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Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme

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Increasing use of antibiotics and the spread of resistant pneumococcal clones in the early 1990s alarmed the medical profession and medical authorities in Sweden. Strama (Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance) was therefore started in 1994 to provide surveillance of antibiotic use and resistance, and to implement the rational use of antibiotics and development of new knowledge. Between 1995 and 2004, antibiotic use for outpatients decreased from 15·7 to 12·6 defined daily doses per 1000 inhabitants per day and from 536 to 410 prescriptions per 1000 inhabitants per year. The reduction was most prominent in children aged 5–14 years (52%) and for macrolides (65%). During this period, the number of hospital admissions for acute mastoiditis, rhinosinusitis, and quinsy (peritonsillar abscess) was stable or declining. Although the epidemic spread in southern Sweden of penicillin-resistant *Streptococcus pneumoniae* was curbed, the national frequency increased from 4% to 6%. Resistance remained low in most other bacterial species during this period. This multidisciplinary, coordinated programme has contributed to the reduction of antibiotic use without measurable negative consequences. However, antibiotic resistance in several bacterial species is slowly increasing, which has led to calls for continued sustained efforts to preserve the effectiveness of available antibiotics.

Introduction

Bacterial resistance to antibiotics, both at the individual and community levels, is an unavoidable side-effect of consumption of these drugs.[1] Antibiotic resistance limits the available treatment options and causes increased morbidity and mortality as well as increased costs because of failure of the empirical therapy.[2,3] During the past two decades, resistance to antibiotics has become a major public-health concern, mainly caused by national and international spread of multiresistant bacterial clones and the declining interest from the pharmaceutical industry in research and development of new antibacterial drugs.

Sweden has a population of about 9 million, and its national health-care insurance system encompasses all inhabitants. The 21 county councils have the main responsibility for health care, which is supplied mainly by public providers, but also by private providers through contracts with the county councils. Primary and secondary care is organised through each county council, and regional university hospitals provide tertiary care services. All outpatient pharmacies belong to one parastatal company, Apoteket AB, which has about 900 pharmacies in the country. The financing of health care is mainly public. Approximately 8·3% of gross national product was spent on health care in 2004, and of this approximately 13·4% was spent on drugs. There is co-payment for both health care and drugs, with separate ceiling costs. On average, about 24% of medicine costs are paid by patients, but the reimbursement is stepwise with full co-payment of up to 900 Swedish krona (US$118) per year. Dental care is not included in health-care reimbursement.

In Sweden, antibiotic use increased constantly during the 1980s and the beginning of the 1990s. The detection of several multiresistant pneumococcal clones in the early 1990s among young children, especially in day-care centres in Skåne county in southern Sweden, alarmed the medical profession and the medical authorities, and prompted coordinated efforts to prevent further spread of these resistant clones.[4] A national organisation, Strama (the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance), was initiated in 1994 and came into action in 1995. The overall aim of Strama is to preserve the effectiveness of available antimicrobial agents. Although pneumococcal resistance in the community was the first target of Strama, the programme has continuously expanded, and today comprises activities within many fields, including primary care, hospital care, nursing homes, and day-care centres. Since 2000, Strama has received financial support from the Swedish government. The aim of this Review is to describe the Strama programme and summarise the results of the first 10 years.

Organisation of Strama

National level

Strama is composed of a national steering group and regional Strama groups in every Swedish county (panel). The national Strama group includes a broad representation of professional organisations and relevant authorities. The main objectives of the national group are to coordinate activities for the containment of antibiotic resistance at the national level. Activities include the analysis of trends in antibiotic resistance and consumption, identification of gaps in knowledge, initiation of studies to fill these gaps, and priority setting of areas for interventions. An executive working committee, supported by a small secretariat, meets approximately once a month. Its role is to work out yearly action plans, coordinate activities, and support the regional Strama groups. A public website (http://www.strama.se) has been available since 1998 with regularly updated regional and national data on antibiotic use and resistance, treatment guidelines, and results from Strama-funded projects. A national meeting is held annually for the members of the regional Strama groups and other interested parties. At these meetings, updates on scientific and medical aspects on antibiotic resistance, annual statistics on antibiotic use and resistance, and results and analysis of studies, interventions, and educational programmes are discussed.

Regional level

At least one multidisciplinary Strama group has been formed in each county (panel). These groups, in most cases led by the county medical officer for communicable disease control, follow antibiotic use and resistance in their region, and disseminate that knowledge and locally adapted guidelines on the prevention and treatment of infections to professionals in the health-care system. The regional Strama groups work in close collaboration with the regional drug and therapeutics committees. The groups were initially focused on outpatient care, but more recently, special hospital units of Strama have been formed.

Antibiotic use

Data on outpatient antibiotic sales has been available in Sweden since 1974 from Apoteket AB (the National Corporation of Swedish Pharmacies) in defined daily doses (DDD) per 1000 inhabitants per day, according to WHO guidelines,[5] and as the number of prescriptions per 1000 inhabitants per year for different age-groups and geographical areas. All regional Strama groups are given regional data on antibiotic use by local pharmacists.

Between 1995 and 2004, total antibiotic use (excluding methenamine, which is a urinary antiseptic) decreased by 15% from 17·3 to 14·6 DDD per 1000 inhabitants per day, and for outpatient use by 20% from 15·7 to 12·6 DDD per 1000 inhabitants per day (figure 1).[6] The number of prescriptions declined by 23% from 536 to 410 per 1000 inhabitants per year. The reduction was most prominent for macrolides (65%), from 48 to 17 prescriptions per 1000 inhabitants per year. The number of prescriptions fell by 37% among children aged 0–4 years, by 52% among children aged 5–14 years, by 23% in those aged 15–64 years, but increased by 12% among those aged 65 years and older (figure 2). The increased use of antibiotics among elderly people between 1995 and 1999 was partly caused by a change in administrative routines, such as the change in use of antibiotics in nursing homes from hospital use to outpatient use (figure 2). Approximately half of the prescribed antibiotics were penicillins, of which phenoxymethylpenicillin constituted 60–70%.[6]

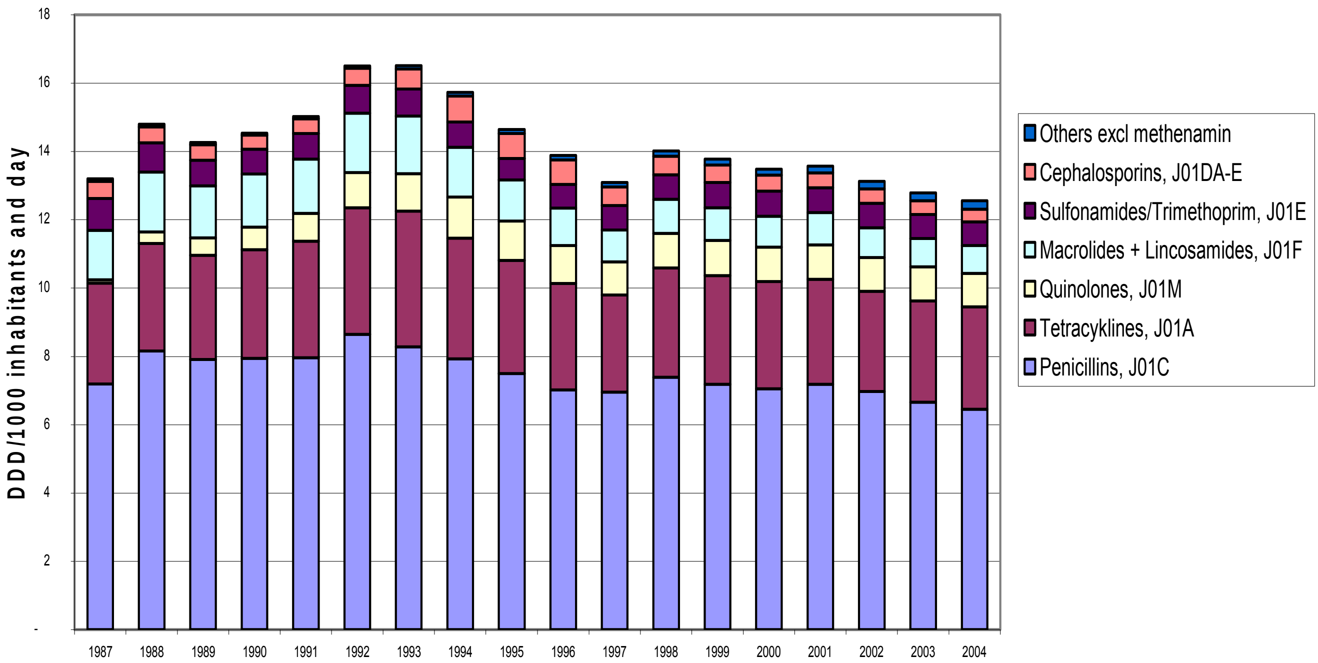

Figure 1. Antibiotic use in out-patients, methenamine excluded, in DDD/TID 1987-2004 in Sweden (National Board of Health and Welfare) (9). Methenamine is a urinary antiseptic, with no influence on resistance.

Indications for antibiotic use

Although the regular dissemination of sales data has attracted substantial interest, especially the large and unexplained geographical variations in antibiotic use, such data do not include indications and cannot be used to assess the quality of antibiotic prescribing. Strama has therefore initiated several large surveys on the indications for antibiotic prescriptions. A diagnosis-prescribing study in primary care was done by Strama in 2000, and repeated in 2002.[7–10] These studies comprised about 150 general practices (about 600 general practitioners), and the total number of patients with infections included in the studies were 7029 and 5377, respectively. The studies showed high antibiotic prescribing in acute otitis media, acute pharyngotonsillitis, and acute bronchitis, indicating that the new guidelines for the treatment of acute otitis media and acute pharyngotonsillitis had not been fully implemented.

In uncomplicated urinary tract infections (UTIs), increased use of pivmecillinam and nitrofurantoin has been advocated in favour of trimethoprim and fluoroquinolones. Increased adherence to these recommendations is indicated in national data on the number of prescriptions of these four antibiotics to women between 2000 and 2005 (Apoteket AB), and data from the Strama diagnosis-prescribing studies showed similar results.[10]

To assess hospital antibiotic use, two point-prevalence studies were done with 54 hospitals participating in 2003, and 49 hospitals in 2004.[11] The antibiotic treatment of approximately 60% of all admitted patients in Sweden (13 536 and 11 348 patients, respectively) during 1 day was assessed.[11] Apart from patient-specific background data, such as underlying diagnoses and immunosuppression, the assessment included reasons for antibiotic treatment, whether the antibiotic was prescribed for a community-acquired or hospital-acquired infection or as peri-operative prophylaxis, and whether relevant samples for culture were taken before treatment. According to preliminary data from the point-prevalence studies,[11] adherence to guidelines on prophylaxis can be improved as well as choice of treatment in UTIs and community-acquired pneumonia. Data in these studies were reported by an internet-based system, and reports and analysis are likewise available on the internet reporting system for the participating Strama groups.

The national trend of increasing antibiotic use in elderly people has prompted a separate study on indications for antibiotic prescribing in nursing homes, which was done in 58 nursing homes in 2004.[12] Preliminary data from this study have shown poor diagnostic routines and antibiotic overprescribing with regard to UTIs. These areas are now subject to different interventions.

Antibiotic resistance

In Sweden, there are 30 clinical microbiological laboratories, with at least one laboratory for each county. The antimicrobial susceptibility testing methods of Swedish laboratories are well standardised through the work of the Swedish Reference Group of Antibiotics, methodology subcommittee (SRGA-M), and the 30 laboratories.[13] Species-specific susceptibility break-points are used. Validation of susceptibility testing by histogram analysis is done annually, and internal control is done daily or weekly by comparing laboratory-specific zone diameters with SRGA-M reference zone distributions of reference strains. The laboratories also test strains from foreign laboratories as an external control.

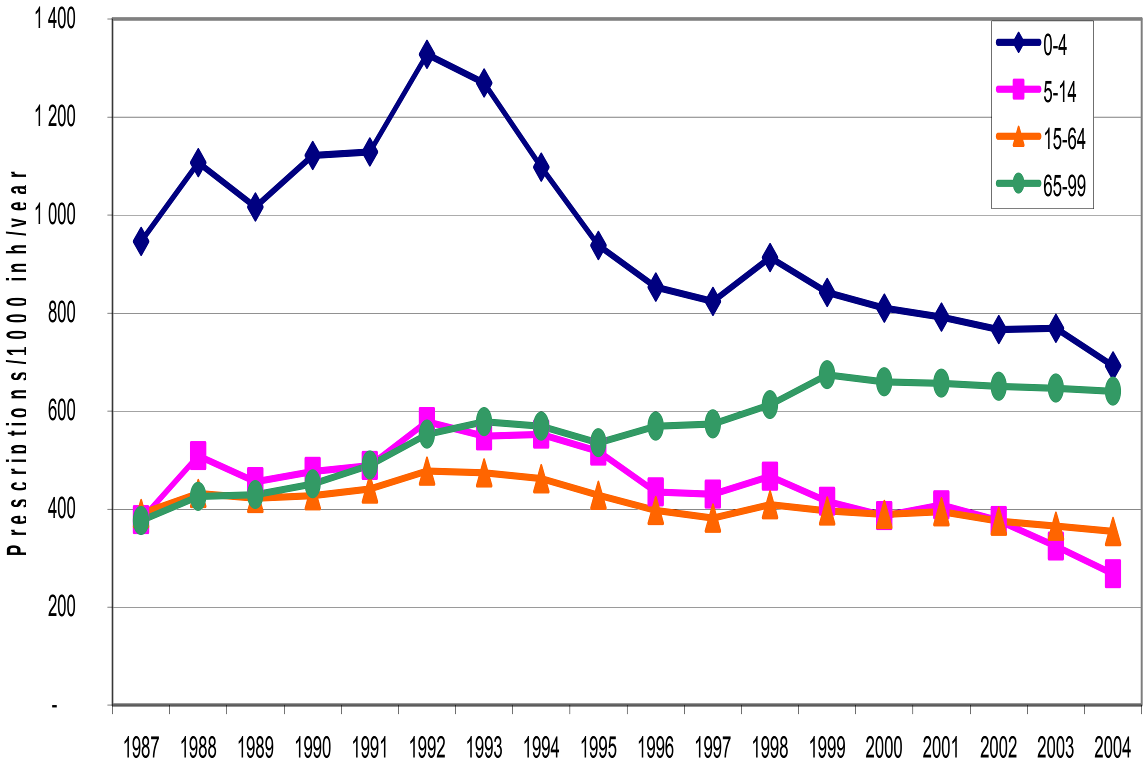

Figure 2. Antibiotic use in out-patients, methenamine excluded, in number of prescriptions/1000 inhabitants and year, for different age-groups, 1987-2004 in Sweden (9). Methenamine is a urinary antiseptic, with no influence on resistance.

Since 1994, each laboratory has collected quantitative antibiotic susceptibility data (zone diameters) for defined antibiotics in at least 100 consecutive clinical isolates of six bacterial species yearly. The data are entered into an internet-based software program. Hereby, resistance among clinical isolates of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Streptococcus pyogenes*, and *Escherichia coli* can be followed annually at a national level.[14]

Infections or colonisation with four different antibiotic-resistant pathogens are notifiable by the Communicable Disease Act: penicillin-resistant pneumococci (PRP; minimum inhibitory concentration for penicillin G ≥0·5 mg/L) since 1996, meticillin-resistant *S aureus* (MRSA), and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* since 2000. Annual data on number and incidence (per 100□000 population) of these pathogens at a national and county level is available.[15] Since 1999, Sweden has participated in the European Antimicrobial Resistance Surveillance System (EARSS). Each participating country collects annual quantitative antibiotic susceptibility data on invasive clinical isolates of *S pneumoniae*, *E coli*, *S aureus*, *E faecalis*, and *E faecium*, and these data are then collated and presented on the EARSS website; Swedish national data are also presented on the Strama website. Additionally, all regional Strama groups are given regional data on resistance by their local microbiological laboratories.

Pneumococcal infection

The spread of resistant pneumococci in Skåne county led to the initiation of communicable disease control measures against the spread of PRP among children of preschool age.[16] No further epidemic spread to other counties has been seen, contrary to what was feared,[17] and since 1995, the rates of penicillin-nonsusceptible pneumococci (PNSP) and PRP in nasopharyngeal cultures have been stable in Skåne.[16] However, national data on pneumococci in nasopharyngeal cultures shows slowly increasing rates of PNSP between 1995 and 2004 (from 4% to 6%),[6] despite the decrease in antibiotic use among children (figure 2 and figure 3). Resistance to erythromycin, tetracyclines, and co-trimoxazole also increased during this period. The lack of decline in resistance was not expected, but might have been caused by too short an observation time, continuing spread among children, or unknown factors. Thus, once resistant strains have become established in a population, the problem may not always be reversible, although some studies have indicated a decline in prevalence after intervention.[16,18,19]

By contrast with most other countries in Europe, no increase of antibiotic resistance among invasive pneumococcal isolates in Sweden has been reported since 2000.[20] The frequency of PNSP in invasive isolates has varied between 2·5% and 5·0% and the number of invasive erythromycin-resistant pneumococci has not increased between 1999 and 2005.

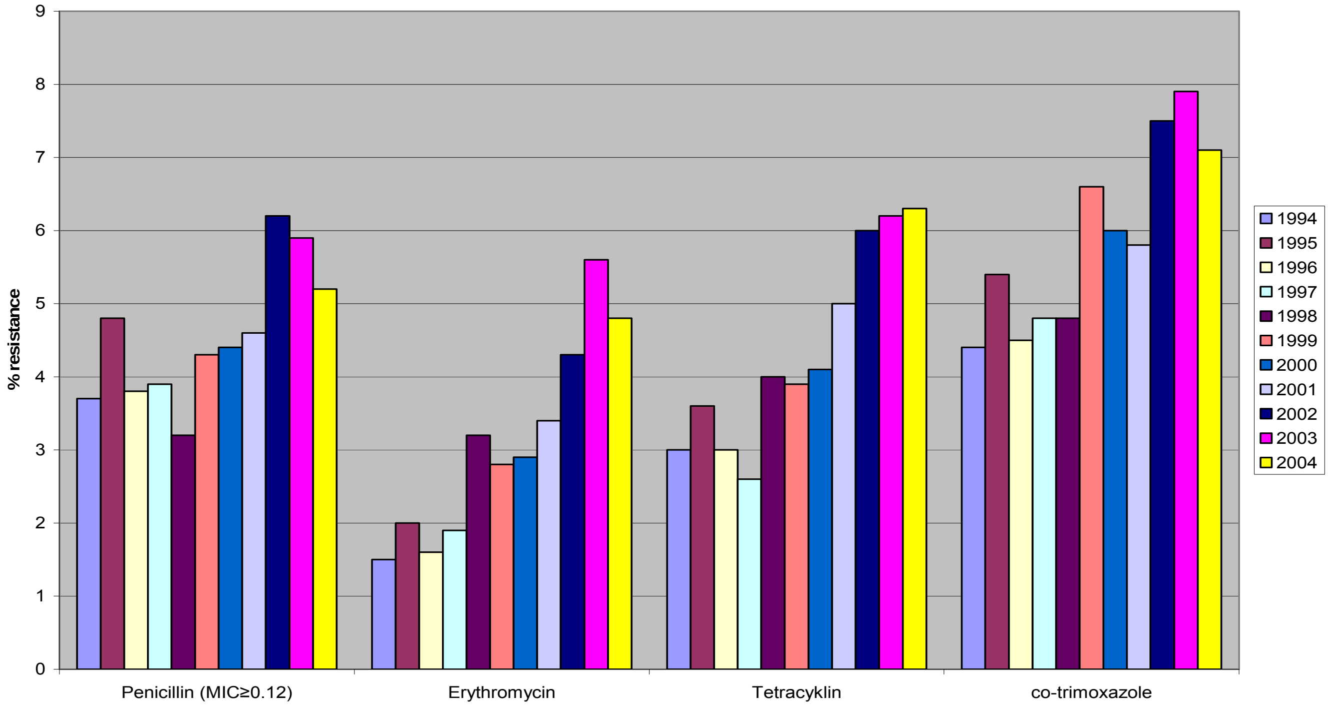

Figure 3. Antibiotic resistance in S. pneumoniae to penicillins, erythromycin, tetracycline and co-trimoxazole (9). For penicillins, all strains with reduced susceptibility are included (MIC≥0.12).

Other bacterial infections

Beta-lactamase-producing *H influenzae* in naso-pharyngeal cultures has remained stable at 10% since 1995. Beta-lactamase-negative ampicillin-resistant *H influenzae* is about 3% in nasopharyngeal cultures, tetracycline resistance is 1%, and resistance to co-trimoxazole is 10%.[6] In *S pyogenes* from throat cultures, tetracycline resistance increased from 6% in 1995 to 14–18% in 1998, but has since remained stable. Resistance to clindamycin is rare (<1%) and erythromycin resistance is about 2·5%.[6] Between 1997 and 2004, the rate of ampicillin-resistant *E coli* in urinary cultures increased from 17% to 24%, and trimethoprim-resistant isolates increased from 8% to 15%. 9% of *E coli* in urinary cultures in 2005 were resistant to fluoroquinolones, as defined by resistance to nalidixic acid.[6]

For *S aureus* isolated from wound infections in 2005, less than 0·5% were meticillin resistant and 2% were clindamycin resistant. In 2001, a clone of *S aureus* resistant to fusidic acid spread and became prevalent in many parts of Sweden, leading to 8–10% resistance at the national level. Less than 1% of the invasive *S aureus* isolates are meticillin resistant.[6]

Between 2001 and 2005, high-level aminoglycoside resistance in invasive enterococci was 12–17% in *E faecalis* and 6–11% in *E faecium*. Vancomycin-resistant *E faecium* has been occasionally reported.[6]

Intensive care

A national programme in intensive care units (ICUs) was started in 1999 to raise awareness of antibiotic resistance and infection control problems among ICU physicians (ICU-Strama).[21] The number of ICUs that took part in the programme has varied over the years with a yearly mean of 28 ICUs between 1999 and 2006. Antibiotic resistance from 14 academic and non-academic ICUs, which participated in the ICU-Strama programme in 1999–2003, showed that 0–1·8% of *S aureus* isolates were meticillin resistant. Similarly, presumptive extended-spectrum beta-lactamase phenotype was found in less than 2·4% of *E coli*, on the basis of cefotaxime susceptibility, except for a peak in 2002 (4·6%). Cefotaxime resistance was found in 2·6–4·9% of *Klebsiella* spp. Resistance to cefotaxime among *Enterobacter* spp (20–33%) and to imipenem (22–33%) and ciprofloxacin (5–21%) among *P aeruginosa* showed no time trend.

In Swedish ICUs, the surveillance programme has shown low prevalences of antibiotic-resistant *S aureus* (MRSA), *E coli*, and *Klebsiella* spp, despite high antibiotic consumption.[22] An explanation for the low prevalence of resistant *E coli*, *Klebsiella* spp, and *S aureus* was probably a low entry to the ICUs of epidemic clones of these organisms because of the low prevalence of these strains in the community. The main cause of the high imipenem and ciprofloxacin resistance among *P aeruginosa* was probably the high consumption of carbapenems and quinolones. Experience from other countries and ICUs show that the situation can change rapidly, and continuous surveillance is therefore necessary to design interventions in antibiotic policy or hygiene procedures when needed.

Infection control

The use of alcohol handrub rather than soap handwashing has been recommended for disinfection of hands between patient contacts in Swedish hospitals since the 1970s. Sweden has been one of few countries with less than 1% resistance to meticillin among invasive isolates of *S aureus*. However, recent spread of MRSA in a few hospitals in Sweden has underscored the need for increasing activities in the field of infection control. Between 1997 and 2000, the largest Swedish outbreak of an endemic strain of MRSA (EMRSA-16) occurred at Sahlgrenska University Hospital in Gothenburg. The outbreak was successfully terminated by use of aggressive infection-control measures and a massive high-cost sampling programme.[23,24] The main lessons learned during this outbreak were that the measures taken were cost effective and that the previously recommended barrier precautions, implemented when identifying new carriers of MRSA, were often introduced too late to be able to curtail the outbreak. In an attempt to be one step ahead of MRSA spread, the uniform use of basic hygiene precautions was introduced during the outbreak.[23] In brief, these rules apply to all patients and staff, including physicians. They include the banning of private clothes and the wearing of finger rings, wrist jewellery, and watches at work. A dress code with short sleeves for all health-care workers was introduced, use of alcohol handrub before and after every patient, and the use of gowns with every close patient contact was recommended. The introduction of these rules was thought to be one of the main reasons for the successful termination of the outbreak, and they have since been adopted as standard in most Swedish hospitals. Thus, Strama recently supported a national study on the estimation of hand-hygiene compliance rates by measurement of alcohol handrub consumption in 44 wards in hospitals nationwide, including ICUs and in surgery and internal medicine wards.[25] Additionally, Strama initiated the formation of a national expert group on hygiene and infection control to make an inventory of relevant areas for future actions and interventions in this important field.

Indicators for detecting antibiotic underprescribing

From the national registry of diagnosis in hospital care (National Board of Health and Welfare), the number of patients with acute sinusitis, quinsy (peritonsillar abscess), and acute mastoiditis was followed for different age-groups between 1987 and 2003. According to this registry, hospital admissions for acute mastoiditis, quinsy, and acute rhinosinusitis in children were stable or decreased during this period (figure 4).[6] Thus, there were no signs of underprescribing. We also noted a large reduction in admissions for pneumonia (not shown), which may have resulted from a reduction in available hospital beds. To fully secure that a further reduction in antibiotic use does not increase the number of complications or give increased durations of illness, improved systems for surveillance of treatment effects are necessary.

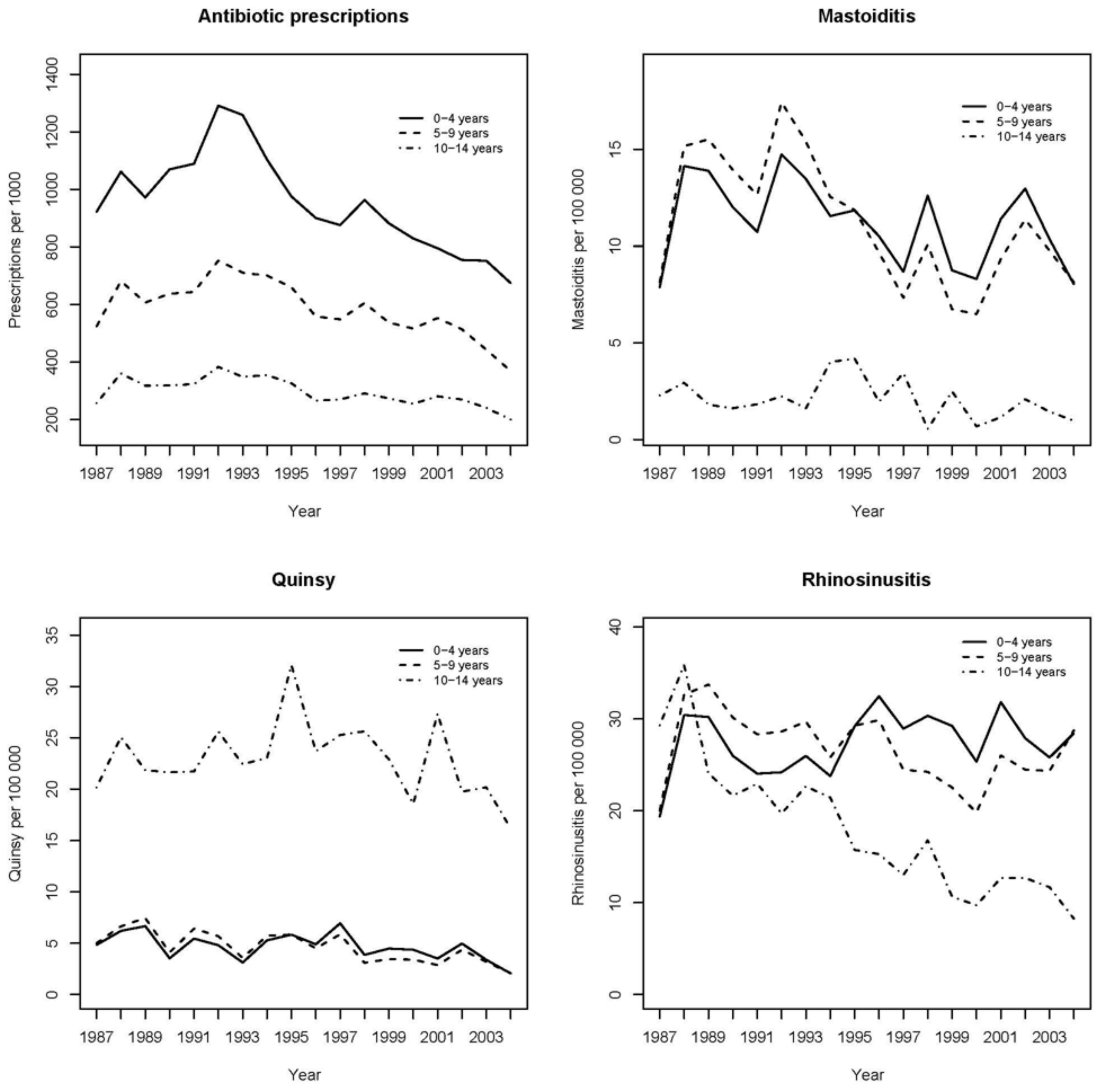

Figure 4. Number of antibiotic prescriptions and number of hospital admissions for acute mastoiditis, quinsy and rhinosinusitis for children in different age-groups between 1987 and 2004.

Other activities

In 2000, the National Board of Health and Welfare, in close cooperation with Strama, prepared a national action plan to contain antibiotic resistance in Sweden.[26] The objectives of this plan are used in the development of the annual work plans for Strama activities.

New national guidelines were developed for the treatment of acute otitis media in 2000, for acute pharyngotonsillitis and impetigo in 2002, and for acute sinusitis in 2005. The guidelines for the treatment of UTIs was updated in 2006, and new guidelines for lower respiratory tract infections will be issued in 2008.

Comparison with other countries and future perspectives

Non-prescribed use of antibiotics is very low in Sweden compared with other European countries.[27,28] The survey of hospital admissions for certain infectious diagnoses that may be related to below optimum antibiotic use showed that these diagnoses have been stable or declining, despite the reduction in prescribing to children (figure 4); these findings are in agreement with a UK study.[29]

Antibiotic use varies between countries, but also with regard to class of antibiotics, dosage, and treatment duration.[30–32] In the empirical choice of antibiotics, ecological aspects should be taken into consideration because some antibiotics and regimens have been shown to be associated with emergence and spread of resistance.[4] For example, the use of macrolides and co-trimoxazole has been related to carriage of PNSP. Strama has therefore advocated narrow-spectrum penicillin as the drug of choice in most respiratory tract infections. Although antibiotic use has been substantially reduced, there are still large seasonal variations.[33,34] Furthermore, the diagnosis-prescribing studies done in primary care have shown that antibiotic prescribing can be further improved and that new guidelines for lower respiratory tract infections are needed.[7–9] These studies also showed that office tests were widely used, although not always according to guidelines. However, there are several reports that the visit rates for different respiratory tract infections has declined (Mölstad S, unpublished data), which indicate larger effects than shown in these studies. Therefore changes in consulting rates will be included among outcome variables in the assessment of future prescribing studies.

Few countries can show reliable data on antibiotic consumption before 2000, or a sustainable reduction at a national level. Declining antibiotic consumption and visiting rates by patients for respiratory tract infections has been reported from the UK and USA.[35–37] Educational campaigns for primary-care clinicians and the public have been launched in Wisconsin, USA, and the reports have shown a reduction in antibiotic prescribing and number of patients requesting antibiotic treatment.[38] In Belgium, the UK, and France, national campaigns to reduce antibiotic consumption have taken place with divergent effects.[39–42] The long-term outcome of those efforts still needs to be shown.

Benefits and limitations

The Strama project was not designed to be scientifically evaluated, but instead to be an ongoing coordinated national effort to decrease antibiotic use and spread of resistance. The project lacks a validated control, but antibiotic use has not decreased in the neighbouring countries of Denmark, Norway, or Finland.[43] We believe that the coordination of different professions and authorities, and the decentralised organisation with regional groups for the dissemination and implementation of guidelines and new knowledge are important factors. Although no coordinated public campaign has been launched in Sweden, as it has in France and Belgium, regular collaboration with news media, both national and regional, has been one of the priories for Strama. Indeed, discussion in the public media probably contributed substantially to the reduction in antibiotic use in the year before Strama was formally organised (figure 1).

Swedish sales data on antibiotic use are highly valid and antibiotics cannot be obtained without a prescription, but resistance data reported from micro-biological laboratories can always be questioned despite well standardised microbiological methods. However, the method to collect resistance data has been identical through the years, and the recommended indications for sampling in primary care have not been widened.

Unfortunately, Strama did not do baseline studies of knowledge and attitudes of physicians and the general population on antibiotics and resistance, which would have been valuable information for the purpose of follow-up. A recent qualitative study among doctors has shown that views on resistance vary. Although some doctors see resistance as a major problem, some doctors do not see resistance as either a present or future problem (Stålsby Lundborg C, unpublished data). Such information is important for the development and implementation of educational interventions to change prescribing practices.

Conclusions

In Sweden, Strama has played a major part in the reduction of total antibiotic use, in preserving phenoxymethylpenicillin as the drug of choice in most respiratory tract infections, and may have limited the spread of multiresistant pneumococcal clones. To reach the long-term aim to preserve the effectiveness of antibiotics, improved basic hygiene precautions, improved antibiotic treatments in terms of choice, dosage, and length of treatment, and further reductions in antibiotic use are needed.

Conflicts of interest

We declare that we have no conflicts of interest.

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