to an increase in its use remains to be evaluated.

Indicators for detecting antibiotic underprescribing

The national registry of diagnosis in hospital care (National Board of Health and Welfare) was used to follow the number of patients in different age groups with acute sinusitis, quinsy and acute mastoiditis between 1987 and 2003. According to the registry, hospital admissions for these diagnoses in children were stable or decreased despite the concomitant reduction in antibiotic consumption.

Public awareness

Knowledge and expectation among the general public with regard to antibiotic treatment is assumed to contribute to inappropriate antibiotic prescribing in the primary care setting. To assess knowledge and expectation on antibiotic treatment among the general public in Sweden, a telephone-based questionnaire survey was conducted in February and March 2006. Findings from structured interviews with 747 individuals appeared to indicate a high degree of knowledge on antibiotic treatment and resistance; however, 46% of the respondents could not name any antibiotic drug when asked. Although one-third believed that antibiotics are effective against viruses, only 19% agreed that antibiotics make common colds pass more quickly.

Discussion

Sweden has been in a favorable situation with regard to antibiotic resistance. Some of the possible "success factors" that might have contributed to making a difference should be mentioned. Sweden is a small country with a limited number of doctors working in the field of infectious disease epidemiology, making personal acquaintance almost a rule. This makes it easier to make things happen even if opinions differ. Also, the long tradition of collaboration between microbiological laboratories has developed into a combined surveillance and QA-system, and consensus on microbiological methods has developed in a way that has been internationally recognized [34]. The possibility of transferring patients infected with MRSA to single or isolation rooms in the infectious disease clinics has also been of great importance in the management of some hospital outbreaks. In addition, a long tradition of collecting data on antibiotic sales from the pharmacies has developed into a database with validated data of good quality covering 100% of pharmacies. Further, since the professionals uniformly warned about the emerging threat from antimicrobial resistance there has been political interest manifested not only by the governmental bill of 2006 but also, for example, by economic support to national and some regional Strama groups. All of these activities drew a lot of attention in the media, which further added to the dissemination of awareness.

One of the cornerstones in the Swedish combat against antibiotic resistance has been the tradition of rather liberally performing cultures, thereby providing the microbiological laboratories with significant material. Results from the laboratories have then highlighted the need for infection control measures, revision of treatment guidelines, more extensive action plans, or data collection. Without the interaction between QA and surveillance, and the consensus and conformity between the Swedish laboratories, as well as the collection and storing of isolates, this would not have been possible. However, surveillance and awareness is not an automatically integrated part of the healthcare system; instead it relies on too few devoted enthusiasts and is in many cases hampered by poorly adapted IT systems. One problem experienced as the MRSA problem grew was that no defined strategy and coordination for epidemiological typing of isolates had been developed. This led to a delay in evaluation of some epidemiological clusters and almost "anarchy" in the in-house nomenclature while PFGE was the recommended method.

Four variants of antibiotic resistance are included in the Communicable Diseases Act and notifiable, one of which, ESBL, is reported only by the laboratories. In general this legislation has been a useful tool in supporting the development and implementation of action plans. However, the quality of the primary information on notifications has been rather poor and some parts of the epidemiological investigation are unfinished at the time of sending reports. This has created unnecessary extra manual work to feed complementary information into the system, causing delay in analysis and feedback, at least at the national level. Thus, the routine procedure for completing notifications in the reporting system needs to be improved.

As a result of the increasing problem of resistance and awareness of healthcare-associated infections, infection control and basic hygiene precautions have been put in focus. The number of positions in infection control has increased, but from time to time they have been difficult to fill, particularly as there is a shortage of doctors. However, an increasing number of nurses working with the municipalities has facilitated transfer from hospitals and probably reduced the risk of transmission from MRSA patients in long-term care facilities and nursing homes. The basic hygiene precautions were adopted as the gold standard in most Swedish hospitals and eventually defined in a regulation by the National Board of Health and Welfare [35]. Many hospitals now have written policies on these and on dress code. In some hospitals and clinics, consumption of hand disinfectants is also measured. The Swedish Association of Local Authorities and Regions has initiated many projects, both local and national, for reducing healthcare-associated infections and transmission. Several projects to study and prevent infections through infection control in the day-care setting have been initiated [36]. Many problems still remain to be solved regarding recruitment of infection control staff, financing of infection control competence (particularly in the municipalities) and a clearer definition of good hygienic standards in different settings.

Antibiotic resistance has been addressed through various approaches. The initial work against pneumococci in outpatient care was clearly multisectorial and interdisciplinary and covered many aspects of rational use of antibiotics, transmission, public awareness and expectations. The somewhat later battle against MRSA, which started in the hospital setting and in long-term care facilities, focused almost solely on infection control and occupational health.

National recommendations against pneumococci were developed, the implementation of which varied between the counties from complete adaptation to no action at all [37]. The rationale for this varied approach, where children carrying PRP at one end of the country were considered healthy and in another were excluded from their ordinary day-care, maybe at home with a parent temporarily not working, was intensely debated in the Swedish Medical Journal. It was shown that day-care intervention was better than no intervention in reducing the risk of being infected [38] and that a program combining infection control and reducing antibiotic consumption limited the spread of PNSP [39].

As with pneumococci, the CDCDCs developed local guidelines to control MRSA in collaboration with the infection control teams. The guidelines were based more or less on experiences of search and contain from Gothenburg, focusing on case finding and extensive infection control measures (including transfer to isolation wards at a clinic for infectious diseases when possible). Again, these modified plans led to variations in interpretation of the restrictions applicable to infected patients and staff. An evaluation of the situation of patients showed that they felt insulted by becoming infected, that they had experienced poorer access to healthcare services and rehabilitation, and that negative reactions from surrounding people were common [40]. A need for national harmonization became obvious, and The National Board of Health and Welfare together with Strama have developed coordinated guidelines for MRSA in healthcare staff, in the day-care setting and in the community. Another document under way, with close collaboration between human and veterinary authorities, deals with the zoonotic potential of MRSA in companion animals.

When ESBL rapidly evolved into a major threat within a few years and was made notifiable in 2007 it was obvious that a coordinated action plan was needed from the beginning in order to coordinate laboratory work, to raise awareness and the need for planning among healthcare providers, and to avoid disharmony in the treatment of patients. Unlike the MRSA program, the need for defined antibiotic policies to limit the selection of resistance has been included. Strama's action plan [15] is coherent, with papers published in a recent supplement of Clinical Microbiology and Infection [41]. The relative importance of food import and the food chain is unknown; these topics need further studies and cannot be addressed here.

The Swedish monopoly system for pharmacies has made it possible to have access to continuously updated validated sales data with 100% coverage down to the municipal and workplace level. This, of course, is highly unusual and has been of great value. Feedback of such data to the prescribers has been a hallmark of the work of the local Strama groups and drug committees and a most useful tool for influencing prescribing patterns. Nevertheless, in addition to discussion of the appropriateness of the DDD and sales data methodology [42], there have been several other problems. There are still some difficulties in analyzing data on the elderly population, because of a mix of prescriptions and differing types of ordering system in long-term care facilities and nursing homes. To calculate hospital consumption according to the number of patient-days or bed-days, data must be collected and combined from different sources, hospital data with one years' delay. Individual statistics on consumption were not available until the National Board of Health and Welfare's drug registry came into operation in 2005. Although it is possible to feed back a profile of prescriptions for an individual doctor, this cannot be done within the hospital setting. Another specific problem is that, in the main, the statistics are managed for feedback to the county councils (drug committees, etc.). The National Corporation of Swedish Pharmacies is responsible for general surveillance of sales at the national level but not at the detailed level needed for analysis of antibiotics. Strama has taken on this responsibility but has problems with limited access to some data combinations; for example, on types of workplace.

After a steady decrease in antibiotic consumption during the 1990s until 2004, consumption started to increase again, mainly because of an increase of penicillin use in pre-school children. The reason for this increase is under investigation. A possible explanation is that the information given to parents in the 1990s about the natural course and limited effect of antibiotics on most upper RTIs has not been sustained and antibiotics seem now to be looked upon as a quick fix and a way for parents to get back to work more quickly. An alternative explanation may be that a change in compensation in the general practice system in some counties might make the doctors more prone to prescribe antibiotics for reasons of "customer satisfaction".

The diagnosis-prescribing surveys in general practice and PPS in the hospitals have added a lot of knowledge about therapeutic traditions and doctors' thinking when ordering antibiotics. In light of an increasing problem with resistance and *C. difficile*, the goal for compliance with therapeutic guidelines for treatment with antibiotics must be set as high as for compliance with infection control.

During the past decade an increasing number of alerts have emerged and a shift has occurred in the epidemiology, from a predominance of "imported problems" with local secondary outbreaks, to a general, although still comparatively limited, endemic multiclonal and multifaceted problem. Many formal processes relating to antibiotic resistance and consumption that may have great implications for future work are ongoing. The Swedish government has commissioned SMI and Strama to investigate present systems for surveillance of antibiotic resistance and antibiotic consumption and suggest systems for the future. The National Board of Health and Welfare has a commission to assess quality aspects on the use of antibiotics, access to competence in infectious diseases and therapeutic guidelines. At the same time, a government bill is under preparation for phasing out the pharmacy monopoly; also another bill regarding new rules for medical records, specifically their relation to medical follow-up, safety of drug use and integrity.

In parallel, a national strategy for IT structure is under development and will ultimately enhance compatibility and exchange of data, anonymized or not, between systems. If all this falls into place, there is opportunity for a great step forward during the next 5–10 years.

Some of the major concerns for the future are that resistance epidemiology in the clinical setting, infection control and other preventive measures are not prioritized, that clinical microbiologists are scarce, that alarm systems and surveillance of multiresistance are not in place, and that diagnosis and treatment are not linked in today's computerized medical records.

To solve some of these problems responsibilities must be made clear. There is a need for formal clarification that surveillance of antibiotic resistance should be regarded as an integrated part of patient safety and QA and thus should be given priority and financed within the system. For antibiotic resistance an even stronger national coordination and combined capacity is desirable, including a common database for all resistance data and monitoring of the environment for new microbial threats. It is obvious that a connection between diagnosis and ordinated/prescribed drugs is necessary for developing QA tools in antibiotic (and other drug) use.

Greater focus is needed on how to communicate information relating to infections and antibiotics to the general public, the medical profession, politicians and stakeholders. Ecological, environmental and zoonotic aspects and the importance of the food chain for spread of antibiotic resistance need to be further investigated in broad collaboration with relevant authorities, such as the newly created Strama VL. In addition, all medical curricula should be modified in order to raise students' awareness of the problem of antibiotic resistance during their period of study.

Strama's multidisciplinary coordinated program has contributed to a reduction of antibiotic use in Sweden without measurable negative consequences. In combination with increasing emphasis on infection control, the spread of resistance has been limited. However, resistance problems are coming closer and growing bigger while at the same time antibiotics can be prescribed by any doctor for self-limiting or viral diseases without questions on quality being asked. A crucial period of transition in Sweden with revision of several related formal frameworks together with possibilities for extensive IT support may enhance patient safety and quality-related follow-up. Nevertheless, antibiotic resistance is a global threat that respects no borders and must be met through international collaboration networks such as ABS-International [43] and institutions such as the EU, ECDC and WHO.

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