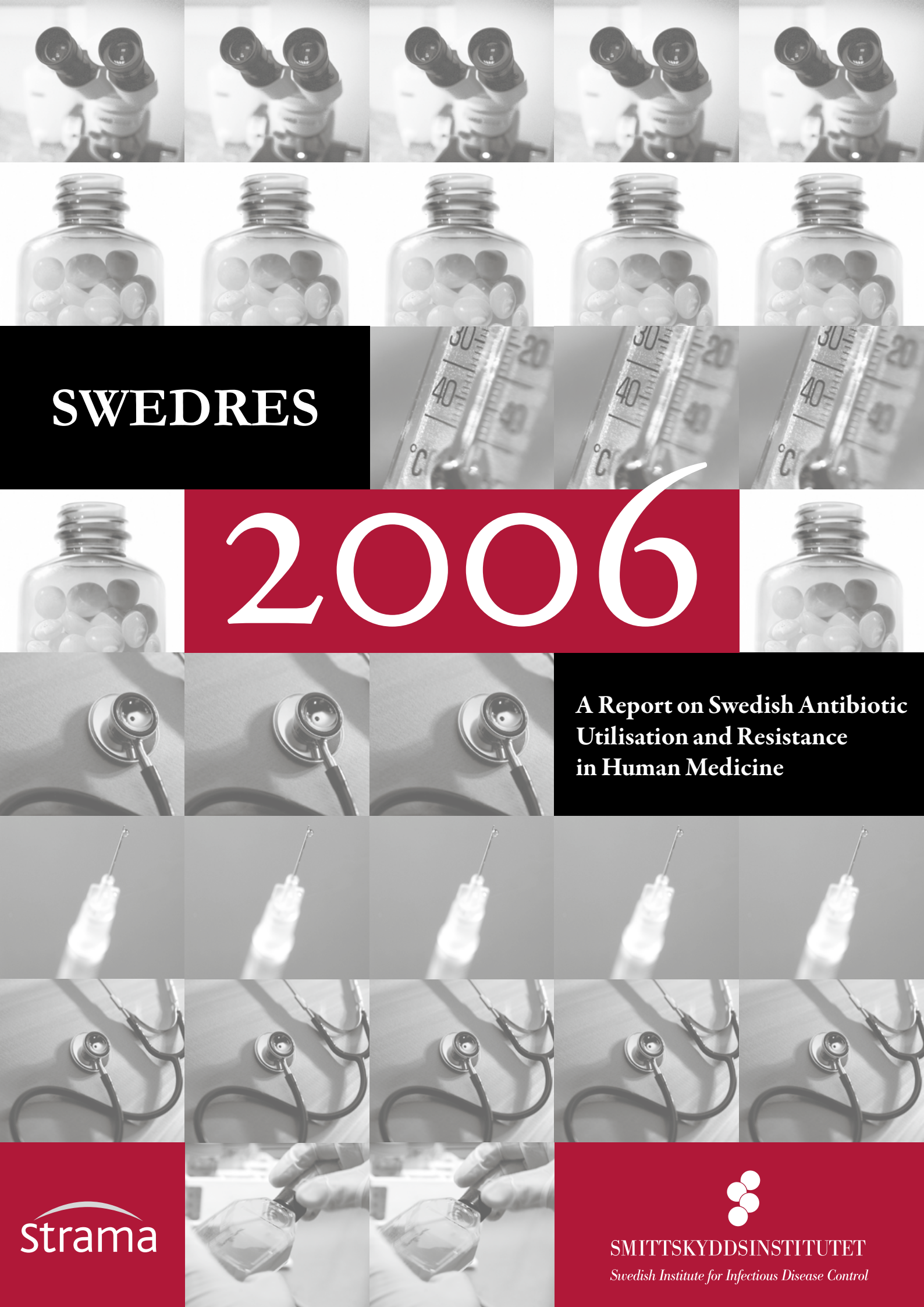

SWEDRES 2006

A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine

Strama

SMITTSKYDDSINSTITUTET

Swedish Institute for Infectious Disease Control

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Swedish Institute for Infectious Disease Control

SMI, The Swedish Institute for Infectious Disease Control (SMI) is a government expert authority with a mission to monitor the epidemiology of infectious diseases among Swedish citizens and promote control and prevention of these diseases.

Strama

Strama, The Swedish Strategic Programme against Antibiotic Resistance was founded in 1995 and has been supported by the government since 2000. An authorisation was made in 2006 and a board was appointed. The assignment is to work on interdisciplinary collaboration on issues aiming to preserve the effectiveness of antibiotics.

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1. Preface

WELCOME TO THE SIXTH Swedish report combing results from the monitoring of antimicrobial resistance and antimicrobial usage in human and veterinary medicine: SWEDRES and SVARM. This joint report will facilitate comparisons of resistance trends and patterns of antibiotic prescribing in the two fields.

Since 1995, Strama has acted as an independent network aiming to minimise the development of antibiotic resistance. In September 2006 Strama was formally authorised by the Swedish government and a board was appointed. One of the main objectives of Strama is to improve the collaboration between authorities and organisations for the common goal to preserve antibiotics as effective medicines.

Data in this report indicate, that the Swedish strategies in human and veterinary medicine have been comparatively successful in containing resistance. However the level of antibiotic use in human medicine has again started to increase the last years. Since our analyses show that certain use of antibiotics still can be assumed to be unnecessary, the work to achieve a more rational use must be intensified. The monitoring of antibiotic resistance, conducted by the Swedish Institute for Infectious Disease Control, is crucial in order to notice increasing trends at an early stage. In an international perspective the levels of resistance in Sweden are still low but increasing. This is for example the case with bacteria containing extended spectrum betalactamases (ESBL) a major global threat where multiple factors are involved: such as spread in the hospital setting and influx of strains into the country e.g. through travel and the food chain.

Another example of the dynamics of antibiotic resistance is that bacteria earlier affecting only humans now are occurring among animals. In 2006 methicillin-resistant *Staphylococcus aureus*, MRSA, was isolated from dogs for the first time in Sweden and MRSA is now included among other zoonotic diseases in Sweden. This experience strengthens the need for a close collaboration between human and veterinary medicine.

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Andrejs Leimanis, The National Board on Health and Welfare, has kindly and patiently provided individually based data on the use of antibiotics.

2.1 Summary

Use of antibiotics

The Swedish total use of antibiotics (methenamine excluded) decreased from 15.3 to 14.3 defined daily doses (DDD)/1000 inhabitants and day in 2001–2004. However, in the last two years, the use has increased again to 15.2 DDD/1000 inhabitants and day.

About 90% of the total use of antibiotics takes place in out-patient care. In 2006, the use in this sector increased by 3% compared to the previous year and more than a quarter of the Swedish population received antibiotics. The most commonly used antibiotics in out-patient care were penicillins and tetracyclines. In 2006, the use of antibiotics for respiratory tract infections in the age group 0–6 years varied considerably between the 21 counties in Sweden. The children in Stockholm received more than twice as much of these antibiotics as the children in Jämtland (646 and 301 prescriptions/1000 inhabitants respectively).

Sales data on antibiotics mostly used for urinary tract infections (UTIs) indicate that guidelines are increasingly being followed. In women, the use of fluoroquinolones is decreasing while the use of pivmecillinam and nitrofurantoin increases. In 2006, 7.6% of all women including children in Sweden received at least one course of an antibiotic mostly used for UTIs.

The use of antibiotics (methenamine excluded) in Swedish hospital care is increasing steadily. The mean length of hospital stay and the number of hospital beds are both decreasing. In 2006, the use of antibiotics increased by 5% in terms of DDD/1000 inhabitants and day. The increase was seen in all classes of antibiotics in hospital care. The use of piperacillin with tazobactam has more than doubled since 2002. The most common antibiotics in hospital care were cephalosporins.

Antibiotic resistance

The vast amount of data on antibiotic resistance in Sweden is gathered by the voluntary reporting from Swedish clinical microbiology laboratories. All laboratories take part in the annual resistance surveillance and quality control (RSQC) programme, and three fourths of the laboratories also contribute with data on defined invasive isolates to the EARSS network database. For some micro-organisms data are produced and presented by laboratories with referral functions and/or with special interest in those species (e.g. *Neisseria* spp.). In this report the most recent data on antibiotic resistance is presented and analysed together with data from previous years.

Staphylococcus aureus: A total of 1057 cases of MRSA were notified in 2006, as compared to 975 cases in 2005. More than half of the reported cases (618 cases) had acquired MRSA in Sweden, and approximately one-third (359 cases) was acquired abroad. Compared to many other European countries, the prevalence of MRSA in Sweden is still low. Invasive isolates of MRSA are close to (0.9%) but still below 1% of all invasive *Staphylococcus aureus*, as seen in the European surveillance network EARSS.

Several of the Swedish counties have experienced an increasing incidence of MRSA cases, while others show a stable or even decreasing incidence. The high incidence noted in Östergötland county in 2005, caused by hospital-related outbreaks, has declined to a level similar to the mean incidence for Sweden after intensive infection control efforts were introduced. The DNA-based method PFGE has been used for typing of all MRSA isolates since the year 2000, but was replaced by spa-typing in 2006. Isolates identical or related to internationally recognized strains are still dominating, but previously unknown types are sometimes imported. The prevalence of MRSA with PVL toxin is increasing. PVL-positive isolates with PFGE-type SE03–5 (spa-type t008) showed the most rapid increase. This PFGE pattern was identical to the one of USA300, an MRSA-type described as being rapidly spreading in the community. *Staphylococcus aureus* from wound infections (RSQC programme) were susceptible to antibiotics in > 95% of all cases, the only exception being fusidic acid resistance which was decreasing but still above 5%.

Streptococcus pneumoniae: In 2006 there were 631 notifications of PRP (*Streptococcus pneumoniae* with MIC of penicillin ≥ 0.5 mg/L) in Sweden. PRP have decreased in annual incidence rate per 100 000 population from 10.1 in 1997 to values between 6 and 8 since 2000. Most cases are identified through nasopharyngeal culture. The majority of PRP cases, independent of year observed, are found in the age group 0–4 years. In 31 cases (5%) the PRP isolates came from invasive sites, i.e. blood and/or spinal fluid. Multiresistance (resistance to penicillin and at least two more antibiotics) was common among PRP. The most common serotypes/groups found were 9, 14, 19, 23, 6 and 35. For all four antibiotics tested on *Streptococcus pneumoniae* in the RSQC programme there was a trend of increasing resistance.

Vancomycin resistant enterococci (VRE), have become important causes of nosocomial outbreaks in many parts of the world, but are still very rare in Sweden. The numbers of reported cases have varied between 18 and 47 in 2000–2006. Four counties have been responsible for the majority of cases, and these are Stockholm (2000–2003), Västerbotten (2000), Skåne (2003–2005) and Örebro (2003). Half of the notified VRE cases in 2006 were acquired domestically, and 10 were reported to be acquired abroad. The majority of VRE reported according to the Communicable Disease Act were *Enterococcus faecium* carrying the *van*B gene. Among invasive isolates not more than ten VRE have been reported to the EARSS network 2001–2006.

Streptococcus pyogenes: Data from the RSQC programme and from a sample of invasive isolates (data derived from nine laboratories using the same data system) in 2006 showed similar patterns with low rates of macrolide/clindamycin-resistance (1–2%) and higher rates of tetracycline resistance (11–14%).

Invasive isolates of *Streptococcus agalactiae* were resistant to macrolide antibiotics in 4.4% of the cases.

Escherichia coli, mainly derived from urinary tract infections, has been included in the national surveillance program (RSQC) since 1996, and invasive isolates have been included in the EARSS network since 2001. Ampicillin resistance, caused by production of plasmid-mediated beta-lactamase (most often of TEM-type)

was equally high in blood isolates as in the urine isolates (28 vs. 25%) in 2006. The level of resistance to third generation cefalosporins among blood isolates has increased to 1.4%, and in the majority of these the resistance was caused by plasmid-mediated ESBLs of CTX-M type. This resistance was often accompanied by resistance to many other antibiotics, e.g. aminoglycosides and fluoroquinolones. Resistance to fluoroquinolones has increased every year and was almost the same in urine as in blood isolates (11 vs. 9%) in 2006.

Other gram-negative bacteria that have been monitored in the RSQC programme and also through the EARSS network are *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The levels of resistance for the antibiotics tested were comparable between the two surveillance programmes for each of the microorganisms. Approximately two percent of *Klebsiella pneumoniae* were cephalosporin resistant and ESBL-producing, and fluoroquinolone resistance varied between 8 and 13%. In *Pseudomonas aeruginosa*, the prevalence of carbapenem resistance was approximately 5% and of fluoroquinolone resistance 10%.

Helicobacter pylori has been monitored locally at a few laboratories. Resistance to clarithromycin is steadily increasing and reached 16% when tested at one laboratory in 2006. For *Campylobacter jejuni/coli* high levels of resistance were seen for fluoroquinolones (> 40%), tetracyclines (> 20%) and lower but increasing levels for erythromycin (from 1 to 4%) in 2006.

Gonorrhoea is a notifiable disease, and in 2006 677 clinical cases of the disease were reported. Isolates from 348 of the notified clinical cases were completely characterised at the Swedish Reference Laboratory for Pathogenic *Neisseria*, Department of Clinical Microbiology, Örebro University Hospital, Örebro, and at the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, representing 51% of the notified cases. In 2006 30% of these isolates were beta-lactamase producing and ampicillin resistant, and > 60% were resistant to ciprofloxacin.

The total number of new cases of TB diagnosed in Sweden decreased from 571 during 2005 to 498 in 2006 (-13%). Resistance to isoniazid was reported in 9.6% of the patients, rifampicin in 1.5%, pyrazinamid in 1.5% and ethambutol in 0.3%. Multi-drug resistance (MDR) i.e. combined resistance against at least isoniazid and rifampicin (MDR-TB) was reported in three patients, all of them born abroad and one of them with relapse after previous treatment for MDR TB in Sweden in 2001. Isolates from a total of 20 of the 44 patients with resistant TB were identified by RFLP (restriction fragment length polymorphism) typing to belong to 11 different "clusters". Eight of these patients belonged to one big cluster (cluster 49) comprising in total 104 patients with isoniazid resistant *M. tuberculosis* diagnosed in Sweden from 1996 through 2006.

National and regional intervention projects

■ Antibiotic resistance is a growing problem and is partly due to overuse of antibiotics. Earlier, only data on the volume of purchased antibiotics have been available in Sweden. Since July 2005, the Swedish National Board of Health and Welfare supplies individually based data on antibiotic use in out-patient care. This data enables individually based analyses e.g. number of purchases per person, or how many individuals have purchased antibiotics during a specific period of time (number of patients). In a study, analyses were made on individually based anonymous data collected for the period July 1st 2005 – June 30th 2006. During this period 2 198 164 persons (24%) of the Swedish population purchased at least one course of antibiotics. Women made 58% of the purchases and men 42%. Treatment with antibiotics was most common in the age groups 3–6 years and ≥80 years.

■ Strama conducted for the third time a diagnosis prescribing survey in 2005. This time the study was conducted in the whole or parts of seven counties as compared to five counties in the two previous surveys in 2000 and 2002. Preliminary results from changes in prescribing pattern were presented in Swedres 2005. In total information regarding 7 498 infectious episodes in primary care was collected in the 2005 study. The GP:s were asked to fill in a form for all patients seeking for an infectious complaint.

When presenting figures from a drug perspective, i.e. for which diagnoses certain antibiotics are prescribed, the result shows that quinolones to a high extent are used for the non recommended indication lower urinary tract infection in women. In 58% of the 153 cases a quinolone was prescribed for lower UTI in women. In addition the result shows that tetracyclines were commonly used for the treatment of acute bronchitis, a diagnosis where the use of antibiotics has been questioned.

In conclusion these results show that there is still room for improvement in the antibiotic prescribing patterns among Swedish GPs.

■ Public knowledge and expectation on 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 public in Sweden, a telephone-based questionnaire survey was conducted in February and March 2006.

According to structured interviews with 747 individuals, knowledge of antibiotic treatment and -resistance seemed high. However, 46% of the respondents could not mention any antibiotic drug when asked. One third believed that antibiotics are effective against viruses. Only 19% agreed that antibiotics pass on common colds more quickly.

■ Strama has initiated pointprevalence studies, PPSs, as a nation wide survey system to describe and analyse the use of antimicrobials in relation to diagnosis in hospital care. In November 2006 the third study was performed with identical design as in the previous studies in 2003 and 2004.

After the two initial studies, three areas were identified for intervention, i) the duration of peri-operative prophylaxis, ii) antimicrobials with narrow spectrum can be used at a higher degree in treatment of community-acquired pneumonia and iii) the use of fluoroquinolones should be restricted in several indications, especially in community-acquired cystitis in women. The studied population in 2006 approximates 77% of all admitted patients in Swedish hospitals during one day.

The 2006 PPS result shows a decrease of peri-operative treatments longer than one day from 47% in 2003 to 31% in 2006. However, single dose peri-operative prophylaxis in the lower gastrointestinal tract surgery has increased from 62% to 77%.

In pneumonia broad-spectrum antimicrobials like cephalosporins and tetracyclines were included in 44% of the therapies and constituted 38% of the given DDDs. The corresponding results for penicillins were 26% of the treatments and 33% of the DDDs. For urinary tract infections in women the use of pivmecillinam and trimethoprim increased while the use of fluoroquinolone declined.

In summary following the interventions during 2005 and 2006, the 2006 PPS showed the desired changes of antimicrobial use with shorter peri-operative prophylaxis and a lower use of fluoroquinolones in the treatment of community acquired cystitis in women. However, in treatment of community-acquired pneumonia cephalosporins still dominate and are included in more than 35% of all therapies.

■ In November 2006 the Swedish Medical Products Agency in association with Strama arranged an expert meeting to prepare new guidelines for the treatment of lower urinary tract infection in women. The guidelines were presented in March 2007 and the main messages are:

- Acute cystitis is harmless in almost all cases and about 30% of the patients recover within a week without treatment.
- Pivmecillinam and nitrofurantoin are equal first line treatment with low resistance for *E. coli*.
- Three to five days of treatment is usually sufficient.
- Asymptomatic bacteriuria should not be treated with antibiotics except during pregnancy.
- Strongly smelling urine and unspecific symptoms like anxiety and confusion in elderly in institutional care should not be regarded as causes for treatment of lower urinary tract infection.
- Methenamine hippurate is not recommended as prophylaxis against recurrent cystitis.

■ Since antibiotic resistance in bacteria can be associated with a biological fitness cost it can be assumed that a reduction of antibiotic use is followed by a reduction in resistance rates. Over the last 10 years trimethoprim resistance in *Escherichia coli* has increased in Sweden, in Kronoberg county from 7% (1990) to 11% (2004). So far no prospective intervention in the community has been carried out to investigate whether a substantial decrease in the use of a single antibiotic will result in a corresponding decrease in antibiotic resistance.

Physicians (n=564) in Kronoberg county, were convinced, by personal visits and mail, to cease using trimethoprim and trimethoprim-sulfamethoxazole during 24 months starting October 1st 2004. Monthly sales data for oral antibiotics were retrieved from the National Corporation of Swedish Pharmacies. All *E. coli* isolated from urinary tract specimens at the Dept of Clinical Microbiology, Växjö, were included in the analysis. The susceptibility testing methodology was stable since 1990 and the baseline consisted of quantitative data from 1991–2004.

An immediate and sustained decrease of 85% in total use of trimethoprim was achieved. Trimethoprim was in most cases replaced by pivmecillinam, nitrofurantoin or ciprofloxacin. A total decrease of 4% in antibiotics used for urinary tract infections was registered. Resistance to trimethoprim did not decrease (10 and 12% in 2005 and 2006, respectively). Resistance to nitrofurantoin and mecillinam did not increase despite a substantial increase, 31 and 69% respectively, in the use of these drugs. Resistance to fluoroquinolones increased from 4 to 10% between 2000 and 2006.

A two year substantial and sustained decrease in the use of trimethoprim did not result in a clinically useful change in resistance rates. Whether the increase in fluoroquinolone-resistance was related to the increase in use remains to be evaluated.

■ ICU-Strama was established in 2000 within the framework of Strama. Since 2005 ICU-Strama is participating in CARE-ICU, a work-package within the EU-funded IPSE-project ”Improving surveillance and controlling antibiotic resistance in ICUs”.

The aim of ICU-Strama and CARE-ICU is to provide a web-based application for the coordinated collection of information about antibiotic policy, antibiotic use, antibiotic resistance, infection control, and intensive care demography and to feed back these data. The purpose is also to use this data (”data for action”) to optimise antibiotic use, infection control and reduce ICU-acquired infections and to prevent the emergence of antibiotic resistant strains within ICUs. The aim is also to establish best practice as regards antibiotic policy and hygiene interventions.

■ There is a great variation in the number of antibiotic prescriptions between Swedish counties and municipalities. The reason for this is unknown. For a period of seven months, October through April, children living in municipalities with low antibiotic prescription rates were compared to those living in municipalities with high antibiotic prescription rates. The aim was to find possible explanations for the different antibiotic prescribing patterns by studying socioeconomic factors, concern about infectious illness, infectious symptoms, and physician consultations. All 18-month old children who came to an ordinary control at the health clinic were asked to participate. Parents of 73% of the children completed a log book registration of all infectious symptoms and measures taken during a month.

There were no differences in number of symptom days between the groups. In the high prescription area 20.5% of the children consulted a physician, corresponding figure in the low prescription area was 15.8%. 11.6% of the children in the high prescription area and 4.7% in the low prescription area were prescribed antibiotics. The differences remained after adjustment for socioeconomic factors, daycare, concern about infectious illness and infectious symptoms for more than 7 days. The differences between the high and low prescription areas in terms of antibiotic prescription rates could not be explained by differences in reported infectious symptoms, differences in socioeconomic factors, daycare, concern about infectious illness in the family or physician consultations.

2.2 Sammanfattning

Antibiotikaförbrukning

Den totala förbrukningen av antibiotika (exklusive metenamin) i Sverige minskade från 15,3 till 14,3 definierade dygnsdoser (DDD)/1000 invånare och dygn under perioden 2001–2004. Under de senaste två åren har förbrukningen dock ökat igen till 15,2 DDD/1000 invånare och dygn.

Cirka 90 % av den totala svenska antibiotikaförbrukningen sker i öppenvården. Under 2006 ökade öppenvårdsförbrukningen med 3 % jämfört med föregående år och mer än en fjärdedel av den svenska befolkningen fick minst en antibiotikakur. De vanligaste antibiotikagrupperna i öppenvård var penicilliner och tetracykliner. Förbrukningen av luftvägsantibiotika i åldersgruppen 0–6 år varierade kraftigt i landet år 2006. Barn i Stockholms län fick mer än dubbelt så mycket av dessa antibiotika som barn i Jämtland (646 respektive 301 recipen/1000 invånare).

Försäljningsdata för urinvägsantibiotika tyder på att behandlingsrekommendationer följs i ökande omfattning. Hos kvinnor minskar förbrukningen av kinoloner medan förbrukningen av pivmecillinam och nitrofurantoin ökar. Under år 2006 fick 7,6 % av alla kvinnor i Sverige minst en kur av något urinvägsantibiotikum.

Förbrukningen av antibiotika (exklusive metenamin) inom slutenvården i Sverige ökar stadigt samtidigt som medelvårdtiden och antalet vårdplatser minskar. Under år 2006 ökade antibiotikaförbrukningen med 5 % räknat i DDD/1000 invånare och dag. Ökningen ses inom alla antibiotikagrupper i slutenvården. Förbrukningen av piperacillin med tazobaktam har mer än fördubblats sedan 2002. Cefalosporiner är den vanligaste antibiotikagruppen inom slutenvården.

Antibiotikaresistens

Frivillig rapportering av resistensdata från de svenska kliniskt mikrobiologiska laboratorierna utgör basen för resistensövervakningen. Alla laboratorier deltar i den årliga insamlingen av data till ResNet, och tre fjärdedelar av laboratorierna bidrar också med data avseende de invasiva isolat som definierats av EARSS. För vissa mikroorganismer sammanställs data av laboratorier med referensfunktion och/eller med speciellt intresse för dessa arter (t.ex. *Neisseria* arter). I denna rapport presenteras resistensdata från 2006 och analyseras tillsammans med föregående års data.

Staphylococcus aureus: Totalt 1057 fall av MRSA anmäldes 2006, en liten ökning från 2005 då 975 fall noterades. Mer än hälften av fallen hade blivit smittade i Sverige (618 fall), och cirka en tredjedel (359 fall) hade blivit smittade utomlands. Jämfört med övriga länder i Europa är förekomsten av MRSA låg i Sverige. Antalet invasiva isolat av MRSA är nära (0,9 %) men har ännu ej nått nivån 1 % av alla invasiva *Staphylococcus aureus* enligt rapportering till den europeiska resistensövervakningen EARSS.

I många län/regioner sågs en ökad incidens av MRSA-fall, medan andra hade en stabil eller minskad incidens. Den höga incidensen av MRSA-fall som noterades i Östergötland 2005, orsakad av två sjukvårdsrelaterade utbrott, hade 2006 reducerats till en nivå jämförbar med riksgenomsnittet tack vare omfattande vårdhygieniska insatser. PFGE, den DNA-baserade metod som har använts för att typa alla MRSA isolat sedan 2000, ersattes under 2006 med spa-typning. Isolat som genetiskt var identiska eller snarlika de vanligaste internationellt spridda stammarna dominerar fortfarande i Sverige, men även nya typer av MRSA förekommer som importfall. Förekomsten av MRSA med PVL-toxin ökar. Den PVL-positiva MRSA-stam som ökat mest hade PFGE-mönster SE03–5 och spa-typ t008. Denna typ är identisk med USA300, beskriven som den snabbast ökande samhällsförvärvade stammen i USA under senare år. *Staphylococcus aureus* i sårinfektioner (data från ResNet) var i mer än 95 % av fallen känsliga för antibiotika med undantag för fusidinsyra, mot vilket fortfarande mer än 5 % av isolaten var resistenta.

Streptococcus pneumoniae: Under 2006 noterades 631 fall med penicillinresistens (MIC av penicillin ≥ 0.5 mg/L, definierade som PRP). Incidensen PRP/100 000 invånare har minskat från 10,1 1997 till 6–8 sedan år 2000. De flesta fallen identifierades genom nasofarynxodling. Majoriteten av PRP-fall var 5 år eller yngre. I 31 fall (5 %) påvisades PRP från blod och/eller spinalvätska. Multiresistens (resistens mot penicillin och minst två ytterligare antibiotika) var vanligt hos PRP. De vanligast förekommande serotyperna/grupperna var 9, 14, 19, 23, 6 och 35. Enligt data rapporterade till ResNet ses en trend av ökande resistens mot samtliga de typer av antibiotika som testas (penicilliner, makrolider, tetracykliner och trimetoprim-sulfa).

Vankomycinresistenta enterokocker (VRE) har ökat i betydelse vid sjukvårdsrelaterade utbrott i många delar av världen och ofta omfattat riskpatienter, men de är fortfarande ovanliga i Sverige. Antalet rapporterade fall per år har varierat mellan 18 och 47 under 2000–2006. Fyra län har bidragit med majoriteten av fall, och de är Stockholm (2000–2003), Västerbotten (2000), Skåne (2003–2005) och Örebro (2003). Hälften av de anmälda VRE-fallen 2006 hade smittats i Sverige, och 10 hade rapporterats som smittade utomlands. Majoriteten av rapporterade VRE var *Enterococcus faecium* med *van*B-gen. Bland invasiva enterokock-isolat rapporterade till EARSS 2001–2006 har endast 10 varit VRE.

Streptococcus pyogenes: Data från ResNet och från ett urval av invasiva isolat (konsekutiva isolat från 9 ADBakt-laboratorier) under 2006 visade likartade resistensmönster med låg frekvens makrolid/klindamycin-resistens (1–2 %) och högre frekvens tetracyklin-resistens (11–14 %).

Invasiva isolat av *Streptococcus agalactiae* var makrolid-resistenta i 4,4 % av fallen.

Escherichia coli, huvudsakligen från urinvägsinfektioner, har övervakats enligt det nationella programmet (ResNet) sedan 1996, och blodisolat har inkluderats i EARSS sedan 2001. Ampicillinresistens, orsakad av plasmidmedierad beta-laktamasproduktion av TEM-typ, återfanns i ungefär samma frekvens bland blodisolat som bland urinisolat 2006 (28 resp. 25 %). Förekomsten av blodisolat med resistens mot tredje generationens cefalosporiner har ökat till 1,4 %, och hos majoriteten av dessa var resistensen orsakad av plasmidmedierade ESBL. Denna resistens

åtföljdes ofta av resistens mot många andra antibiotika som t ex aminoglykosider och kinoloner. Resistens mot kinoloner har ökat årligen och var något högre hos urinisolat jämfört med blodisolat (11 resp. 9 %).

Andra gram-negativa bakterier som övervakats nationellt och/eller internationellt är *Klebsiella pneumoniae* och *Pseudomonas aeruginosa*, och båda inkluderades i EARSS-programmet från juli 2005. Resistensnivåerna hos respektive patogen var desamma oberoende av övervakningsprogram och typ av prov. Hos *K. pneumoniae* var cirka 2 % resistenta mot cefalosporiner och ESBL-producerande, och resistens mot fluorokinoloner förekom i 8–13 %. Hos *P. aeruginosa* var karbapenemresistensen cirka 5 % och kinolonresistensen 10 %.

Helicobacter pylori har övervakats vid några laboratorier. Resistens mot klaritromycin ökar stadigt och har lokalt vid ett laboratorium nått 16 % under 2006. Hos *Campylobacter jejuni/coli* var kinolonresistensen > 40 %, tetracyklinresistensen > 20 % och erytromycinresistensen hade ökat från 1 till 4 %.

Gonorré är en anmälningspliktig sjukdom och 2006 rapporterades 677 kliniska fall. Isolat från 348 av dessa (51 % av fallen) har undersökts antingen vid det svenska referenslaboratoriet i Örebro eller vid laboratoriet för klinisk bakteriologi, Karolinska Universitetssjukhuset Huddinge, Stockholm. Trettio procent av isolaten var beta-laktamasproducerande och därmed ampicillinresistenta och > 60 % var resistenta mot ciprofloxacin.

Antalet anmälda nya fall av tuberkulos minskade från 571 under 2005 till 498 under 2006 (- 13 %). Resistens mot isoniazid var vanligast (10,3 % av fallen), följt av pyrazinamid (1,3 %), rifampicin (1,1 %) och etambutol (0,7 %). *Mycobacterium tuberculosis* med resistens mot minst två antibiotika (MDR-TB) rapporterades hos tre patienter, samtliga födda utomlands. Isolat från 20 av de 44 patienterna med resistent TB identifierades med RFLP tillhöra 11 olika kluster. Åtta patienter tillhörde ett stort kluster (kluster 49) som omfattar totalt 104 patienter med isoniazid-resistent TB diagnostiserad i Sverige 1996–2006.

Nationella och lokala projekt

■ Antibiotikaresistens är ett växande problem, delvis till följd av överanvändning av antibiotika. Till nyligen har endast data över sålda volymer antibiotika varit tillgängliga i Sverige. Från och med juli 2005 tillhandahåller emellertid Socialstyrelsen individbaserade data över antibiotikaförsäljning i öppenvård. Dessa data möjliggör individbaserade analyser av exempelvis antal utköp per person, eller hur många individer som har köpt antibiotika under en viss tidsperiod. I en studie analyserades anonyma data insamlade mellan den första juli 2005 och den 30 juni 2006. Under denna period köpte 2 198 164 personer (24 % av den svenska befolkningen) minst en antibiotikakur. Kvinnor gjorde 58 % av utköpen. Antibiotikabehandling var vanligast i åldersgrupperna 3–6 år och ≥80 år.

■ Strama organiserade för tredje gången en diagnos-receptstudie under 2005. Denna gång omfattades, helt eller delvis, sju län (att jämföra med de fem län som deltog i studierna 2000 och 2002). Preliminära resultat av förändringar i förskrivningsmönster presenterades i Swedres 2005. Sammantaget registrerades information angående 7 498 infektionsepisoder i primärvård under studien 2005. Deltagande läkare ombads fylla i ett formulär för varje patient som sökte för infektionssymtom.

Analys av vilka diagnoser som medför specifika antibiotika visar att kinoloner används i hög utsträckning (58 % av fallen) på den icke rekommenderade indikationen nedre urinvägsinfektion hos kvinnor. Studien visar också att tetracykliner ofta används vid behandling av akut bronkit, en diagnos för vilken värdet av antibiotikabehandling har ifrågasatts.

■ Allmänhetens kunskap och förväntningar kring antibiotikabehandling antas bidra till olämplig antibiotikaförskrivning inom öppenvården. För att kartlägga den svenska allmänhetens kunskaper och förväntningar genomfördes en telefonbaserad utfrågning i februari och mars 2006. Enligt strukturerade intervjuer med 747 personer verkade kunskaperna om antibiotikabehandling och -resistens goda. Av de tillfrågade kunde dock 46 % inte nämna något antibiotikapreparat när de tillfrågades. En tredjedel trodde att antibiotika är effektivt mot virusinfektioner. Bara 19 % instämde i att antibiotika botar förkylningar.

■ Strama har initierat punktprevalensstudier, PPS, som ett nationellt system för att beskriva och analysera användningen av antibiotika i relation till slutenvårdsdiagnos. I november 2006 genomfördes den tredje studien med samma design som 2003 och 2004. Efter de första två studierna identifierades tre interventionsområden: i) omfattningen av kirurgisk profylax, ii) smalspektrumantibiotika kan användas i högre utsträckning vid behandling av samhällsförvärvad pneumoni och iii) användningen av kinoloner ska begränsas vid flera indikationer, främst samhällsförvärvad cystit hos kvinnor. Den population som studerats 2006 omfattar 77 % av alla patienter i somatisk vård på svenska sjukhus under en dag. Resultaten från PPS 2006 visar en minskning av perioperativ profylax längre än en dag från 47 % 2003 till 31 % 2006. Däremot har endosprofylax vid kirurgi i nedre gastrointestinalkanalen ökat från 62 % till 77 %.

Vad gäller behandling av pneumoni är cefalosporiner och tetracykliner fortfarande de vanligaste preparaten. Användningen av dessa har inte förändrats sedan 2003. Vid behandling av urinvägsinfektion hos kvinnor används mer pivmecillinam och trimetoprim, medan användningen av kinoloner minskar. Sammanfattningsvis kan sägas att PPS 2006 visar önskad utveckling inom områdena perioperativ profylax och urinvägsinfektioner hos kvinnor, medan behandlingen av samhällsförvärvad pneumoni inte förändrats nämnvärt.

■ I november 2006 anordnade Läkemedelsverket och Strama ett expertgruppsmöte för att ta fram nya riktlinjer för behandling av nedre urinvägsinfektion hos kvinnor. Riktlinjerna presenterades i mars 2007 och huvudbudskapen är:

- Akut cystit är i de allra flesta fall ofarligt, och cirka 30 % av patienterna blir symtomfria utan behandling efter en vecka.
- Pivmecillinam och nitrofurantoin är likvärdiga förstahandspreparat med låg resistens hos *E. coli*.
- Tre till fem dygns behandling är ofta tillräcklig.
- Asymtomatisk bakteriuri skall inte antibiotikabehandlas utom under graviditet.
- Starkt luktande urin och ospecifika symtom som oro och förvirring hos äldre i vård och omsorg tyder inte på behandlingskrävande nedre UVI.
- Metenaminhippurat rekommenderas inte som profylax mot recidiverande cystit.

■ Eftersom resistens hos en bakterie medför belastning för den, kan det antas att minskad användning av antibiotika leder till en lägre andel resistenta bakterier. Under de senaste tio åren har trimetoprimresistensen hos *E. coli* ökat i hela landet. I Kronobergs län ökade den från 7 % 1990 till 11 % 2004. Inga prospektiva interventioner har gjorts för att undersöka huruvida en kraftig minskning i användningen av ett enstaka antibiotikum medför motsvarande tillbakagång i resistens.

Via brev och personliga besök uppmanades 564 läkare i Kronobergs län att upphöra med förskrivning av trimetoprim och trimetoprim-sulfametoxazol under 24 månader från och med den första oktober 2004. Försäljningsdata för orala antibiotikaberedningar samlades in månadsvis från Apoteket AB. Alla *E. coli*-isolat från urinvägar vid Avdelningen för Klinisk Mikrobiologi, Växjö, inkluderades i analysen. Testmetoden för känslighet var stabil sedan 1990, och baslinjedata omfattade 1991 till 2004.

En omedelbar och bestående minskning av trimetoprimförskrivningen med 85 % erhölls. Trimetoprim ersattes i de flesta fall med pivmecillinam, nitrofurantoin eller ciprofloxacin. En minskning av den totala antibiotikaförskrivningen med 4 % registrerades. Ingen kliniskt användbar förändring i resistensläget skedde under de två åren. Resistensen mot trimetoprim minskade inte (10 respektive 12 % under 2005 och 2006). Trots en kraftig ökning i användningen av nitrofurantoin och mecillinam (31 repektive 69 %), ökade inte resistensen mot dessa preparat. Resistensen mot fluorokinoloner ökade från 4 % 2005 till 10 % 2006.

■ IVA-Strama etablerades inom Strama år 2000. Sedan 2005 deltar IVA-Strama i CARE-ICU, vilket ingår i det EU-finansierade IPSE-projektet (Improving surveillance and controlling antibiotic resistance in ICUs). Syftet med IVA-Strama och CARE-ICU är att tillhandahålla en webb-baserad tjänst för insamling av information kring antibiotikapolicy, -användning, och -resistens, infektionskontroll och intensivvårdsdemografi, samt att ge återkoppling på dessa uppgifter. Avsikten är också att använda insamlade data för att optimera antibiotikaanvändning och infektionskontroll, och att förebygga uppkomsten av resistenta stammar inom intensivvårdsavdelningar. Dessutom syftar man till att etablera goda rutiner vad gäller antibiotikapolicy och vårdhygien.

■ Det råder stora variationer i antalet antibiotikaförskrivningar både på läns- och kommunnivå i Sverige. Orsaken till detta är okänd. Under en sjumånadersperiod, oktober – april, jämfördes barn i kommuner med låg frekvens antibiotikaförskrivning med barn i kommuner med hög förskrivning av antibiotika. Syftet var att finna tänkbara förklaringar till skillnaderna i antibiotikaförskrivningsmönster genom att studera socioekonomiska faktorer, oro för smittsam sjukdom, infektionssymtom och rådfrågning av läkare. Alla 18 månader gamla barn som kom för en rutinkontroll vid vårdcentralen ombads delta. Föräldrarna till 73 % av barnen fyllde i en anteckningsbok där de registrerade alla infektionssymtom och vidtagna åtgärder under en månad.

Det var inga skillnader i antalet dagar med symtom mellan grupperna. I området med hög antibiotikaförskrivning rådfrågade föräldrar till 20,5 % av barnen läkare, motsvarande siffra i området med låg förskrivning var 15,8 %. 11,6 % av barnen i området med hög förskrivning och 4,7 % i området med låg förskrivning förskrevs antibiotika. Skillnaderna kvarstod efter standardisering med avseende på socioekonomiska faktorer, barnomsorg, oro för smittsam sjukdom samt infektionssymtom under längre tid än 7 dygn. Skillnaderna i nivå av antibiotikaförskrivning mellan de olika områdena kunde inte förklaras av skillnader i antalet rapporterade infektionssymtom, skillnader i socioekonomiska faktorer, barnomsorg, oro för smittsam sjukdom i familjen eller rådfrågning av läkare.

3. Use of antimicrobials

3.1 Use of antibiotics

Statistics on antibiotic sales are obtained from The National Corporation of Swedish Pharmacies. This data is expressed either as defined daily doses, DDD, per 1000 inhabitants and day (DDD/1000/day), or as prescriptions per 1000 inhabitants and year (Prespricptions/1000/year). Since July 2005, the Swedish National Board of Health and Welfare supplies an individually based register on all drugs prescribed in out-patient care. This data gives 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 (Pat/1000/year). Data on number of admissions, patient-days, beds and mean length of hospital stay derives from The Swedish Association of Local Authorities and Regions. For further details on sales statistics see Appendix 3.

Total antibiotic use

During the years 2001–2004, there was a decrease in the total use of antibiotics in Sweden. However, in the last few years the use has increased, Table 3.1.1.

Table 3.1.1. Total use of antibacterial drugs for systemic use in Sweden 2000–2006, DDD/1000/day.

	2000	2001	2002	2003	2004	2005	2006
J01 excl methenamine	15.2	15.3	14.8	14.6	14.3	14.8	15.2
Methenamine	1.6	1.5	1.6	1.7	1.9	1.9	1.9
Total J01	16.8	16.8	16.4	16.3	16.2	16.6	17.1

Out-patient care

Approximately 90% of the total Swedish antibiotic use takes place in out-patient care. The use of antibacterial drugs in out-patient care is presented in Table 3.1.2. As for the total antibiotic use, there was a decreasing trend up to 2004. However, between 2005 and 2006, the antibiotic use (methenamine excluded) increased by 3%.

Table 3.1.2. Total use of antibacterial drugs for systemic use, DDD/1000/day, in out-patient care 2000–2006.

	2000	2001	2002	2003	2004	2005	2006
J01 excl methenamine	13.7	13.8	13.3	13.0	12.8	13.1	13.5
Methenamine	1.5	1.5	1.6	1.7	1.8	1.8	1.8
Total J01	15.2	15.3	14.9	14.7	14.6	14.9	15.3

Figure 3.1.1 presents the distribution between different classes of antibiotics in 2006. The most common antibiotics in out-patient care were penicillins and tetracyclines.

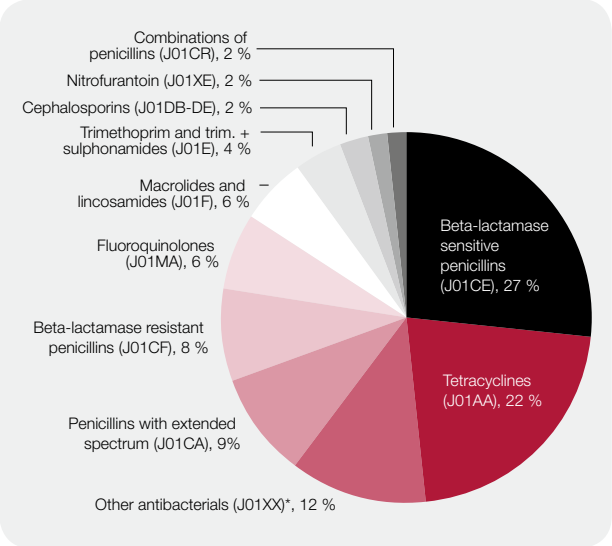

Figure 3.1.1. Antibiotics in out-patient care in 2006, percent of total DDD/1000/day. * Methenamine represents 99.8% of the group "other antibacterials (J01XX)".

In Table 3.1.3 figures for different groups of antibiotics and age groups in 2002–2006 are presented in DDD/1000/day and in prescriptions/1000/year. The number of patients/1000/year in 2006 is shown as well.

Table 3.1.3. Antibiotics in out-patient care, different groups of antibiotics and different age groups, DDD/1000/day and Prescriptions/1000/year, 2002–2006. Patients/1000/year in 2006 is presented as well.

	DDD/1000/day					Prescriptions/1000/year					Pat/1000/year
Age group (years)	2002	2003	2004	2005	2006	2002	2003	2004	2005	2006	2006
Tetracyclines (J01AA)											
0–6	0.0	0.0	0.0	0.0	0.0	0	0	0	0	0	0
7–19	2.1	2.3	2.4	2.7	3.1	24	25	25	29	33	20
20–59	3.4	3.3	3.4	3.5	3.6	68	64	63	67	66	52
60–79	3.7	3.8	3.9	4.2	4.1	90	91	92	100	96	74
80–	2.9	2.9	2.8	3.0	2.9	78	78	76	83	76	60
All age groups	3.0	3.0	3.1	3.3	3.3	61	59	59	63	63	47
Penicillins with extended spectrum (J01CA) excl pivmecillinam											
0–6	1.4	1.3	1.3	1.4	1.6	95	91	85	85	87	67
7–19	0.4	0.4	0.3	0.4	0.4	15	13	11	13	14	12
20–59	0.7	0.7	0.6	0.7	0.7	18	17	17	18	18	16
60–79	1.3	1.3	1.4	1.6	1.6	36	37	39	41	41	33
80–	1.5	1.5	1.7	1.8	1.8	43	43	45	48	47	39
All age groups	0.9	0.8	0.8	0.9	1.0	29	28	27	29	30	24
Pivmecillinam (J01CA08)											
0–6	0.0	0.0	0.0	0.0	0.0	2	0	0	0	1	1
7–19	0.1	0.1	0.1	0.2	0.2	7	6	7	9	11	10
20–59	0.3	0.3	0.3	0.3	0.3	15	15	15	17	20	17
60–79	0.7	0.7	0.7	0.7	0.7	32	32	33	36	40	32
80–	2.1	2.0	2.1	1.9	1.8	98	96	97	100	107	81
All age groups	0.4	0.4	0.4	0.4	0.4	20	20	21	22	26	21
Beta-lactamase sensitive penicillins (J01CE)											
0–6	4.1	3.8	3.3	3.4	3.6	377	348	308	311	327	238
7–19	3.9	3.5	2.9	3.0	3.4	170	150	121	122	135	112
20–59	4.6	4.3	4.2	4.2	4.3	119	112	106	105	108	92
60–79	4.0	4.1	4.3	4.3	4.5	97	100	105	103	107	90
80–	3.5	3.4	3.3	3.4	3.3	94	90	87	87	84	72
All age groups	4.3	4.1	3.9	3.9	4.1	142	133	123	123	128	105
Beta-lactamase resistant penicillins (J01CF)											
0–6	0.4	0.4	0.3	0.3	0.3	36	39	34	32	36	28
7–19	0.7	0.7	0.7	0.7	0.7	35	36	32	31	34	27
20–59	0.9	0.9	0.9	0.9	0.9	32	33	32	32	34	27
60–79	2.0	2.0	1.9	1.9	2.0	55	56	55	54	57	39
80–	4.7	4.6	4.5	4.4	4.4	131	129	124	122	123	69
All age groups	1.2	1.2	1.2	1.2	1.3	42	43	41	41	43	32
Combinations of penicillins (J01CR)											
0–6	0.8	0.8	0.7	0.7	0.7	61	55	49	52	51	36
7–19	0.2	0.2	0.2	0.2	0.2	8	7	5	6	6	5
20–59	0.2	0.1	0.1	0.2	0.2	4	3	3	4	4	4
60–79	0.2	0.2	0.2	0.2	0.2	3	3	4	4	5	4
80–	0.1	0.1	0.1	0.1	0.2	3	3	2	3	3	2
All age groups	0.2	0.2	0.2	0.2	0.2	9	8	7	8	8	6
Cephalosporins (J01DB-J01DE)											
0–6	0.6	0.6	0.5	0.5	0.5	54	56	50	46	49	39
7–19	0.4	0.4	0.3	0.3	0.3	25	24	21	20	21	17
20–59	0.3	0.3	0.3	0.3	0.3	19	18	17	17	17	14
60–79	0.5	0.5	0.5	0.5	0.5	25	24	24	23	23	18

	DDD/1000/day					Prescriptions/1000/year					Pat/1000/year
Age group (years)	2002	2003	2004	2005	2006	2002	2003	2004	2005	2006	2006
80–	0.9	0.9	0.8	0.8	0.7	48	46	43	42	41	31
All age groups	0.5	0.4	0.4	0.4	0.4	27	26	23	23	23	18
Trimethoprim (J01EA)											
0–6	0.1	0.1	0.1	0.1	0.1	15	16	16	15	16	11
7–19	0.2	0.2	0.2	0.2	0.2	13	13	12	12	12	11
20–59	0.4	0.4	0.4	0.3	0.3	21	20	19	17	17	15
60–79	1.0	1.0	0.9	0.9	0.8	48	48	45	42	41	31
80–	2.7	2.6	2.5	2.3	2.2	151	146	136	126	120	74
All age groups	0.6	0.6	0.5	0.5	0.5	30	30	28	26	26	20
Trimethoprim with sulphonamides (J01EE)											
0–6	0.2	0.2	0.2	0.2	0.2	21	20	18	18	18	14
7–19	0.1	0.1	0.1	0.1	0.1	5	4	4	4	4	3
20–59	0.1	0.1	0.1	0.1	0.1	3	3	3	3	3	2
60–79	0.3	0.3	0.3	0.3	0.4	7	7	8	8	9	6
80–	0.3	0.3	0.4	0.3	0.4	11	11	12	12	12	9
All age groups	0.2	0.2	0.2	0.2	0.2	6	6	6	6	6	4
Macrolides (J01FA)											
0–6	0.9	0.8	0.7	0.8	0.8	44	36	35	37	37	30
7–19	0.8	0.6	0.6	0.7	0.8	24	20	18	21	22	18
20–59	0.6	0.6	0.5	0.6	0.5	20	17	16	17	16	13
60–79	0.5	0.5	0.5	0.5	0.5	15	14	14	15	15	11
80–	0.4	0.3	0.3	0.3	0.3	11	10	10	10	9	7
All age groups	0.6	0.6	0.6	0.6	0.6	21	18	17	18	18	15
Lincosamides (J01FF)											
0–6	0.0	0.0	0.0	0.0	0.0	5	5	4	5	5	4
7–19	0.1	0.1	0.1	0.1	0.1	7	7	7	7	8	6
20–59	0.2	0.2	0.2	0.2	0.3	11	12	13	13	14	11
60–79	0.4	0.5	0.5	0.5	0.5	17	20	21	22	24	16
80–	0.6	0.7	0.7	0.8	0.8	27	30	30	32	33	18
All age groups	0.2	0.3	0.3	0.3	0.3	12	13	14	14	15	11
Fluoroquinolones (J01MA)											
0–6	0.0	0.0	0.0	0.0	0.0	1	1	1	1	1	0
7–19	0.1	0.1	0.1	0.1	0.1	6	6	6	6	6	5
20–59	0.8	0.8	0.8	0.8	0.8	36	35	33	32	30	22
60–79	2.0	2.1	2.1	2.1	2.1	93	92	88	85	80	54
80–	3.4	3.3	3.1	3.1	3.0	187	173	158	149	137	93
All age groups	1.0	1.0	1.0	1.0	1.0	46	45	43	41	39	27
Nitrofurantoin (J01XE)											
0–6	0.1	0.1	0.1	0.1	0.1	7	7	7	6	6	4
7–19	0.1	0.1	0.1	0.1	0.1	4	4	5	5	5	4
20–59	0.2	0.2	0.2	0.2	0.2	6	7	7	9	9	7
60–79	0.2	0.2	0.3	0.3	0.4	8	9	12	14	15	11
80–	0.5	0.6	0.7	0.8	0.8	24	27	31	37	37	24
All age groups	0.2	0.2	0.2	0.2	0.2	7	8	9	10	11	8
All agents (J01 excl methenamine)											
0–6	8.7	8.1	7.2	7.5	8.0	719	674	606	609	635	346
7–19	9.3	8.9	8.1	8.8	9.8	343	316	274	283	311	203
20–59	12.7	12.3	12.1	12.4	12.6	371	356	344	351	358	224
60–79	16.8	17.2	17.7	18.0	18.3	530	537	541	550	555	297
80–	23.7	23.3	23.0	23.2	22.7	912	886	856	854	833	382
All age groups	13.3	13.0	12.8	13.1	13.5	454	438	418	426	436	252

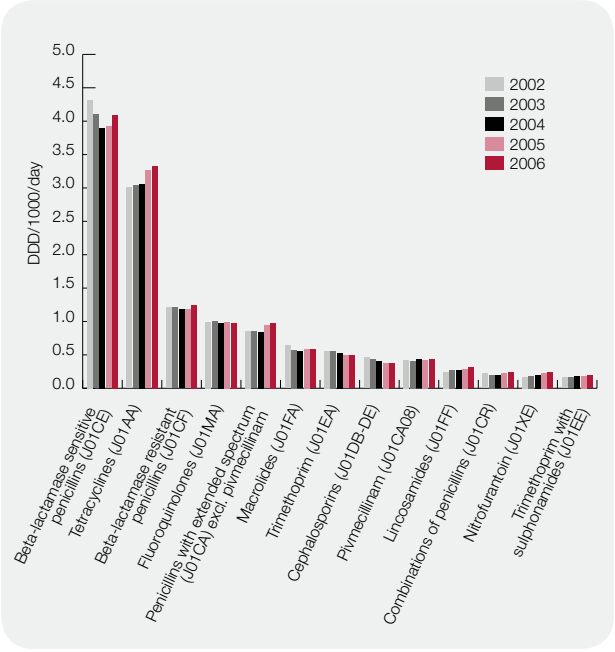

Figure 3.1.2. Antibiotics in out-patient care 2002–2006, DDD/1000/day.

Among other things, Table 3.1.3 shows that there has been an increase in the use of beta-lactamase sensitive penicillins in all age groups except for the elderly in the last few years. In the age group older than 80 years there has been a decrease in the use of trimethoprim and fluoroquinolones and an increase in the use of nitrofurantoin and pivmecillinam in terms of prescriptions/1000/year. However, the number of DDD/1000/day of pivmecillinam in this age group has decreased. This may be because a new smaller package size of 14 tablets was introduced on the market in 2005. Approximately 38% of the elderly (382 Patients/1000/year) and 35% of the young children (346 Patients/1000/year) were given any kind of antibiotic in out-patient care in 2006. More than one quarter of the Swedish population received at least one course of antibiotics in out-patient care in 2006.

Figure 3.1.2 summarises the antibiotic use in terms of DDD/1000/day. The use of tetracyclines has increased, especially the 100-tablet package of lymecycline (not shown), often used in the treatment of acne. However, doxycycline is still the tetracycline largest in use and the most common diagnosis for tetracycline prescribing is respiratory tract infections (see Table 5.2.2, section 5.2). In the last few years, fluoroquinolones have become less expensive in Sweden. Nevertheless, there has been no increase in their use. The use of trimethoprim has decreased.

Figure 3.1.3 presents the out-patient antibiotic use in the 21 counties of Sweden. These gender and age standardized data range from 9.27 (Dalarna) to 14.33 (Stockholm) DDD/1000/day. Västerbotten has a relatively low use of antibiotics but on the other hand a relatively small proportion of penicillins.

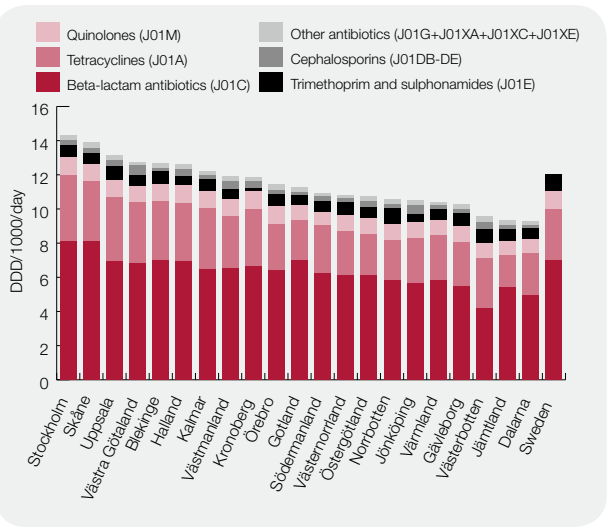

Figure 3.1.3. Antibiotics in out-patient care 2006 per county, DDD/1000/day. Gender and age standardized data.

As shown in figure 3.1.3, there are considerable variations in prescription pattern between counties, regarding both amount and class of antibiotics. Data on the actual number of patients treated, provided from The Swedish National Board of Health and Welfare adds a new dimension to the surveillance of antibiotic consumption (see section 5.1). More than a quarter of the Swedish population were treated with at least one course of an antibacterial drug in out-patient care in 2006. The numbers range from 199 (Västerbotten) to 280 (Stockholm) patients/1000 inhabitants as presented in Table 3.1.4.

Table 3.1.4. Total use of antibacterial drugs for systemic use (J01) in out-patient care per county in 2006, patients/1000/year.

	Patients/1000/year
Stockholm	280
Skåne	270
Halland	269
Blekinge	266
Västra Götaland	261
Värmland	261
Kronoberg	255
Västmanland	246
Uppsala	245
Kalmar	245
Södermanland	236
Gotland	233
Jönköping	228
Västernorrland	227
Östergötland	226
Norrbotten	224
Örebro	224
Gävleborg	218
Jämtland	208
Dalarna	206
Västerbotten	199
Sweden	**253**

Antibiotics used for respiratory tract infections

Sales figures for antibiotics often used in the treatment of respiratory tract infections (RTIs) are presented in Figure 3.1.4. The previously decreasing trend in the use of penicillin V has turned upwards as well as the use of doxycycline and amoxicillin. The use of cephalosporins is decreasing. One theory is that general practitioners are changing from cephalosporins to amoxicillin in the treatment of RTIs.

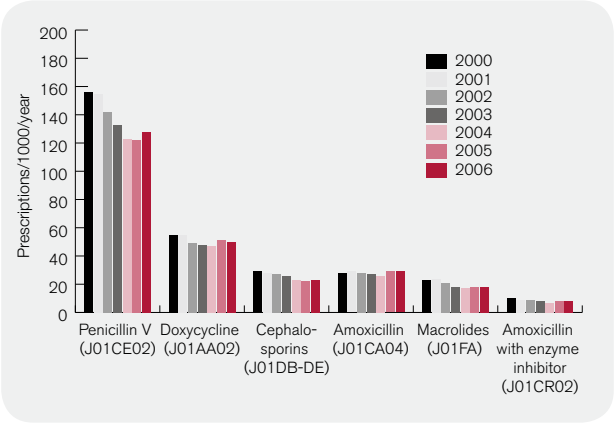

Figure 3.1.4. Antibiotics mostly used for respiratory tract infections, out-patient care 2000–2006, prescriptions/1000/year.

Figure 3.1.5 presents county data on antibiotics for RTIs in children aged 0–6 years in 2006. The children in Stockholm were given more than twice as much of these antibiotics as the children in Jämtland, 646 and 301 prescriptions/1000 respectively. Within each county there is also a substantial variation in the proportion of the different groups of antibiotics used. The county of Värmland uses the largest proportion of penicillin V and Stockholm the smallest, 73 and 51% respectively. Eight counties, Västernorrland, Örebro, Västerbotten, Östergötland, Norrbotten, Jönköping, Gotland and Värmland use more amoxicillin with enzyme inhibitor than amoxicillin alone.

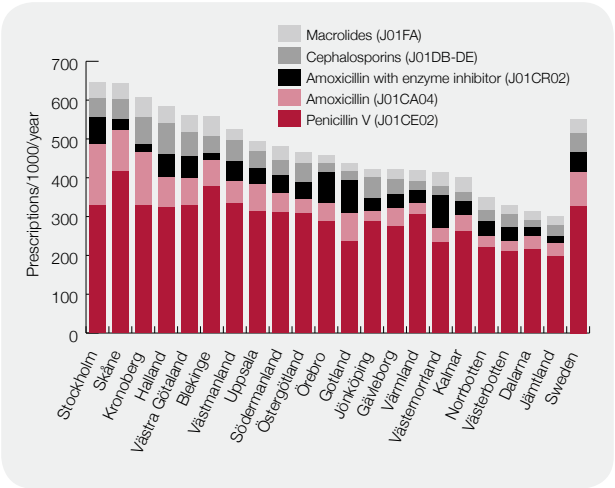

Figure 3.1.5. Antibiotics mostly used for respiratory tract infections, out-patient care in 2006, children aged 0–6 years, prescriptions/1000/year.

Antibiotics used for urinary tract infections in women

Figure 3.1.6 presents sales figures for antibiotics mostly used for urinary tract infections (UTIs) in women 2000–2006. The fluoroquinolone group contains ciprofloxacin package sizes mostly used for UTIs and all norfloxacin package sizes. The figure indicates that UTI guidelines are increasingly being followed. The use of fluoroquinolones is decreasing steadily while pivmecillinam and nitrofurantoin are increasing in use. The increase in nitrofurantoin use in 2006 is relatively small. One reason might be delivery problems regarding nitrofurantoin for approximately one month in the autumn of 2006.

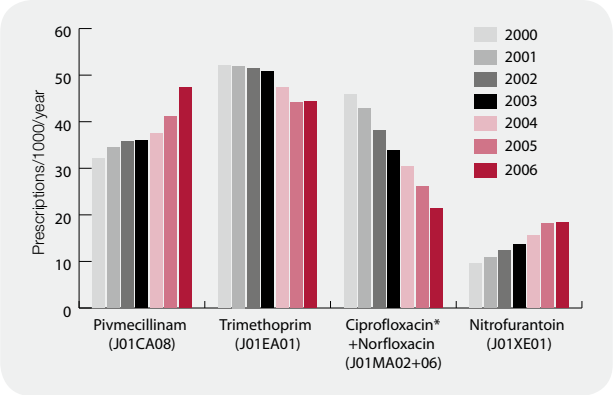

Figure 3.1.6. Antibiotics mostly used for urinary tract infections. Out-patient care 2000–2006, women, prescriptions/1000/year. *Ciprofloxacin package sizes; 100 mg: 6 and 10 tablets, 250 mg: 10 tablets, 500 mg: 10 tablets.

The distribution between different UTI antibiotics varied in the counties of Sweden in 2006, as shown in Figure 3.1.7. Blekinge had the highest fluoroquinolone proportion, 20%, and Kalmar the lowest, 10%. An intervention study was conducted in Kronoberg in October 2004 – September 2006. The prescribing of trimethoprim and trimethoprim with sulphonamide for UTIs was reduced to very low levels during this period, hence the very small proportion of trimethoprim in the county.

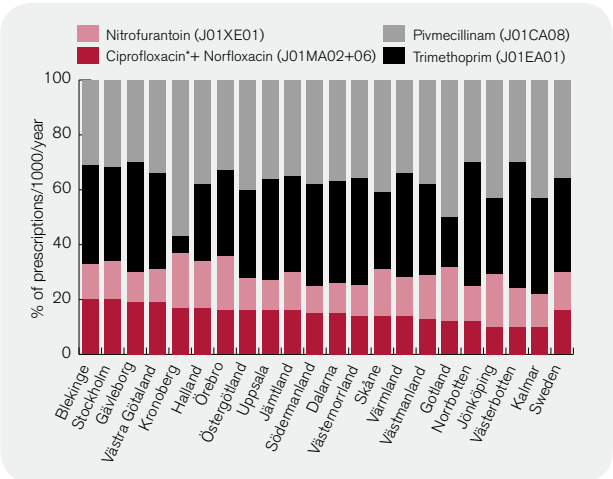

Figure 3.1.7. Antibiotics mostly used for urinary tract infections. Women in out-patient care in 2006, per county. Distribution between different substances/groups of antibiotics, percent of total prescriptions/1000/year. *Ciprofloxacin package sizes; 100 mg: 6 and 10 tablets, 250 mg: 10 tablets, 500 mg: 10 tablets.

In 2006, 7.6% of all women including children in Sweden received at least one course of an antibiotic mostly used for UTIs. The most common substances in terms of patients/1000 inhabitants were pivmecillinam and trimethoprim, as presented in Table 3.1.5.

Table 3.1.5. Antibiotics mostly used for urinary tract infections. Outpatient care in 2006, women of all ages, patients/1000/year.
***Ciprofloxacin package sizes; 100 mg: 6 and 10 tablets, 250 mg: 10 tablets, 500 mg: 10 tablets.**

	Pat/1000/year
Pivmecillinam	39
Trimethoprim	31
Nitrofurantoin	13
Norfloxacin + Ciprofloxacin*	12
All UTI agents above	76

Hospital care

The total use of antibiotics in Swedish hospital care is increasing steadily. Between 2005 and 2006, the use increased by 5% (Table 3.1.6).

Table 3.1.6. Total use of antibacterial drugs for systemic use, hospital care 2000–2006, DDD/1000/day.

	2000	2001	2002	2003	2004	2005	2006
J01 excl methenamine	1.3	1.3	1.3	1.3	1.4	1.4	1.5
Methenamine	0.0	0.0	0.0	0.1	0.1	0.1	0.1
Total J01	1.3	1.3	1.3	1.4	1.4	1.5	1.6

The two most commonly used antibiotics in hospital care are cephalosporins and beta-lactamase resistant penicillins (Figure 3.1.8). The increase is seen for all classes of antibiotics in hospital care (Figure 3.1.9).

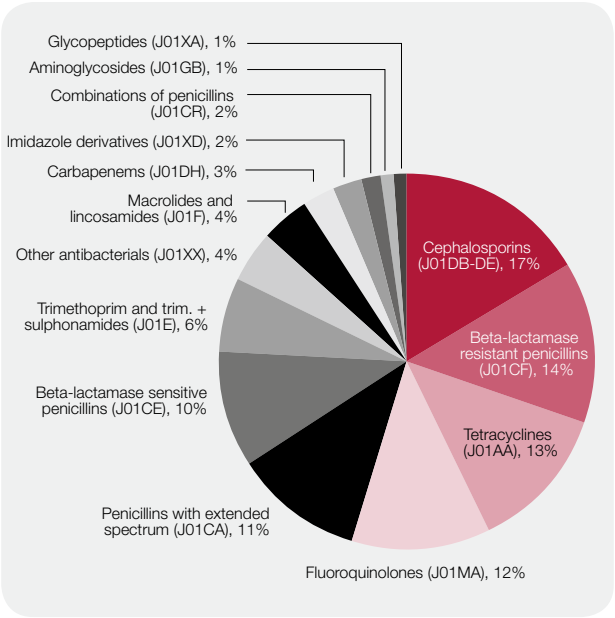

Figure 3.1.8. Antibiotics in hospital care 2006, percent of total DDD/1000/day.

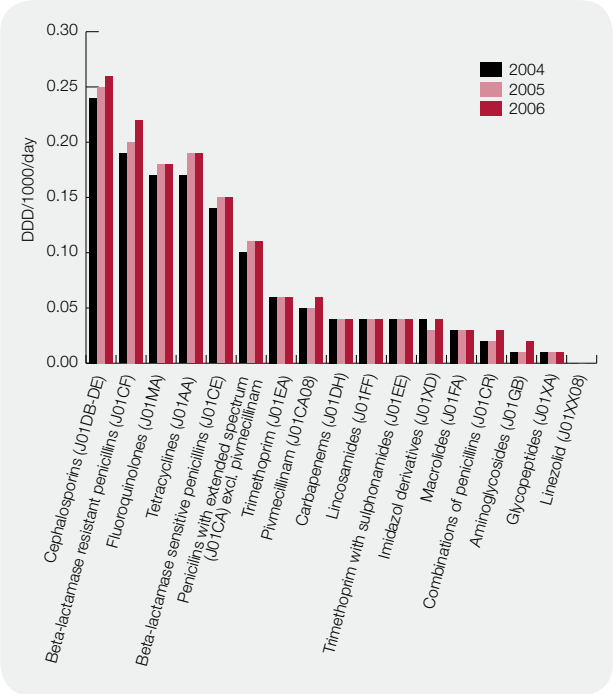

Figure 3.1.9. Antibiotics in hospital care 2004–2006, DDD/1000/day.

The increase in use of beta-lactamase resistant penicillins may be explained by a change in dosage of the oral preparations from twice a day to three times daily, increasing the daily dose by 50%. The use of pivmecillinam has increased, reflecting increasing adherence to guidelines for treatment of urinary tract infections. The most common cephalosporin is cefuroxim. Its use is increasing steadily and in 2006 it represented 70% of the total use of cephalosporins in hospital care (Figure 3.1.10).

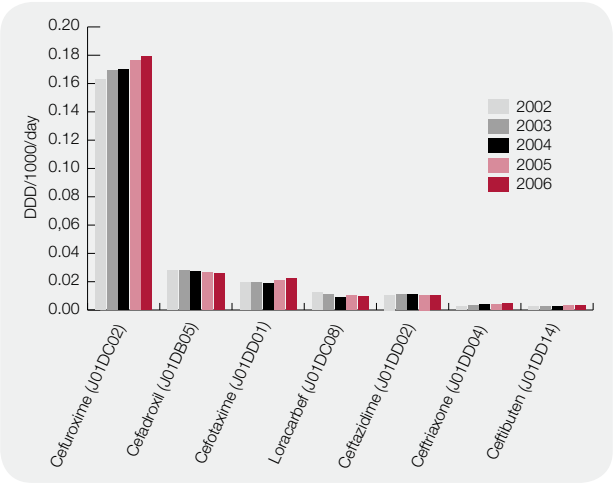

Figure 3.1.10. The most commonly used cephalosporins in hospital care 2002–2006, DDD/1000/day.

The hospipatal use of combinations of penicillins is presented in Figure 3.1.11. The use of amoxicillin with clavulanic acid is increasing steadily, but piperacillin with tazobactam even more so. Piperacillin with tazobactam is recommended as an alternative to carbapenems and cephalosporins for the treatment of nosocomial pneumonia.

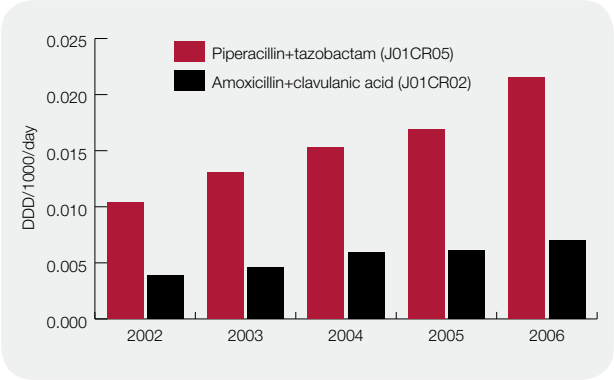

Figure 3.1.11. Combinations of penicillins in hospital care 2002–2006, DDD/1000/day.

Tables 3.1.7 and 3.1.8 present hospital care data on antibiotic use per 100 admissions and 100 patient-days respectively. The use has increased steadily since 1997. At the same time the mean length of hospital stay and the number of beds in somatic medical care have decreased, shown in Figure 3.1.12. In short, patients are given more antibiotics during shorter periods of hospital stay.

Table 3.1.7. Antibiotics in hospital care 1997–2005, DDD/100 admissions.

	1997	1998	1999	2000	2001	2002	2003	2004	2005
Tetracyclines (J01AA)	31.8	33.1	34.9	34.8	33.6	34.3	34.9	36.4	42.2
Penicillins with extended spectrum (J01CA)	21.6	22.9	24.8	26.8	28.0	29.3	31.8	34.7	36.3
Beta-lactamase sensitive penicillins (J01CE)	38.8	33.1	31.9	31.7	30.5	30.4	30.7	29.5	33.8
Beta-lactamase resistant penicillins (J01CF)	37.9	36.9	36.9	37.9	40.2	41.4	42.3	42.5	44.4
Combinations of penicillins (J01CR)	1.9	2.1	2.3	2.8	2.8	3.2	4.0	4.7	5.2
Cephalosporins (J01DB-E)	49.8	52.7	53.4	54.6	54.0	55.0	56.4	55.6	57.3
Carbapenems (J01DH)	5.2	6.1	6.5	7.0	7.1	7.4	8.2	8.7	9.4
Trimethoprim (J01EA)	6.8	6.5	7.0	7.4	7.7	8.5	10.0	10.4	13.5
Trimethoprim with sulfonamides (J01EE)	5.9	6.0	6.1	6.6	6.6	6.9	7.2	7.7	8.2
Macrolides (J01FA)	6.5	6.4	6.5	6.3	6.3	5.9	5.5	5.4	5.8
Lincosamides (J01FF)	5.3	6.1	6.1	7.0	7.6	7.1	8.2	8.1	8.1
Aminoglycosides (J01GB)	2.9	2.8	2.9	3.1	3.0	2.9	3.0	3.2	3.3
Fluoroquinolones (J01MA)	33.5	34.9	35.5	36.5	37.4	37.1	39.4	38.9	41.2
Glycopeptides (J01XA)	1.9	2.3	2.2	2.3	2.5	2.5	2.8	3.0	3.1
Imidazole derivatives (J01XD)	7.0	7.4	7.6	8.1	8.1	8.5	8.3	8.1	7.9
Methenamine (J01XX05)	5.8	7.3	8.0	7.1	6.9	6.4	10.0	14.6	16.5
Linezolid (J01XX08)	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.2
All agents (J01)	264.1	268.5	274.9	282.2	284.5	288.9	305.5	314.6	340.1

Table 3.1.8. Antibiotics in hospital care 1997–2005, DDD/100 patient-days.

	1997	1998	1999	2000	2001	2002	2003	2004	2005
Tetracyclines (J01AA)	4.7	5.0	5.4	5.7	5.4	5.6	5.8	6.2	7.3
Penicillins with extended spectrum (J01CA)	3.2	3.5	3.8	4.4	4.5	4.8	5.3	5.9	6.3
Beta-lactamase sensitive penicillins (J01CE)	5.8	5.0	4.9	5.1	4.9	5.0	5.1	5.0	5.8
Beta-lactamase resistant penicillins (J01CF)	5.7	5.6	5.7	6.2	6.5	6.8	7.1	7.2	7.7
Combinations of penicillins (J01CR)	0.3	0.3	0.4	0.4	0.5	0.5	0.7	0.8	0.9
Cephalosporins (J01DB-E)	7.4	8.0	8.3	8.9	8.8	9.0	9.4	9.5	9.9
Carbapenems (J01DH)	0.8	0.9	1.0	1.1	1.2	1.2	1.4	1.5	1.6
Trimethoprim (J01EA)	1.0	1.0	1.1	1.2	1.3	1.4	1.7	1.8	2.3
Trimethoprim with sulfonamides (J01EE)	0.9	0.9	1.0	1.1	1.1	1.1	1.2	1.3	1.4
Macrolides (J01FA)	1.0	1.0	1.0	1.0	1.0	1.0	0.9	0.9	1.0
Lincosamides (J01FF)	0.8	0.9	0.9	1.1	1.2	1.2	1.4	1.4	1.4
Aminoglycosides (J01GB)	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6
Fluoroquinolones (J01MA)	5.0	5.3	5.5	5.9	6.1	6.1	6.6	6.6	7.1
Glycopeptides (J01XA)	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5
Imidazole derivatives (J01XD)	1.1	1.1	1.2	1.3	1.3	1.4	1.4	1.4	1.4
Methenamine (J01XX05)	0.9	1.1	1.2	1.2	1.1	1.0	1.7	2.5	2.9
Linezolid (J01XX08)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
All agents (J01)	39.4	40.5	42.6	45.8	46.1	47.4	50.8	53.5	58.9

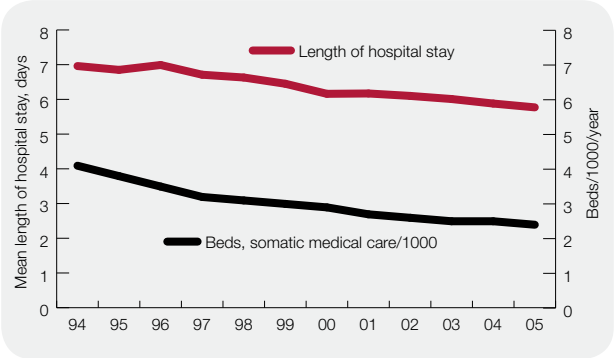

Figure 3.1.12. Mean length of hospital stay and number of beds in somatic medical care/1000 inhabitants, Sweden 1994–2005.

Antibiotic consumption in Europe

Sweden participates in the ESAC (European Surveillance of Antimicrobial Consumption) project. Sales data have been collected since 2001, retrospectively from 1997. The out-patient use of antibiotics in 25 European countries in 2003 is presented in Figure 3.1.13. Sweden has a relatively low use of antibiotics and the group "others" constitutes a relatively large proportion of the total Swedish antibiotic use. This group includes methenamine, which is not an antibiotic, but an antibacterial. Its use does not give rise to antibiotic resistance.

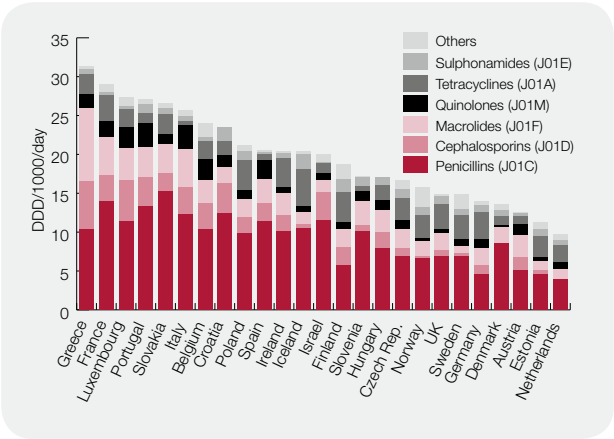

Figure 3.1.13. Total out-patient antibiotic use in 25 European countries in 2003. Cephalosporins include monobactams and carbapenems; macrolides include lincosamides and streptogramins; sulphonamides include trimethoprim and others include J01B, J01G, J01R and J01X. For Iceland total data are used, for Poland 2002 data are used. Source: ESAC.

In 2005, Sweden had the lowest total use of antibiotics (methenamine excluded) of all the Nordic countries (Figure 3.1.14).

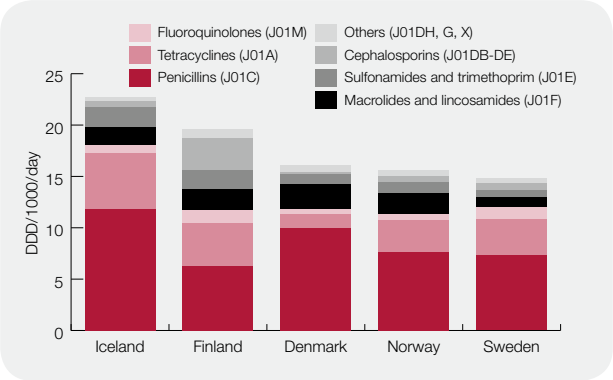

Figure 3.1.14. Antibiotics (methenamine excluded) in the Nordic countries, total sales in 2005.

Ulrica Dohnhammar, Gunilla Stridh

Adverse reactions

Spontaneously reported drug-related adverse reactions are continuously registered in SWEDIS, a national data-base administered by the Swedish Medical Products Agency (Läkemedelsverket). The reports originate from medical personnel and the reactions are categorised as probably or not probably drug-related. The frequencies of antibiotic related adverse reactions, judged as probably drug-related, during the last six years (2001–2006) were analysed for various groups of agents. The five most commonly reported categories of adverse reactions, judged as probably related to the use of systemic antibiotic drugs (J01), during the period 2001–2006 were skin- and subcutaneous tissue disorders (n=465), hepato-biliary disorders (n=250), gastrointestinal disorders (n=208), musculoskeletal disorders (n=196), and general disorders (n=178). The majority of the reports (61%) concerned female patients.

The 10 antibiotic substances most commonly associated with adverse reactions, during the last 6 years unadjusted for the consumption and regardless of the cause of the report, were ciprofloxacin, flucloxacillin, trimethoprim, levofloxacin, nitrofurantoin, doxycycline, fenoxymethylpenicillin, clindamycin, norfloxacin and sulphamethoxazol plus trimethoprim, Table 3.1.9.

Table 3.1.9. Number of reports to the Swedish Medical Products Agency 2001–2006.

Antibiotic	Total number of adverse reactions	Number of 'serious' reports	Number of fatal cases (causal relationship possible)
Ciprofloxacin	196	106	2
Flucloxacillin	139	103	4
Trimethoprim	110	47	0
Levofloxacin	98	49	0
Nitrofurantoin	90	50	0
Doxycycline	86	34	2
Fenoxymethylpenicillin	86	40	1
Clindamycin	85	36	1
Norfloxacin	76	38	4
Sulphamethoxaxol + trimethoprim	67	42	1

During the last years certain alterations in prescription patterns have been recorded, mainly as a consequence of amended treatment recommendations. The decreased consumption of fluoroquinolones in the treatment of uncomplicated urinary tract infections is mirrored by a subsequent trend of decreased totally reported adverse events, Table 3.1.10. In contrast, for nitrofurantoin which has been increasingly prescribed during the last six years, there are some indications of increased numbers of reported adverse events during this period. A higher number of serious respiratory events were mainly responsible for the increase in nitrofurantoin-associated events. However, due to the overall low numbers and since the figures are based on spontaneous reports, no clear conclusions can be drawn from these data. Nevertheless, an increased awareness of possible consequences in terms of safety parameters due to altered treatment recommendations is considered important.

Table 3.1.10. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2001-2006.

	2001	2002	2003	2004	2005	2006	2001-2006
Fluoroquinolones							
Total adverse events	100	100	84	75	77	78	514
Musculoskeletal	20	38	22	34	24	19	157
tendinitis	11	23	14	15	13	11	88
tendon rupture	5	9	5	12	5	3	39
Skin- and subcutaneous tissue	16	11	16	7	11	6	67
Psychiatric disorders	7	6	9	4	10	8	44
Nitrofurantoin							
Total adverse events	13	17	32	48	26	38	174
Respiratory system	3	5	10	10	8	12	48
dyspnoea	1	1	4	3	2	4	15
interstitial pneumonia	-	-	4	2	2	2	10
lung fibrosis	-	2	-	1	-	2	5
Skin- and subcutaneous tissue	1	6	5	7	1	7	27
General disorders	5	3	9	11	7	8	43
fever	2	3	5	6	6	4	26

No significant trends could be identified for frequencies of adverse events reported for beta-lactamase-sensitive penicillins (J01CE), beta-lactamase resistant penicillins (J01CF), tetracyclines (J01A), cephalosporins (J01D), trimethoprim with or without sulphonamides (J01E), macrolides (J01FA) or lincosamides (J01FF), in spite of altered consumption during the present period.

Charlotta Edlund, Bengt Lindeskog

3.2 Use of antifungals

Hospital care

The total use of antifungals administered systemically in hospital care increased by 8% (from 0.046 to 0.050 DDD/1000/day) from 2005 to 2006. The fungistatic drug fluconazole, a relatively low-cost agent with a spectrum of activity restricted to Candida and Cryptococcus species, accounts for most of the rise (Figure 3.2.1). Fluconazole constitutes 80% of the total antifungal use in hospital care, a figure that places Sweden among the EU countries with highest relative use of this substance. The use of caspofungin also shows an increment during the last year. Caspofungin, mainly indicated for the treatment of invasive candidiasis and aspergillosis, represents a new group of antifungals. A possible reason for the observed increase in the use of caspofungin is the improved side-effect profile of this agent in comparison to amphotericin B. Additionally, awareness has increased in regards to the risks associated with the use of fluconazole to treat *C. non-albicans* infections, in particular those caused by azole-resistant species such as *C. glabrata, C. krusei,* and *C. norvegiensis*.

Following the trend observed in recent years, the use of amphotericin B decreased by 20% from 2005 to 2006. Since 2001, the reduction has been 58%. Amphotericin B is a broad-spectrum antimycotic with high activity against many fungal species. Development of resistance under amphotericin B treatment is very unusual but side effects are common.

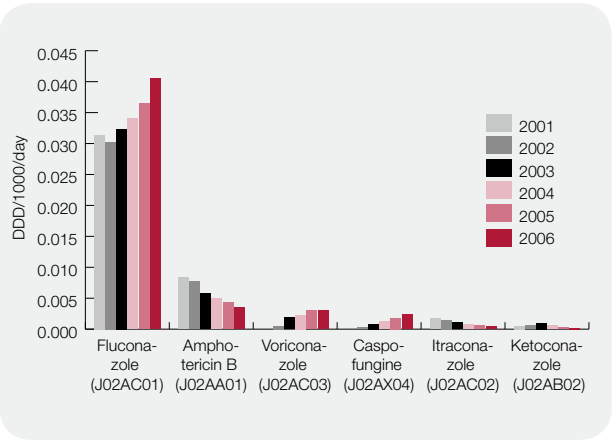

Figure 3.2.1. Use of antifungals in hospital care, 2001–2006, DDD/1000/day.

Out-patient care

Over 90% of the total consumption of antimycotics takes place in out-patient care. During 2006, the rate of out-patient antifungal prescription (DDD/1000 inhabitants/day) was highest for miconazole, an agent used for the topical treatment of dermatophytosis as well as cutaneous and vulvovaginal candidiasis. Ketoconazole, a substance used for topical and oral medication of dermatophyte and yeast infections in skin, nails and hair was the antifungal most sold over the counter.

Victor Fernandez

4. Antimicrobial resistance

IN SWEDEN, antibiotic susceptibility testing of clinical isolates is routinely performed using standardized methods (Appendix 4). The first finding of methicillin resistant *Staphylococcus aureus* (MRSA), pneumococci with decreased susceptibility to penicillin G (MIC ≥0,5 mg/L) or vancomycin resistant enterococci (VRE) in a patient is notifiable according to the communicable disease act, regardless of whether it is a clinical infection or asymptomatic carriage. In addition to this mandatory notification a national programme for the surveillance of resistance was initiated in 1994 (Appendix 5). Thus, well-characterised data on resistance in many bacterial pathogens are now available for several years both at regional and national level.

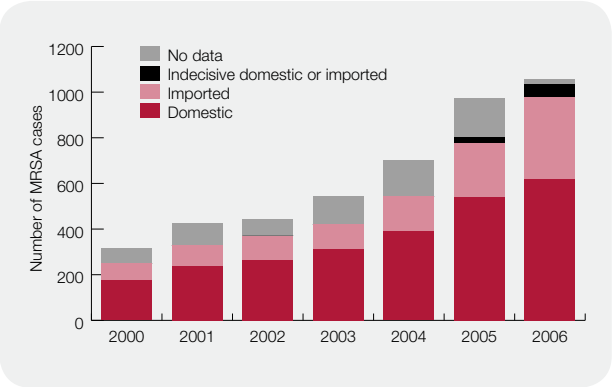

Figure 4.1.1. Number of notified cases of MRSA per year by country of infection, Sweden 2000-2006.

Staphylococcus aureus

Background

Following an extensive regional outbreak and increasing alertness responding to the situation seen in other European countries MRSA was made mandatorily notifiable in the year 2000. Compared to many other European countries, where the proportion of MRSA commonly reaches 50% of invasive *S. aureus* isolates, the prevalence of MRSA among such isolates is still below 1% in Sweden (see details on EARSS data in the following text). Infection control programmes based on screening of patients with risk factors, contact tracing around and isolation of MRSA positive cases, and intensive campaigns on barrier precautions have been developed and implemented locally under supervision by the local county medical officers of communicable disease control. This has led to an increase in the number of screening cultures and positive samples from asymptomatic cases.

Notifications of MRSA according to the Communicable Disease Act

The following presentation is based on data collected in the web-based notification system "SmiNet 2" as they are recorded at the county level. An active effort has been made to improve quality and collect missing data for 2006. Together with the county medical officers of communicable disease control the notifications have been reviewed and complemented with available relevant information from the investigation of the cases. A total of 1057 cases of MRSA were notified in 2006, as compared to 975 cases in 2005 (Figure 4.1.1).

Fifty-eight per cent (618 cases) of all reported MRSA cases 2006 were acquired in Sweden. Approximately one-third (359 cases) was acquired abroad. USA (32 reported cases), the Philippines (24), Spain (20), Thailand (19) and China (18 cases), made up the five most common countries for imported MRSA infection during 2006. In six percent of the cases Sweden were notified as the primary country for the MRSA infection but additional countries were assigned as well (hence "Indecisive").

The main increase in the number of identified domestic cases in recent years have occurred in the age groups under 50 years of age (Figure 4.1.2).

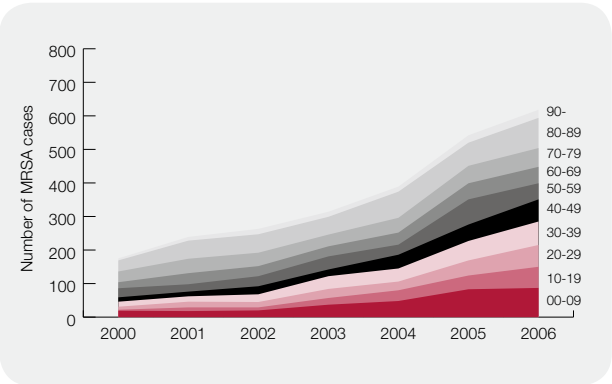

Figure 4.1.2. Age distribution among notified domestic cases of MRSA, Sweden 2000-2006.

The majority of the domestic cases have, at least for the last couple of years, been identified by clinical symptoms or through targeted contact tracing (Fig 4.1.3). Even though aggregated data on the total number of clinical cultures is not available at present, it is reasonable to assume that the number of cultures have increased as culturing even of furuncula and minor blisters in primary care is widely encouraged. Thus, increased indications for culturing in combination with spread of PVL (Panton-Valentine leucocidin)-positive strains (see p. 21–22) in the community probably explains the increase of clinical isolates during the last couple of years.

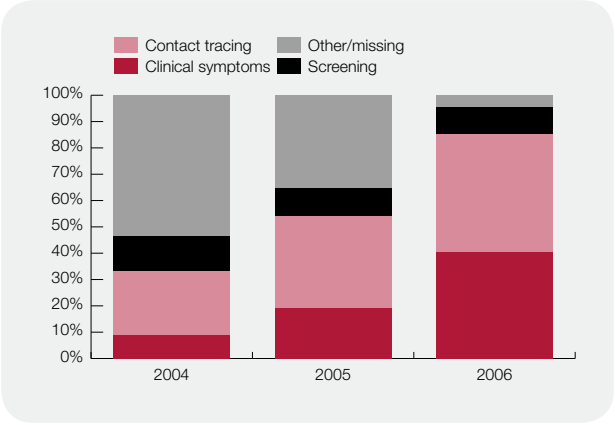

Figure 4.1.3. The reason for detection of domestic MRSA cases in Sweden 2004-2006.

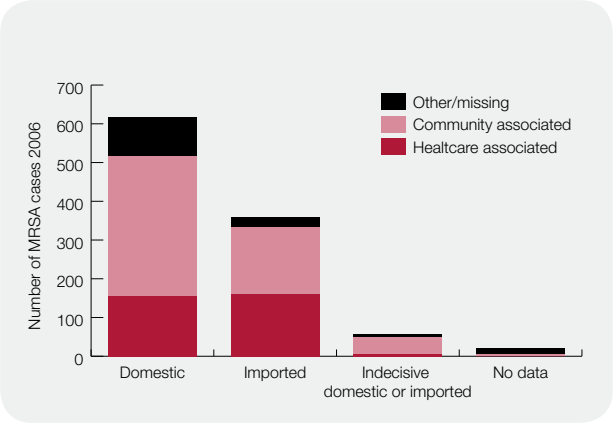

Figure 4.1.4. Healthcare-associated vs community-associated acquisition of MRSA by country of infection, Sweden 2006.

Categorization of the place for acquisition of MRSA (not where diagnose was made) is based on epidemiological information.

Whereas community associated infections (including patients in long-term care) dominated among domestic cases 2006, healthcare associated MRSA were relatively more common among imported cases, 161/359 (45%) vs. 155/618 (25%) among domestic cases (Figure 4.1.4). Differences in the present quality of data at the national level make comparisons over time difficult.

In 2006, 13 of the Swedish counties had an increasing incidence of the total number of reported cases of MRSA while 8 counties reported decreasing incidence (Table 4.1.1).

The high incidence noted in Östergötland county in 2005, caused by a large hospital-related outbreak, has declined to a level similar to the mean incidence for Sweden after intensive infection control efforts, including screening and contact tracing, were introduced.

Table 4.1.1. MRSA notified in 2000-2006 by county according to the Communicable Disease Act.

County	2000		2001		2002		2003		2004		2005		2006	
	No	Inc*	No	Inc*	No	Inc*	No	Inc*	No	Inc*	No	Inc*	No	Inc*
Stockholm	97	5.3	166	9	205	11.1	228	12.3	277	14.8	315	17.1	356	18.9
Uppsala	19	6.5	17	5.7	10	3.3	12	4	26	8.6	28	9.2	24	7.9
Södermanland	2	0.8	1	0.4	4	1.5	2	0.8	8	3.1	11	3.8	9	3.4
Östergötland	2	0.5	7	1.7	7	1.7	14	3.4	14	3.4	101	24.3	48	11.5
Jönköping	7	2.1	6	1.5	5	1.5	24	7.3	14	4.3	40	12.1	44	13
Kronoberg	1	0.6	0	0	4	2.3	5	2.8	17	9.5	11	6.1	14	7.8
Kalmar	3	1.3	5	0.9	5	2.1	6	2.6	16	6.8	23	9.7	26	11.1
Gotland	1	1.8	10	17.5	3	5.3	2	3.5	1	1.7	10	17.3	4	6.9
Blekinge	7	4.7	1	0.7	3	2	2	1.3	3	2	9	5.9	4	2.7
Skåne	22	1.9	76	6.7	68	5.9	104	9.1	128	11.3	162	13.9	179	15.5
Halland	10	3.6	26	9.4	13	4.7	13	4.6	9	3.2	21	7.4	23	8.1
Västra Götaland	114	7.6	56	3.7	48	3.2	63	4.2	118	7.8	125	8.1	177	11.6
Värmland	9	3.3	7	2.6	6	2.2	11	4	18	6.6	9	3.2	13	4.8
Örebro	8	2.9	7	2.6	16	5.9	8	2.9	11	4	16	5.8	35	12.8
Västmanland	3	1.2	8	3.1	6	2.3	11	4.2	12	4.6	35	13.4	48	18.4
Dalarna	0	0	5	1.8	1	0.4	2	0.7	3	1.1	6	2.1	11	4
Gävleborg	2	0.7	1	0.4	12	4.3	5	1.8	5	1.8	24	8.6	17	6.1
Västernorrland	14	5.7	12	4.9	7	2.9	10	4.1	5	2	4	1.6	9	3.7
Jämtland	0	0	0	0	2	1.6	5	3.9	1	0.8	8	6.2	4	3.1
Västerbotten	3	1.2	17	6.7	10	3.9	13	5.1	16	6.2	10	3.8	7	2.7
Norrbotten	3	1.2	5	2	7	2.8	9	3.6	7	2.8	8	3.1	5	2
Total, Sweden	**327**	**3.7**	**429**	**4.8**	**442**	**4.9**	**549**	**6.1**	**709**	**7.8**	**975**	**10.8**	**1057**	**11.7**

* = Incidence / 100 000 inhabitants in Sweden.

Voluntary reporting and outbreaks – MRSA in a Swedish Small Animal Hospital

For the first time in Sweden, methicillin-resistant *Staphylococcus aureus*, MRSA, was diagnosed in pet animals during the autumn of 2006. Two dogs with post-operative wound infections had cultures taken and both were MRSA positive. (For further information about MRSA in animals, see SVARM 2006.)

In Sweden, MRSA is classified as a serious infectious disease in humans under the Communicable Diseases Act dated July 1st, 2004. MRSA has no such status among animals. However, not only suspected spread of infectious diseases between humans but also from any source to humans, is included in the above mentioned act. According to this act, contact tracing is compulsory in serious infectious diseases. Therefore, bacteriological samples were taken from staff at the animal hospital as well as from members of the owner families.

Samples were taken from nostrils, throat and any skin lesion and if MRSA positive the sampling was repeated. Furthermore, environmental samples were taken from different sites at the veterinary hospital. No guidelines or hygienic precautions in relation to MRSA infection were available at the time at the hospital.

Typing of the MRSA strains identified in the two dogs showed spa-type t032 in both animals and both isolates were fluoroquinolone resistant. The PFGE patterns were also identical. Spa-type t032 comprise EMRSA-15, which has been prevalent in hospital transmission in Stockholm, but with a different antibiogram. None of the five members of the two owner families had any MRSA when sampled. Seventy-one staff members were sampled and 13 (18%) were MRSA positive. All staff members had the same MRSA strain tested according to antibiogram, PFGE and spa-type, and the isolates were identical with the MRSA strain found in the dogs. All twenty-eight environmental samples were negative for MRSA.

The PFGE analyses revealed a unique strain of MRSA also found in two patients diagnosed in September 2007. One patient had a clinical infection, the other was found in contact tracing. The patient with infection had a dog that had been attending the veterinary hospital earlier the same year. When sampled 10 months later the dog was MRSA negative.

The guidelines for MRSA prevention were presented to the staff of the veterinary hospital along with the standard hygienic precautions. The staff have thereafter adapted the guidelines to suit their hospital and implemented hygienic precautions. During the last years several reports on MRSA transmission from humans to pets and from pets to humans have become available from other countries.

We found as many as 18% of the staff contaminated with MRSA, all with the same strain. This result is in accordance with a previous study from the UK which showed 18% of the staff at a small animal hospital contaminated with MRSA but different MRSA strains were involved. However, it exceeds by far our experience from transmission to hospital staff which is less than 1% in the county of Stockholm. The reasons for the extensive transmission of MRSA in veterinary hospitals are not well known, in particular in relation to the lack of findings in the environmental samples. Based on this experience and need for close collaboration between human and veterinary medicine on this matter, MRSA is now included among other zoonotic diseases in Sweden.

Typing of MRSA

DNA-based methods have been used for typing of all MRSA isolates since the year 2000. During 2000–2005 pulsed field gel electrophoresis (PFGE) was the standard method, and during the first half of 2006 it was run in parallel with spa-typing, which thereafter was used as the primary typing method. PFGE patterns of the Swedish isolates are always compared with international reference strains (epidemic MRSA from European countries, the Harmony project), and the PFGE patterns are named as described in previous SWEDRES reports. Spa typing is based on sequencing of the polymorphic X-region of the *Staphylococcus aureus* species-specific protein A gene, spa, and the Ridom StaphType® software is used for analysis.

The prevalence of different PFGE groups (each including several related PFGE patterns) of MRSA in Sweden 2000–2005 is illustrated in Figure 4.1.5. Based on data from 2006, the most common spa-type per group was t008 (group including UK E1/Fra A/Fra B), t002 (Bel EC-3a/UK E3), t032 (UK E15), t018 (UK E16), t015 (Berlin IV), and t044 (DK E97–1).

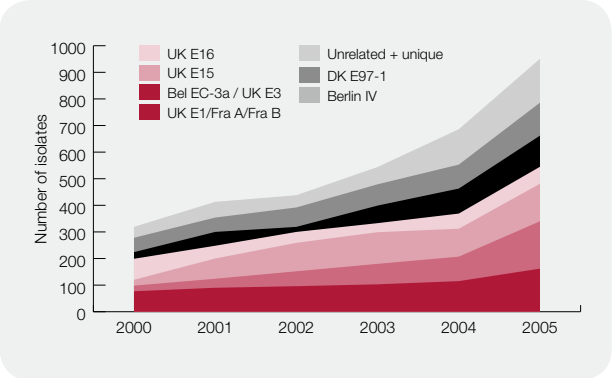

Figure 4.1.5. PFGE groups of MRSA isolated in Sweden 2000–2005.

Isolates with PFGE patterns identical or related to Bel EC-3a/UK E3 were the most common in 2005. This was largely due to the hospital epidemic of PFGE type SE01–9 (spa-type t149) in Östergötland. Various PFGE types of this genetically related and globally recognized group have been reported from many counties. In 2006, isolates of this group were even more dominating, constituting more than 20% of all isolates. Isolates with PFGE patterns identical or related to UK E15 (spa-type t032 most common) were the most frequently found in 2002 and 2003, but has since become less dominating, to a large extent depending on the favourable development of the situation in Stockholm county. PFGE type DK E97–1 (spa-type t044 most common, PVL-positive) has been found in all Swedish counties, but was seen relatively less often in 2006. Isolates with Berlin IV like PFGE patterns (spa-type t015 most common) are continuously found in all parts of Sweden. There was an increase in the number of isolates with PFGE patterns identical or related to UK E16 (spa-types t018 and t019 most common). Isolates with UK E1 like PFGE patterns were often found among imported cases, and the same goes for several of the so called unrelated SE patterns.

MRSA isolates have been analysed for the presence of genes coding for the Panton-Valentine leucocidin (PVL). All isolates of the PFGE type DK E97–1 were positive, one type in the UK E16

group (SE00–3), and two types in the UK E1/FraA/FraB group (SE00–7 and SE03–5). Several other PFGE types were also PVL-positive (e.g. SE01–3, SE01–7, SE02–18).

Among the PVL-positive isolates, those of PFGE-type SE03–5 (spa-type t008) belonged to the most rapidly growing type. It was identified as having the same PFGE pattern as USA300, an MRSA-type described as being rapidly spreading in the community.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Staphylococcus aureus from wound infections are included in the annual RSQC programme since 2001 (Appendix 5). Twenty-nine laboratories deliver data on consecutive isolates using the disk diffusion method for cefoxitin (from 2004 used as screen disk for detection of MRSA), clindamycin, fusidic acid, aminoglycoside (gentamicin or tobramycin) and vancomycin. Since 2004 erythromycin and ciprofloxacin have also been tested. Resistance rates are presented in Figure 4.1.6.

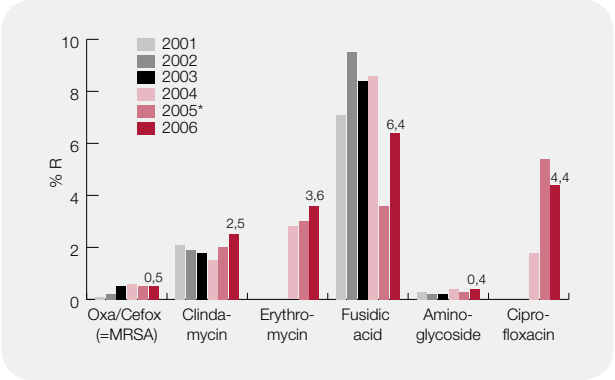

Figure 4.1.6. Resistance rates for *Staphylococcus aureus* 2001–2006 (data from the annual RSQC programme, approximately 3000 isolates per year). *In 2005 resistance rates were recorded in *S. aureus* isolated from wounds and secretions from elderly people (> 65 years).

It can be seen that resistance rates for macrolides and clindamycin are increasing, and that the prevalence of fusidic acid resistant isolates is decreasing. For fusidic acid the lower level of resistance in 2005 is explained by the selection criteria used that year, including only patients older than 65 years of age. The frequency of MRSA in wound infections has not continued to increase in 2005 and 2006. The high numbers of screening cultures taken might contribute to this slight decrease.

Data on invasive isolates reported to EARSS

Twenty-one of the Swedish laboratories (covering approximately 75% of the population) are reporting susceptibility data on invasive isolates of *S. aureus* to EARSS (Appendix 5). In 2006, 0.9% of the invasive *S. aureus* isolates were MRSA (identified by the cefoxitin screen disk and confirmed by detection of the *mecA* gene) (Table 4.1.2). This is in the same order of magnitude as during recent years. Thus, Sweden is still below the level 1% which has been defined as an upper limit not to be passed.

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Table 4.1.2. *Staphylococcus aureus* susceptibility results (number of strains and percentage) using the disk diffusion method and confirmation of the mecA gene according to SRGA in Sweden. Data reported from SMI to EARSS.

Year	S	I	R
2001	1618 (99.1%)	0	14 (0.9%)
2002	1830 (99.4%)	0	12 (0.6%)
2003	1839 (99.1%)	0	16 (0.9%)
2004	1891 (99.3%)	0	14 (0.7%)
2005	1756 (99%)	0	18 (1.0%)
2006	1849 (99.1%)	0	16 (0.9%)

Streptococcus pneumoniae

Background

S. pneumoniae with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (henceforth designated PRP) became notifiable according to the Communicable Disease Act in 1996 after reports of increasing resistance in Southern Sweden.

Notifications according to the Communicable Disease Act Surveillance

In 2006 there were 631 notifications of PRP in Sweden. 59 percent of the cases were reported to be infected domestically and 12% of the cases abroad. In the remaining 189 cases no country of infection was given.

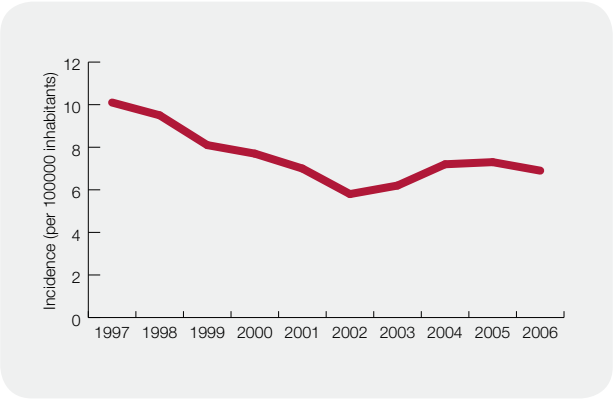

Figure 4.1.7. Annual incidence of *S. pneumoniae* with reduced susceptibility to penicillin, (PRP, MIC > 0.5 mg/L) in Sweden 1997-2006

The 2006 annual PRP incidence in Sweden was 6.9/100 000, similar to that of 2005 (Figure 4.1.7). Previous analysis has indicated that the declining incidence from 1997 to 2002 was related to a concurrent decrease in nasopharyngeal culturing propensity. There is no difference in the proportion of the reported cases with regard to sex. The majority of PRP cases, independent of year observed, are found in the age group 0–4 years (Fig 4.1.8).

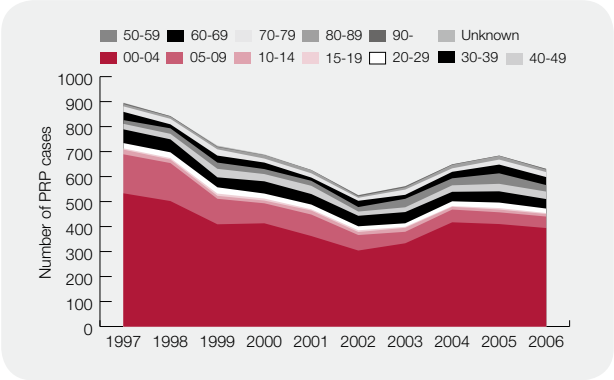

Figure 4.1.8 Age distribution among all cases reported with PRP in Sweden 1997–2006.

PRP were reported from all 21 counties with Stockholm and Skåne accounting for 75% of all notifications. Case finding intensity varies between different counties in Sweden, both due to regional differences in general culturing propensity, as well as presence of targeted screening programmes in some counties. This makes comparison of regional incidence rates difficult.

The majority of the PRP are found in nasopharyngeal samples. Thirty-one isolates reported 2006 were invasive (blood (29), cerebrospinal fluid (2)).

Compared to previous years the distribution of serotypes of PRP has changed and is now dominated by serogroup 19. Other prevalent serogroups/serotypes are 9, 14 and 6.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pneumococci have been included since 1994 in the surveys by Swedish laboratories. These isolates are mainly derived from nasopharyngeal cultures. Approximately 3000 consecutive isolates per year from all the clinical laboratories have been tested for resistance to penicillin (by means of oxacillin 1 µg screen disk = PNSP), erythromycin, tetracycline, and trimethoprim-sulfamethoxazol, using the disk diffusion method. The national summary of the results is shown in Figure 4.1.9. For all four antibiotics there is a trend of increasing resistance. This trend was most pronounced for erythromycin with an increase from less than 2% in 1994 to 7.2% in 2006, and for trimethoprim-sulfamethoxazol with an increase from 4.4% in 1994 to 9.2% in 2006.

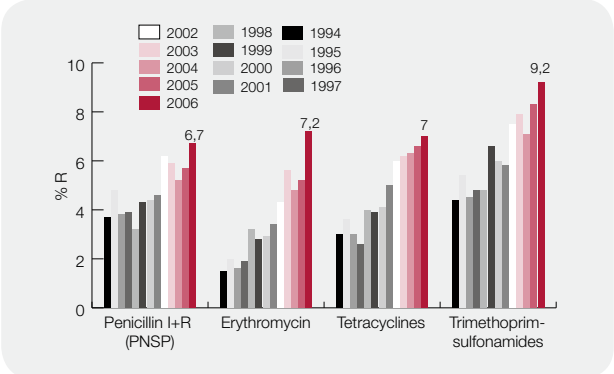

Figure 4.1.9. Resistance rates for *Streptococcus pneumoniae* 1994–2006 (data from the annual RSQC programme, approximately 3000 isolates per year.

Data on invasive isolates reported to EARSS

Twenty-one of the Swedish clinical microbiology laboratories, covering approximately 75% of the population, are reporting susceptibility data on invasive isolates of *S. pneumoniae* to EARSS.

The Swedish data on susceptibility to penicillin and erythromycin is given in Table 4.1.3. Levels of resistance are lower among invasive isolates than in the nasopharyngeal isolates from the RSQC programme. Also, there is no trend of increasing resistance among invasive isolates, contrary to the nasopharyngeal isolates.

Table 4.1.3. Invasive isolates of *Streptococcus pneumoniae* reported to EARSS.

Penicillin * (I+R = PNSP)				
Year	S%	I%	R%	Total
2001	97.2	2.3	0.5	**788**
2002	97.5	2.4	0.1	**783**
2003	95.0	5.0	0	**920**
2004	96.8	2.8	0.4	**955**
2005	96.4	3.1	0.5	**1017**
2006	97.9	2.1	0	**936**
Erythromycin				
Year	S%	I%	R%	Total
2001	95.4	0.2	4.4	**653**
2002	94.7	0.1	5.2	**700**
2003	94.9	0.1	5.0	**736**
2004	94.7	0.1	5.2	**869**
2005	94.3	0.3	5.4	**924**
2006	94.8	0.4	4.8	**813**

* S < 0.12 mg/L; I 0.12-1.0 mg/L; R > 1.0 mg/L

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Enterococcus faecium and *faecalis*

Background

Vancomycin resistant enterococci (VRE) have become important causes of nosocomial infections in many parts of the world, usually involving high-risk populations such as immunosuppressed and intensive care patients. Like MRSA, VRE were made notifiable according to the Swedish Communicable Disease Act in the year 2000 and since 2004 contact tracing is also mandatory.

Notifications of VRE according to the Communicable Disease Act

There were 24 notified cases of VRE during 2006. Reports came from 10 out of 21 Swedish counties with Jönköping, Skåne and Västra Götaland accounting for half of the notifications (4 cases each). From 2000 to 2005 the number of reported cases of VRE have been 20, 18, 19, 47, 21 and 35 respectively. The median age for all cases was 69 years, the same as in 2005. Half of the notified VRE cases in 2006, were acquired domestically, whilst 10 were

reported to be acquired abroad. For 2 cases, no information about country of infection was reported.

During 2006, 17/24 notified cases had Entercoccus faecium. Nine of the isolates carried the *van*A-gene, three the *van*B-gene and for five isolates no gene was reported. *Enterococcus faecalis* were reported in four cases, two with *van*A and two with no information given. In three cases both bacterial species were isolated. The majority of VRE reported according to the Communicable Disease Act 2000–2005 were *Enterococcus faecium* carrying the *van*B gene (n=148), whereas eight were *Enterococcus faecium* with *van*A, three *Enterococcus faecalis* with *van*A and one *Enterococcus faecalis* with *van*B.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Enterococcus faecalis was not included in the RSQC programme on antibiotic resistance for 2006.

Data on invasive isolates reported to EARSS

Since the year 2001, *Enterococcus faecalis* and *Enterococcus faecium* are included in the EARSS network (Appendix 5). The main focus has been on vancomycin resistance, but also on high-level resistance to aminoglycoside antibiotics. Twenty-one of the Swedish laboratories (covering approximately 75% of the population) are reporting susceptibility data on invasive isolates of these two pathogens.

In 2003 the first four vancomycin-resistant invasive isolates of *Enterococcus faecium* were reported, and in 2004 three isolates were found, representing 1.2% (Tables 4.1.4 and 4.1.5). Molecular typing of these vancomycin-resistant isolates indicated relatedness only between two of them, from the same hospital. In 2006 only two resistant blood isolates were found, one was *Enterococcus faecalis* with *van*A gene and the other Entercoccus faecium with *van*B gene.

High-level aminoglycoside resistance (HLAGR) was more prevalent in *Enterococcus faecalis* (13–20%) than in *Enterococcus faecium* (4–14%) during this period. In 2006 all laboratories used gentamicin (GEN) as test disk for detection of HLAGR.

Table 4.1.4. Resistance among invasive isolates of *Enterococcus faecalis* reported to EARSS 2001–2006.

Year	Vancomycin-R (%)	HLAGR (%)	Total number (number tested for HLAGR by GEN)
2001	0	12.7	395 (212)
2002	0	17	430 (235)
2003	0	17.5	593 (440)
2004	0	15.4	592 (533)
2005	0	18.7	567 (492)
2006	0.4	19.9	579 (563)

Table 4.1.5. Resistance among invasive isolates of *Enterococcus faecium* reported to EARSS 2001–2006.

Year	Vancomycin-R (%)	HLAGR (%)	Total number (number tested for HLAGR by GEN)
2001	0	9.1	169 (99)
2002	0	6.3	181 (96)
2003	2.2	11.2	231 (170)
2004	1.2	7	260 (227)
2005	0	4.3	253 (211)
2006	0.3	14	286 (286)

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Streptococcus pyogenes

Annual Resistance Surveillance and Quality Control (RSQC) programme

Streptococcus pyogenes was included in the RSQC programme on antibiotic resistance in 2006 after a two-year pause. Approximately 2 600 clinical isolates of *Streptococcus pyogenes* (50–100 consecutive isolates from each of the clinical microbiology laboratories) have been tested for resistance to erythromycin, clindamycin and tetracycline, using the disk diffusion method. Laboratories were advised to interpret D-zones caused by interaction between erythromycin and clindamycin as clindamycin-R, thereby giving a presumptive identification of the resistance mechanisms. The national overview of these data is given in Figure 4.1.10.

The average low level of erythromycin resistance has remained stable. The even lower resistance to clindamycin indicates that the main mechanism of macrolide resistance in *Streptococcus pyogenes* is efflux-mediated (mef genes). Resistance to tetracycline is still above 10%.

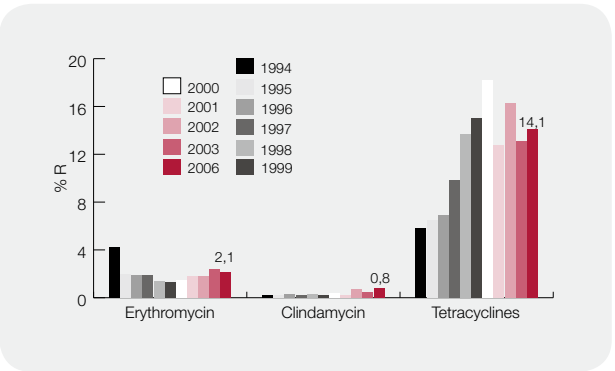

Figure 4.1.10. Resistance rates (resistant isolates in percent of all *Streptococcus pyogenes* isolates) for four groups of antibiotics 1994–2006.

Data on invasive isolates

Data on all positive blood cultures were obtained from nine laboratories using the laboratory information system ADBakt. From a total of 8235 positive blood cultures during 2006, 95 (1.2%)

were *Streptococcus pyogenes* (GAS). One of the isolates (1.1%) was resistant to erythromycin and clindamycin, and 11 (11.1%) were resistant to tetracycline.

Streptococcus agalactiae

Data on invasive isolates

Data on all positive blood cultures were obtained from nine laboratories using the laboratory information system ADBakt. From a total of 8 235 positive blood cultures during 2006, 114 (1.4%) were *Streptococcus agalactiae* (GBS). Five of the isolates (4.4%) were resistant to erythromycin and clindamycin. The majority of the isolates were retrieved from adults, but 17 (14.9%) were isolated from children < one year old.

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Escherichia coli

Annual Resistance Surveillance and Quality Control (RSQC) programme

Escherichia coli, mainly derived from urinary tract infections, has been included in the national surveillance program several times since 1996 and every year since 2001. Resistance to commonly prescribed oral antibiotics for treatment of UTI were tested each year. The average resistance rates to ampicillin have increased yearly, from 17 up to > 25% (Figure 4.1.11). The same trend is seen for trimethoprim with an average increase from 10 to 17%. Quinolone resistance, detected by the screening disk nalidixic acid since 2002, has shown an increase during this period and reached an average of 11.2% in 2006.

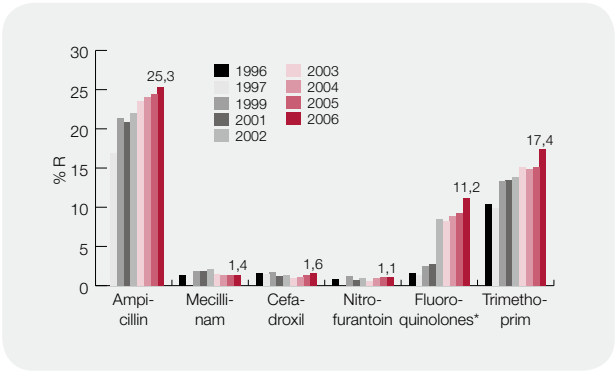

Figure 4.1.11. Resistance rates (resistant isolates in percent of all *Escherichia coli* isolates) for six antibiotics 1996–2006. * Between 1996–2001 fluoroquinolone resistance was detected with Norfloxacin, from 2002 with Nalidixic acid.

Data on invasive isolates reported to EARSS

Escherichia coli derived from invasive infections (blood isolates) have been part of the European Antimicrobial Resistance Surveillance System (EARSS) since 2001. Focus for the surveillance activities has been on resistance to beta-lactam antibiotics, especially occurrence of strains producing beta-lactamases with so called extended spectrum (ESBL), and on resistance to aminoglycosides and fluoroquinolones.

Twenty-one Swedish laboratories have taken part in this surveillance and have delivered data on more than 3 300 blood isolates in 2006. Results for 2001–2006 are presented in Table 4.1.6. Ampicillin resistance, caused by production of plasmid-mediated beta-lactamase (most often of TEM-type) was slightly higher in blood isolates than in the urine isolates tested in the RSQC programme, (Figure 4.1.11). However, the data was incomplete for the blood isolates since one third of participating laboratories do not include ampicillin in susceptibility testing of invasive isolates. The figures for Sweden are still much lower compared to most other countries in Europe where ampicillin resistance often exceeds 50%. The level of resistance to third generation cefalosporins among blood isolates has increased to 1.4% in 2006. In the majority of the cefotaxime-R isolates the resistance was attributed to the presence of ESBLs of CTX-M type. Aminoglycoside resistance in *Escherichia coli* is still extremely rare in Sweden. Resistance to fluoroquinolones increased for some years but has stabilised round 10% since 2004. Taking into account both resistant (R) and intermediate (I) isolates, the rates of quinolone resistance are almost the same in blood as in urine isolates.

Table 4.1.6. *E. coli* from blood cultures in Sweden 2001-2006, reported to EARSS.

Year	Ampi-cillin-R *	Cefo-taxime-R (ESBL / other	Aminogly-coside-R **	Fluoro-quino-lone-I/R ***	Total number
2001	26.5	0.5	1	5.5	2627
2002	24.9	0.5	0.6	7.1	3062
2003	28.5	0.4	1	8.3	3300
2004	23	0.5 / 0.6	1.5	11.1	3336
2005	26	0.9 / 0.4	1.5	8.9	3212
2006	28.1	1.3 / 0.1	1.7	8.7	3514

*Only 60% of isolates were tested against ampicillin; **gentamicin or tobramycin, *** ciprofloxacin.

Voluntary reporting and outbreaks – The Kristianstad outbreak of *E. coli* with ESBL

Spread of a multiresistant *Escherichia coli* carrying the gene for CTX-M-15 ESBL has occurred at a hospital in the south of Sweden. More than 35 patients were affected. In the majority of the cases the strain was isolated from urine samples, but in five cases from wounds and in three cases also from blood. Most of the patients were elderly women. There was an epidemiological link between 27 of the cases, having been treated in the same ward. Epidemiological typing by PFGE has verified this link.

The epidemic was detected in the autumn of 2005, and hygiene routines in the implicated ward were reinforced. Enhanced culturing was introduced, both of patients, environment and personnel. During late spring 2006 a second cluster of epidemiologically linked cases were detected. Regular follow-up of the patients by repeated cultures has shown that the period of carriage of the multiresistant strain has been more than one year in many cases.

Barbro Olsson-Liljequist, Gunnar Kahlmeter, Rolf Alsterlund

Klebsiella pneumoniae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Klebsiella pneumoniae was included in the 2005 RSQC programme for the first time in 1994. The reasons for this were that *Klebsiella pneumoniae* is one of the most important bacterial species from a hospital infection control point of view, and that this species was also included in the EARSS programme from July 2005. It should therefore be of value to have comparable resistance data from two sets of samples.

In the RSQC programme isolates from urine samples dominated, and both oral and intravenous antibiotics were tested (Figure 4.1.12). The data for 2006 indicate a decrease in resistance to aminoglycosides (from an already low level), quinolones (tested by nalidixic acid screen disk), and trimethoprim-sulfamethoxazole. However, these trends must be verified by comparable data collected during a longer period.

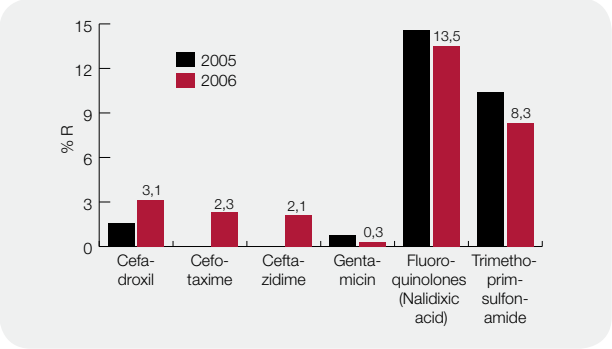

Figure 4.1.12. Resistance rates (resistant isolates in percent of all *Klebsiella pneumoniae* Isolates) for four groups of antibiotics 2005–2006.

Data on invasive isolates reported to EARSS

From 1st July 2005, participants in the EARSS network have contributed with data on blood isolates of *Klebsiella pneumoniae*. From Sweden a total of 281 isolates from 20 laboratories were reported in 2005, and 610 isolates in 2006. Results are shown in Table 4.1.7.

Table 4.1.7. *Klebsiella pneumoniae* from blood cultures in Sweden 2005–2006, reported to EARSS.

	2005 Total (% R)	2006 Total (% R)
Cefotaxime (ESBL / other R)	281 (0.7 / 0.7)	517 (1.0 / 0.5)
Aminoglycosides*	279 (1.4)	610 (0.3)
Fluoroquinolones**	265 (9.8)	530 (8.5)

*gentamicin, tobramycin, **ciprofloxacin

Voluntary reporting and outbreaks – The Uppsala outbreak of *Klebsiella pneumoniae* ESBL

Cases of both *Klebsiella pneumoniae* and Klebsiella oxytoca, exhibiting high-level resistance to third generation cefalosporins, often caused by ESBLs, are found with increasing frequencies. In *Klebsiella pneumoniae*, as in *Escherichia coli*, the ESBLs most frequently encountered are those of CTX-M-type. In *Klebsiella pneumoniae* they are present together with the species-specific chromosomal beta-lactamase SHV-1. In Klebsiella oxytoca no true ESBLs have been found, but a number of strains with hyperproduction of the chromosomal betalactamase typical of this species (OXY-1 or OXY-2) appear.

Multiresistant *Klebsiella pneumoniae* producing ESBL is locally reported to public health authorities in Uppsala county since 18 Sept 2006. ESBL from stool screening cultures has been diagnosed by culture on selective media and disk diffusion tests. PFGE typing is performed on clinical and screening culture isolates of *Klebsiella pneumoniae*, showing that all isolates with the same antibiogram belong to one outbreak strain. From May 2005 to March 2007, 232 patients carrying the strain have been found.

More than 90% of the patients come from Uppsala county and have been treated in Uppsala University Hospital. In the beginning of the outbreak, most of the cases were found by clinical urinary cultures. From October 2006, the majority of new cases carried the strain in stool only. From October 2006- February 2007, all patients admitted to Uppsala University Hospital were screened on admission and discharge, in total more than 16 000 cultures. The patients have been geriatric or surgical/immunosuppressed. No cases have been found in intensive care units since screening started.

Transmission has occurred by direct and indirect contact, and probably faecal-orally. Risk factors of importance has been antimicrobial chemotherapy with monobactams, cephalosporins and quinolones. Patients with a urinary culture positive for the outbreak strain are >5 times more likely to have diarrhoea, urinary catheter, enteral feeding and discharging wounds when compared to patients with *E. coli* in their urine and nursed in the same wards.

The hospital has undertaken several measures to reduce transmission and to lower patients' risk of exposure to the strain. Basic precautions have been reinforced. Usage of hand disinfection has been doubled, reaching a level of > 90mL per patient day as an average for all wards.

The incidence of new cases is going down during the spring months, both in 2005, 2006 and 2007. This is also the experience from other countries experiencing similar outbreaks. Therefore one cannot yet say that the outbreak has been adequately controlled.

Ulrika Ransjö, Barbro Olsson-Liljequist, Gunnar Kahlmeter

Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Data in the RSQC programme on *Pseudomonas aeruginosa* for 2006 is compared to data from all Swedish laboratories in 2003 and 2004 (Figure 4.1.13). All these isolates were selected and tested in the same way, i.e. respiratory tract isolates were excluded, and tests were performed by disk diffusion. There were small fluctuations in resistance rates for all antibiotics, the most surprising being the decrease in quinolone resistance from 14 to 10%.

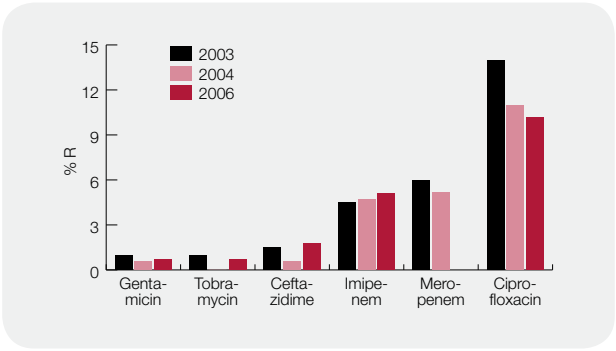

Figure 4.1.13. Resistance rates (resistant isolates in percent of all *Pseudomonas aeruginosa* isolates) for four groups of antibiotics 2003–2006.

Data on invasive isolates reported to EARSS

From July 1st 2005, participants in the EARSS network have been asked to contribute with data on blood isolates of *Pseudomonas aeruginosa*. From Sweden a total of 149 isolates from 20 laboratories were tested during the second half of 2005, and these data are compared to data for 2006 (Table 4.1.8). An unexpectedly high rate of imipenem resistance was seen in 2005. This could probably be explained by selective testing and reporting of data during this first year. The level of imipenem resistance in 2006 was lower and more in agreement with the data from the RSQC programme (Figure 4.1.13).

Table 4.1.8. *Pseudomonas aeruginosa* from blood cultures in Sweden 2005-2006, reported to EARSS.

	2005 Total (%R)	2006 Total (%R)
Ceftazidime	149 (4.7)	296 (2.6)
Imipenem	57 (17.5)	226 (4.4)
Aminoglycosides*	149 (0.0)	243 (0.5)
Fluoroquinolones **	133 (9.0)	247 (10.4)

* gentamicin, tobramycin, ** ciprofloxacin

Barbro Olsson-Liljequist

Haemophilus influenzae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Haemophilus influenzae was not included in the RSQC programme on antibiotic resistance in 2006.

Helicobacter pylori

Annual Resistance Surveillance

Helicobacter pylori derived from gastric biopsies has been monitored locally at a few laboratories. In vitro resistance to metronidazole has been reported in 10–40% of Scandinavian isolates. Resistance to clarithromycin is less common but increasing and has locally (one laboratory) reached over 10% since 2004 and was as high as 16% in 2006. Frequencies of resistance to clarithromycin and metronidazole in clinical isolates from southwest of Sweden are presented in Table 4.1.9, representing a population of approximately 300 000.

Table 4.1.9. *Helicobacter pylori* University Hospital MAS, Malmö, Sweden 2001–2006, % R.

Year	Total number	Clarithro-mycin	Metronida-zole
2001	188	8.8	40.2
2002	124	9.0	44.1
2003	112	7.2	42.6
2004	151	11.6	41.0
2005	217	11.2*	nt
2006	257	16.0*	nt

* Molecular biology technique from 2005

Salmonella and *Shigella spp.*

Annual Resistance Surveillance

Salmonella spp. and *Shigella* spp. derived from faecal cultures have been monitored locally by a few laboratories. Since most of the *Salmonella* and more than 90% of the *Shigella* strains isolated in Sweden originate from Swedes having visited a foreign country, the resistance patterns reflect the geographical origin. Too few strains are included in the Swedish survey to obtain conclusive results. However fluoroquinolone resistance is high, between 20–25%, among *Salmonella* strains, and among *Shigella* spp isolates producing ESBL have been detected.

Campylobacter spp.

Annual Resistance Surveillance

Campylobacter spp. derived from patients with diarrhoea has been monitored locally at a few laboratories. Approximately 50% of *Campylobacter* strains are imported. Since resistance to fluoroquinolones is of major concern worldwide it is interesting to notice that the small decline in quinolone resistance among *Campylobacter* isolates noticed a few years ago has now regained the former level of about 50% (Table 4.1.10). When screening for fluoroquinolone resistance using nalidixic acid disks was introduced in Sweden in 2001, it was expected to influence the resistance rates dramatically. The data for nalidixic acid and ciprofloxacin in parallel show, however, that the two disks are equally able to detect quinolone resistance in *Campylobacter*.

Mats Walder

Table 4.1.10. *Campylobacter jejuni/coli* University Hospital MAS, Malmö, Sweden 2001–2006, % R.

Year	Nalidixic acid	Ciprofloxacin	Tetracycline	Erythromycin
2001	32	30	28	1
2002	29	28	30	0.5
2003	48	46	22	0
2004	50	47	29	2
2005	57	52	18	1
2006	50	44	21	4

Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable disease/infection and in 2006, 677 clinical cases of the infection were reported. Most of the cases were identified in the three largest counties of Sweden, which comprise the cities Stockholm, Göteborg and Malmö, respectively. Clinical isolates were characterised at the Swedish Reference Laboratory for Pathogenic *Neisseria*, Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden and at the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden.

In 2006, isolates from 348 of the notified clinical cases were completely characterised at these laboratories, representing 51% of the notified cases. In total, 352 different *N. gonorrhoeae* strains were cultured from these cases (n=348). Susceptibility testing was performed according to standardized methodology using Etest for MIC determination of ampicillin, cefixime, ceftriaxone, azithromycin, ciprofloxacin, and spectinomycin. The used SIR-breakpoints have been determined by The Swedish Reference Group for antibiotics (SRGA; http://www.srga.org). Production of beta-lactamase was examined by using Nitrocefin discs. Results for 2006 are compared with those from 2000 to 2005 in Table 4.1.11.

Hans Fredlund, Magnus Unemo

Table 4.1.11. Antibiotic resistance rates (%) and β-lactamase production of Swedish *Neisseria gonorrhoeae* strains from 2000 to 2006.

	2000 (n=131)	2001 (n=141)	2002 (n=120)	2003 (n=130)	2004 (n=149)	2005 (n=497)*	2006 (n=352)*
Beta-lactamase pos.	37	37	39	22	26	23	30
Penicillin G	42	38	48	-	-	-	-
Ampicillin	37	37	39	22	26	23	30
Cefuroxime	2	0	4	-	-	-	-
Cefixime	-	-	0	0	0**	0	0
Ceftriaxone***	-	-	0	0	0	0	0
Azithromycin	-	-	0	<1	0**	0	1
Tetracycline	52	56	54	-	-	-	-
Ciprofloxacin***	47	52	58	56	51	49	61
Spectinomycin	0	0	0	0	0	0	0

(- = not analysed)

* Data from the Swedish Reference Laboratory for Pathogenic *Neisseria*, Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden and the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. From 2000 to 2004, only data from the Swedish Reference Laboratory were reported.

** *N. gonorrhoeae* strains resistant to azithromycin (n=14) and to cefixime (n=2) were identified in Stockholm, Sweden during 2004 (Personal communication, Bengt Wretlind, Karolinska University Hospital Huddinge).

*** For ceftriaxone and ciprofloxacin, new SIR breakpoints were introduced in 2006 and the results from previous years have been recalculated.

Neisseria meningitidis

Notifications according to the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease. In 2006, 52 clinical cases of the disease were reported. A total of 44 clinical isolates from blood or cerebrospinal fluid were analysed at the Swedish Reference Laboratory for pathogenic *Neisseria*, Department of Clinical Microbiology, Örebro University Hospital.

Susceptibility testing was performed according to standardized methodology using Etest on Müller Hinton II agar medium with 5% defibrinated horse blood for determination of MIC for bensylpenicillin (pcG), fenoxymethylpenicillin (pcV), cefotaxime, ciprofloxacin, chloramphenicol and rifampicin. Production of beta-lactamase was examined by Nitrocefin discs.

None of the isolates produced beta-lactamase. Eight isolates (18%) had reduced susceptibility to pcG (MIC>0.064 mg/L). The MIC for pcV is normally 5–10 times higher. All the isolates had cefotaxime – MIC ≤0.008 and ciprofloxacin – MIC ≤0.008. Chloramphenicol – MIC varied between 0.094 and 1.5 and rifampicin was not higher than 0.094 mg/L.

The MIC breakpoints within the SIR-system (as determined by SRGA, www.srga.org) are for pcG 0.25/1 (e.g. sensitive ≤0.25 mg/L and resistant >1 mg/L), pcV 1/1, cefotaxime 0.12/0.12, ciprofloxacin 0.03/0.06, chloramphenicol 2/8 and rifampicin 1/1.

Per Olcén

Mycobacterium tuberculosis

The total number of new cases of TB diagnosed in Sweden decreased from 571 during 2005 to 498 in 2006 (-13%). Eighty per cent (%) of the cases were confirmed by culture in 2006 compared to 78% in 2005.

Resistance against at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) was reported in 44 patients i.e. 10.9% of the 395 patients with culture confirmed *M. tuberculosis*. This proportion was somewhat lower than the 11.6% resistant cases reported in 2005, Table 4.1.12.

Resistance to isoniazid was reported in 9.6% of the patients, followed by rifampicin in 1.5%, pyrazinamid in 1.5% and ethambutol in 0.3%. Multi-drug resistance (MDR) i.e. combined resistance against at least isoniazid and rifampicin (MDR-TB) was reported in three patients, all of them born abroad and one of them with relapse after previous treatment for MDR TB in Sweden in 2001.

Resistant TB was reported in 9.3% of the Swedish born TB patients (10/108) and in 11,6% of patients born abroad (33/ 285). Four of the ten Swedish born TB patients with resistant TB were children or young adults born to immigrated parents. Four of the 44 patients with resistant TB had a previous history of TB after 1949 i.e 19% of the total 21 patients with a culture confirmed relapse in 2006.

Isolates from a total of 20 of the 44 patients with resistant TB were identified by RFLP (restriction fragment length polymorphism) typing to belong to 11 different "clusters". Eight of these patients belonged to one big cluster (cluster 49) comprising in total 104 patients with isoniazid resistant *M. tuberculosis* diagnosed in Sweden from 1996 through 2006.

The proportion of patients with isoniazid resistant *M. tuberculosis* has increased from about 5 to 6% during the period from 1991 to 1998 to about 9 to 10% per year 1999–2006. During the same two periods MDR-TB was reported in 1% and 1.3% of all culture confirmed cases, respectively, which corresponds to an average of five cases per year during the whole period from 1991 to 2006.

XDR-TB is defined as MDR-TB and in addition resistance to any fluoroquinolone and at least one of the three injectable drugs: capreomycin, kanamycin and amikacin. In Sweden, so far two cases have been identified with XDR-TB.

Genetic typing with RFLP indicate ongoing spread of isoniazid resistant strains of *M. tuberculosis*, especially in the Stockholm area. Most cases occurred in the foreign born population, half of them from Africa. However, several cases have also been identified in the Swedish born population. Furthermore, latent tuberculous infection have been diagnosed in an unknown number of contacts to patients with isoniazid resistant tuberculosis.

Sven Hoffner, Victoria Romanus

Antifungal resistance

There is no aggregated data of antifungal resistance for 2006.

Table 4.1.12. Drug resistant tuberculosis in Sweden. Resistance among initial isolates of *Mycobacterium tuberculosis*i or *africanum* to at least one of the four drugs: isoniazid, rifampicin, ethambutol or pyrazinamid.

Year of diagnosis	2000	2001	2002	2003	2004	2005	2006
No of culture confirmed *M. tuberculosis* or *M. africanum*	366	354	346	345	368	448	395
Any resistance total (%)	12.3	10.7	10.4	9.28	11.7	11.6	10.9
Isoniazid	10.1	8.8	9.8	7.5	9.5	10.3	9.6
Rifampicin	1.4	1.7	1.2	2.9	1.6	1.1	1.5
Ethambutol	0.5	0.8	0.3	1.4	0.8	0.7	0.3
Pyrazinamid	3.0	1.7	1.2	2.0	3.3	1.3	1.5
Isoniazid + rifampicin (MDR)	1.4	1.1	1.2	2.3	1.4	0.9	0.8

5. National and regional projects

5.1 Individually based data on antibiotic use

Antibiotic resistance is a growing problem and is partly due to overuse of antibiotics. Previously, only data on the volume of purchased antibiotics has been available in Sweden. Since July 2005, the Swedish National Board of Health and Welfare supplies individually based data on antibiotic use in out-patient care. This data enables individually based analyses, e.g. number of purchases per person or number of individuals who have purchased antibiotics during a specific period of time (number of patients).

The aim of the study was to collect data from the National Board of Health and Welfare to (i) determine the proportion of the Swedish population that purchased at least one course of antibiotics during one year (number of patients), (ii) examine whether the same individuals received several courses of antibiotics, (iii) study the most common groups of antibiotics and (iv) see how the sale was distributed according to gender, age and among the different counties of Sweden.

Antibiotic sales data from the National Board of Health and Welfare were received in tables of frequency. Analyses were made on individually based anonymous data collected for the period July 1st 2005 – June 30th 2006. Total data is presented for the country and divided per county. The total number of patients and the number of patients per 1000 inhabitants is presented as well.

As presented in Table 5.1.1, 2 198 164 persons (24%) of the Swedish population purchased at least one course of antibiotics during one year. Women made 58% of the purchases and men 42%. Treatment with antibiotics was most common in the age groups 3–6 years and ≥80 years. In the age group ≥80 years, 1.2% of the men and 1.9% of the women received more than 10 courses of antibiotics. The counties with the highest number of patients per 1000 inhabitants were Stockholm (270), Skåne (260) and Halland (260). The lowest numbers of patients per 1000 inhabitants were seen in Jämtland (200), Dalarna (200) and Västerbotten (190), Figure 5.1.1. Five percent of the population received penicillin V, which was the most commonly used antibiotic, followed by doxycycline (1.9%), flucloxacillin (1.5%) and amoxicillin (1.1%).

These new individually based data give possibilities to a detailed image of the use of antibiotics in Sweden.

Anita Tapia, Christer Norman, Cecilia Stålsby Lundborg

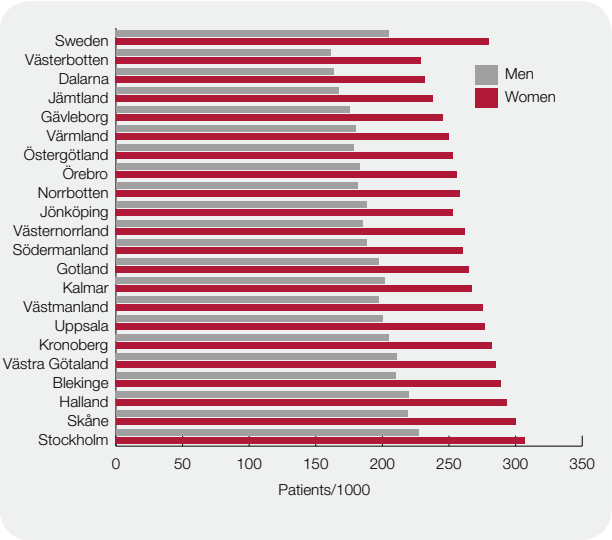

Figure 5.1.1. July 1st 2005 – June 30st 2006. Number of individuals (patients) that have purchased at least one course of antibiotics (J01) per 1000 inhabitants, by county and gender.

5.2 For which diagnoses are fluoroquinolones and tetracyclines prescribed? Results from the Strama 2005 diagnosis prescribing survey

Strama conducted for the third time a diagnosis prescribing survey in 2005. This time the study was conducted in the whole or parts of seven counties as compared to in five counties in the two previous surveys in 2000 and 2002. Preliminary results from changes in prescribing pattern were presented in Swedres 2005. In total information regarding 7 498 infectious episodes in primary care were collected in the 2005 study. The GPs were asked to fill a form for all patients seeking for an infectious complaint. In reports from the diagnosis prescribing survey the results are commonly reported using the diagnosis as the base, i.e. which antibiotics are prescribed for a certain diagnosis. Here we present some figures from the drug perspective, i.e. for which diagnoses certain antibiotics are prescribed. We have chosen to present the diagnoses for which fluoroquinolones and tetracyclines are prescribed (Tables 5.2.1 and 5.2.2, respectively).

Table 5.1.1. Antibiotics in Sweden July 1st 2005 – June 30th 2006. Number of patients and number of patients per 1000 inhabitants, by gender and age group.

	Patients			Patients/1000		
Age (years)	Men	Women	Total number of patients	Men	Women	Total number of patients/1000
0–2	42 019	34 813	76 832	269	235	252
3–6	69 477	65 765	135 242	360	359	359
7–15	86 075	89 617	175 692	166	182	174
16–64	516 835	773 578	1 290 413	176	271	224
65–79	136 540	184 733	321 273	272	321	296
80–	69 151	129 561	198 712	393	417	405
Total	**920 097**	**1 278 067**	**2 198 164**	**205**	**280**	**243**

Table 5.2.1. Number of fluoroquinolone prescriptions (%) presented per diagnosis.

Diagnosis	Number of fluoroquinolone prescriptions (%)
Common cold	1 (0.5)
Pneumonia	2 (1)
Acute otitis media	1 (0.5)
Acute bronchitis	1 (0.5)
Lower and recurrent urinary tract infections	155 (64)
Upper urinary tract infection	40 (16)
Urethritis	3 (1)
Skin and soft tissue infection	5 (2)
Fever of unspecified origin	1 (0.5)
Other diagnosis	29 (12)
No diagnosis given	5 (2)
Total	**243 (100)**

Ciprofloxacin was prescribed in 124 cases and norfloxacin in 118 cases, while ofloxacin was prescribed in one case.

Table 5.2.2. Number of tetracycline prescriptions (%) presented per diagnosis.

Diagnosis	Number of tetracycline prescriptions (%)
Throat infection	9 (2)
Common cold	17 (4)
Pneumonia	98 (21)
Acute otitis media	5 (1)
Acute sinusitis	65 (14)
Acute bronchitis	119 (26)
Acute exacerbation of chronic bronchitis	58 (13)
Unspecified respiratory tract infection	24 (5)
Lower and recurrent urinary tract infections	2 (0.5)
Urethritis	6 (1)
Skin and soft tissue infection	3 (0.5)
Other diagnosis	44 (10)
No diagnosis given	7 (2)
Total	**457 (100)**

In all cases except 11 the tetracycline used was doxycycline.

The results show that fluoroquinolones to a high extent is used for the non recommended indication lower urinary tract infection in women. In 58% of the 155 cases where a fluoroquinolone was prescribed for lower UTI it was prescribed for a woman (not shown). In addition, the results show that tetracyclines are commonly used for acute bronchitis, a diagnosis where the use of antibiotics has been questioned.

In conclusion these results show that there is still room for improvement in the antibiotic prescribing patterns among Swedish GPs.

Cecilia Stålsby Lundborg, Åsa Vernby, Sigvard Mölstad

5.3 Public knowledge of antibiotic treatment: preliminary results from a Strama-questionnaire in Sweden

To assess knowledge and expectation on antibiotic treatment among the general public, which is assumed to contribute to inappropriate antibiotic prescribing, a telephone-based questionnaire survey was conducted in February and March 2006. A letter with information was sent to 1000 randomly selected persons aged 21–80 in the whole country. Structured interviews were completed with 747 individuals.

Knowledge of antibiotic treatment- and resistance seemed high. Most respondents had heard of penicillin and also believed that antibiotics are effective against bacteria. One third believed that antibiotics are effective against viruses. Only 19% agreed that antibiotics pass on common colds more quickly. Almost 95% disagreed that you can end a prescribed regimen if you feel better. Only 54% of the respondents could mention any antibiotic drug when asked. Penicillin was mentioned by 14% and Kåvepenin by 24%. More respondents (74%) agreed with the statement "Pharmacists often inform on antibiotic use", than with the statement "Doctors often inform on antibiotic use" (51%). Also more of those agreeing that doctors inform, agreed that they trust the doctor, both when antibiotics are prescribed (91%) and when antibiotics are not prescribed (92%).

In general, less trust in the doctor prescribing an antibiotic drug was consistent with higher educational level. In conclusion, better patient-doctor communication could lead to increased patient satisfaction when antibiotics are not prescribed, as well as increased trust that patients accept the decision on antibiotic prescribing, among doctors.

Johanna Berg, Cecilia Stålsby Lundborg

5.4 The Strama Point Prevalence Study, PPS 2006

Strama has initiated point prevalence studies, PPSs, as a nation wide survey system to describe and analyse the use of antimicrobials in relation to diagnose in hospital care. In November 2006 the third study was performed with identical design as in the previous studies in 2003 and 2004.

From the results of the two initial studies, three areas were identified for intervention towards a more rational use of antibiotics in hospitals. First, the duration of peri-operative prophylaxis is too long. Secondly, antimicrobials with narrow spectrum can be used in a higher degree in treatment of patients hospitalised for community-acquired pneumonia in Sweden. Thirdly, the use of fluoroquinolones should be restricted in several indications, especially in community-acquired cystitis in women.

Demographic data of the three studies are presented in Table 5.4.1. The studied population in 2006 approximates 77% of all patients admitted to somatic medical care in Swedish hospitals during one day.

Table 5.4.1. Demographic data.

PPS	2003	2004	2006
Participating Strama-groups (out of 21)	19	18	20
No. of hospitals involved	54	49	64
University hospitals	9	7	9
County hospitals	20	19	23
Local hospitals	25	23	32
No. of patients admitted	13 536	11 348	17 113
No. of patients treated	4 178	3 622	5 588
Percent treated	30.9%	31.9%	32.6%
Patients treated at:			
University hospitals	1 538	1 112	2 040
County hospitals	1 855	1 734	2 325
Local hospitals	785	776	1 223
Percent women treated	49.9%	49.9%	49.4%
No. of children treated	266	192	280

Table 5.4.2 shows the indications for the antibiotic therapy. Since one patient can have more than one therapy reason the total percentage is higher than the percentage of treated patients. Hospital acquired infection includes only those treated with antimicrobials.

Table 5.4.2. Indications for antibiotic therapy in percent of all patients admitted to somatic medical care.

	2003	2004	2006
Community-acquired infection	17.0	18.0	18.7
Hospital acquired infection	9.2	9.4	9.9
Perioperative prophylaxis	4.6	4.5	4.7
Medical prophylaxis	1.7	1.9	1.8

The most frequently used antimicrobial drugs in treatment are cephalosporins. Table 5.4.3 shows the distribution of the drugs in treatment and peri-operative and medical prophylaxis. Isoxazolyl-penicillin is the most frequently used group regarding prophylaxis. The total amount of antimicrobials used for adults was 43.4 DDD/100 admitted patients in the 2006 study.

The 2006 PPS result shows a decrease of peri-operative treatments longer than one day from 47% in 2003 to 31% in 2006. The single-dose peri-operative prophylaxis in lower gastrointestinal tract surgery has increased from 62% to 77%. Co-trimoxazole was used in 45% of the therapies and cephalosporins in 41%.

In pneumonia, cephalosporins are still the most commonly used class of antibiotics. There was no change in their use between 2003 and 2006 (Figure 5.4.1).

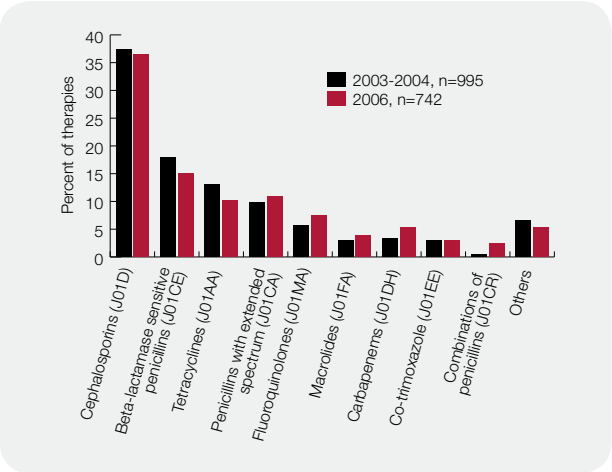

Figure 5.4.1. Comparison of pooled data from 2003 and 2004 with 2006 of the distribution of antimicrobials in treatment of community-acquired pneumonia, percent of the total number of therapies.

Table 5.4.3. Most commonly used antibiotics for adults in percent of DDD for treatment and for prophylactic use.

	2003		2004		2006	
	Therapy	Prophylaxis	Therapy	Prophylaxis	Therapy	Prophylaxis
No. of DDD	4 084	1 000	3 708	904	5 675	1 328
Cephalosporins	22	18	23	15	23	16
Isoxazolyl-penicillins	12	45	12	45	10	53
Fluoroquinolones	12	9	13	7	12	4
Broad-spectrum penicillins	10	4	10	4	9	<1
Beta-lactamase sensitive pc	9	3	8	3	7	3
Imidazoles	5	7	3	7	5	8
Tetracyclines	5	3	5	4	5	2
Carbapenems	4	<1	5	<1	6	<1

For urinary tract infections in women the use of pivmecillinam and trimethoprim increased while the use of fluoroquinolones declined (Figure 5.4.2). The fluoroquinolone consumption is still probably too high as the diagnosis community-acquired cystitis most probably includes many asymptomatic bacteriurias.

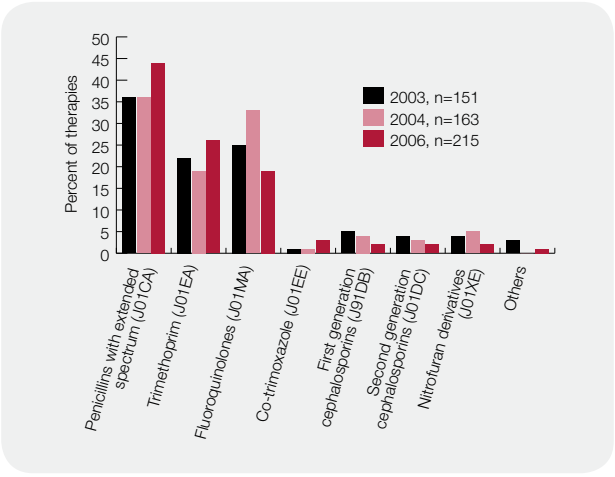

Figure 5.4.2. Distribution of antimicrobials in treatment of community-acquired cystitis in women, percent of the total amount of therapies.

In summary, following the interventions during 2005 and 2006, the 2006 PPS shows the desired changes with shorter peri-operative prophylaxis and a lower use of fluoroquinolones in treatment of community-acquired cystitis in women. However, in treatment of community-acquired pneumonia the cephalosporins still dominate and are included in more than 35% of all therapies.

Gunilla Skoog, Mats Erntell

5.5 New Swedish guidelines for treatment of lower urinary tract infection in women

In November 2006 the Swedish Medical Products Agency in collaboration with Strama arranged an expert meeting to prepare new treatment guidelines for lower urinary tract infection in women. The guidelines were presented in March 2007 and the main messages are:

- Acute cystitis is harmless in almost all cases and about 30% of the patients recover within a week without treatment.
- Treatment with antibiotics aims primarily to reduce the duration of symptoms.
- Clinical history is important. When typical new symptoms occur (dysuria, urgency and urinary frequency) in a non-pregnant woman there is usually no need for further diagnostics.
- The bacterial resistance in the local area and the patients' age and kidney function are factors that influence the choice of antibiotics.
- Pivmecillinam and nitrofurantoin are equal first line treatment with low resistance for *E. coli*. Despite high resistance rate trimethoprim can still be considered for empirical treatment.
- Three to five days of treatment is usually sufficient.
- Suspected cystitis during pregnancy should be object for urinary culture and treatment should be started without waiting for the result of the culture.
- Asymptomatic bacteriuria should not be treated with antibiotics except during pregnancy.
- Strongly smelling urine and unspecific symptoms like anxiety and confusion in elderly in institutional care should not be regarded as causes for treatment of lower urinary tract infection.
- Methenamine hippurate is not recommended as prophylaxis against recurrent cystitis.

Christer Norman

5.6 The Trimethoprim Intervention in the County of Kronoberg

Since antibiotic resistance in bacteria can be associated with a biological fitness cost it is assumed that a reduction in antibiotic use is followed by a reduction in resistance rates. Over the last 10 years trimethoprim (TRI) resistance in *Escherichia coli* has increased in Sweden. In Kronoberg county, the trimethoprim resistance has increased from 7% (1990) to 11% (2004). So far no prospective intervention in the community has been carried out to investigate whether a substantial decrease in the use of a single antibiotic will result in a corresponding decrease in antibiotic resistance.

Physicians (n=564) in Kronoberg county were convinced, by personal visits and mail, to cease using trimethoprim and trimethoprim-sulfamethoxazole during 24 months starting October 1st 2004. Monthly sales data for oral antibiotics were retrieved from the National Corporation of Swedish Pharmacies and made known to the physicians. All *E. coli* isolates from urinary tract specimens at the Dept of Clinical Microbiology, Växjö, were included in the analysis. The susceptibility testing methodology was stable since 1990 and the baseline consisted of quantitative

data from 1991–2004. An immediate and sustained decrease of 85% in total use of trimethoprim was achieved (Figure 5.6.1.). Trimethoprim use was in most cases replaced by pivmecillinam, nitrofurantoin and ciprofloxacin. A total decrease of 4% in antibiotics used for the treatment of UTIs was registered. Resistance to trimethoprim did not decrease (10 and 12% in 2005 and 2006, respectively). Resistance to nitrofurantoin and mecillinam did not increase despite a substantial increase, 31 and 69% respectively, in the use of these drugs. Resistance to fluoroquinolones increased from 4–10% between 2000 and 2006.

A two year substantial and sustained decrease in the use of trimethoprim did not result in a clinically useful change in resistance rates. Whether the increase in fluoroquinolone-resistance was related to the increase in use remains to be evaluated. During the intervention all *Enterobacteriacae* isolated from urinary tract infections in Kronoberg were stored. So far 4 200 of these have been phenotyped using th PhenPlateTM System. The frequency of the five most common dfr-genes, encoding trimethoprim resistance have been analysed during three time periods of the intervention. Growth experiments are being performed in order to evaluate the fitness cost of resistance in clinical isolates.

Martin Sundqvist

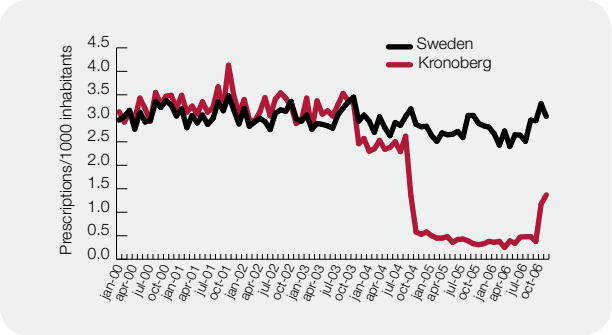

Figure 5.6.1. Total number of trimethoprim and trimethoprim-sulfamethoxazole prescriptions in Sweden and Kronoberg county 2000–2006.

5.7 ICU-Strama and CARE-ICU

ICU-Strama was established in 2000 within the framework of Strama. Since 2005, ICU-Strama has invited ICUs and national networks from all EU countries to participate in the project and it has been renamed "CARE-ICU": Controlling Antibiotic Resistance in ICUs. CARE-ICU is funded by the European Commission (DG SANCO) through a work-package within the IPSE-project "Improving surveillance and controlling antibiotic resistance in ICU" (http://ipse.univ-lyon1.fr/). Participants are national ICU-networks and individual ICUs.

The aim of ICU-Strama and CARE-ICU is to provide a web-based application for the coordinated collection of information about antibiotic policy, antibiotic use, antibiotic resistance, infection control, intensive care demography and to feed back these data. The purpose is also to use these data ("data for action") to optimise antibiotic use, infection control and reduce ICU-acquired infections and to prevent the emergence of antibiotic resistant strains within the ICUs. The aim is furthermore to establish best practice as regards antibiotic policy and hygiene interventions. This may vary between and within ICUs and will certainly vary over time, but as this is a long-term project, it will allow continuous revision in the struggle to control antibiotic resistance. The project has a local perspective and has become a resource for local initiatives aimed at promoting more appropriate use of antibiotics and improved infection control. The incentive for participating has been the possibility of receiving statistical analyses of antibiotic consumption, antibiotic resistance and quality of infection control for each individual ICU and national network.

Håkan Hanberger

5.8 A study of the causes for geographical differences in antibiotic prescribing

There is a great variation in the number of antibiotic prescriptions between Swedish counties and municipalities, especially for children aged 0–6 years. The reason for this is unknown.

Based on official statistics we studied children living in municipalities with low antibiotic prescription rates versus those living in municipalities with high antibiotic prescription rates. Our aim was to find possible explanations for the different antibiotic prescribing patterns by studying socioeconomic factors, concern about infectious illness, infectious symptoms and physician consultations. The study took place between October and April. All 18-month old children who came to an ordinary control at the health clinic were asked to participate. Parents of 73% of the children (n=848) completed a log book registration of all infectious symptoms and measures taken during one month.

There were no differences in number of symptom days between the groups. In the high prescription area 20.5% of the children consulted a physician. The corresponding figure in the low prescription area was 15.8%. Of the children 11.6% in the high prescription area and 4.7% in the low prescription area were prescribed antibiotics. The differences remained after adjustment for socioeconomic factors, daycare, concern about infectious illness and infectious symptoms more than 7 days.

The differences between the high and low prescription areas in terms of antibiotic prescription rates could not be explained by differences in reported infectious symptoms, differences in socioeconomic factors, daycare, concern about infectious illness in the family or physician consultations.

Katarina Hedin

Appendix 1. Abbreviations

AST Antibiotic susceptibility testing

ATC The Anatomical Therapeutic Chemical classification system

DDD Defined daily dose

DST Drug susceptibility testing

EARSS European Antimicrobial Resistance Surveillance System

ICU Intensive care unit

MDR Multidrug resistance

MIC Minimal Inhibitory concentration

MLST Multi Locus Sequence Typing

MRSA Methicillin resistant *Staphylococcus aureus*

PFGE Pulsed field gel electrophoresis

PNSP Penicillin non-susceptible pneumococci, MIC ≥ 0,12 mg/L

PRP Penicillin non-susceptible pneumococci, MIC ≥ 0,5 mg/L

PVL Panton-Valentine leukocidin

RSQC Resistance Surveillance and Quality Control Programme

RTI Respiratory tract infection

SRGA-M The Swedish Reference Group of Antibiotics- subcommittee on Methodology

ST Sequence type

Strama Swedish Strategic Programme against Antibiotic Resistance

TB Tuberculosis

UTI Urinary tract infection

VRE Vancomycin resistant enterococci

Appendix 2. Demographics and denominator data

Table App 2.1. Population by county and age group December 31st, 2005.

	0-6 years	7–19 years	20–59 years	60–79 years	80-years	All ages
Stockholm	162 944	295 674	1 052 582	293 884	84 861	1 889 945
Uppsala	23 763	51 258	166 305	49 316	13 725	304 367
Södermanland	19 094	44 304	130 982	52 503	15 012	261 895
Östergötland	30 017	69 376	216 767	76 814	23 329	416 303
Jönköping	25 057	57 982	166 168	61 329	19 643	330 179
Kronoberg	12 788	29 569	91 260	34 121	10 705	178 443
Kalmar	15 166	38 875	115 652	49 176	15 075	233 944
Gotland	3 699	9 938	29 229	11 387	3 235	57 488
Blekinge	10 596	23 756	75 431	31 847	9 066	150 696
Skåne	87 569	187 694	615 019	214 876	64 306	1 169 464
Halland	22 393	50 017	143 923	53 824	15 711	285 868
Västra Götaland	114 606	251 070	810 154	270 527	82 149	1 528 506
Värmland	18 047	44 583	137 291	56 565	16 802	273 288
Örebro	19 683	45 353	140 353	52 391	16 341	274 121
Västmanland	18 596	43 843	133 083	51 420	14 449	261 391
Dalarna	18 408	46 546	137 036	56 485	17 280	275 755
Gävleborg	18 404	44 868	138 429	57 510	16 783	275 994
Västernorrland	16 930	38 719	121 427	51 903	14 757	243 736
Jämtland	8 515	20 784	64 004	25 469	8 256	127 028
Västerbotten	17 913	42 741	135 926	47 986	13 086	257 652
Norrbotten	16 878	41 147	128 958	52 164	12 593	251 740
Total country	**681 066**	**1 478 097**	**4 749 979**	**1 651 497**	**487 164**	**9 047 803**

Table App 2.2. Population of Sweden 2004–2006 (the numbers represents the population on December 31st the previous year).

	2004	2005	2006
Population	8 975 669	9 011 391	9 047 803

Table App. 2.3. Number of admissions and patient-days in somatic medical care 1997–2005.

	Admissions	Patient-days
1997	1 536 549	10 308 954
1998	1 534 480	10 166 192
1999	1 494 701	9 635 382
2000	1 446 371	8 908 831
2001	1 439 003	8 873 260
2002	1 421 954	8 670 503
2003	1 421 614	8 545 109
2004	1 433 826	8 424 038
2005	1 452 515	8 385 110

Table App 2.4. Denominator data from the microbiological laboratories. NP=test not performed

	Number of analyses 2006							Number of positive cultures 2006			
Laboratory	Blood (pair of bottles)	Cerebro-spinal fluid (CSF)	Nasopharynx	Throat	General culture	Screen MRB	Faeces SSYC	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*E coli*
Borås	11997	162	3592	4686	10049	1013	6391	4126	704	741	6905
Eskilstuna	7331	167	5263	4728	8057	1664	4533	3526	777	567	7295
Falun	10348	215	2337	1649	4537	3235	4504	3492	392	395	7021
Gävle	8003	164	1721	1246	6954	1512	3305	3075	329	273	5850
Göteborg	27594	1452	3238	4327	15702	20447	14071	10829	763	953	16258
Halmstad	9128	144	2913	3066	8559	8750	6019	3082	620	634	6453
HS, Stockholm	28326	1942	15419	5847	30683	60350	11501	12570	562	1679	19692
Jönköping	12340	205	2980	4280	11450	9140	6400	4530	520	860	9220
Kalmar	7860	313	3699	3087	8014	16239	4468	4188	546	474	8375
Karlskrona	3945	58	13337	2400	5395	705	3360	1964	254	356	4187
Karlstad	12570	189	971	2244	11674	4081	4453	5582	298	553	6928
Kristianstad	7181	101	5538	5097	11610	8221	5605	4420	975	789	8666
KS, Stockholm	26437	2151	21628	9289	45256	61313	13607	10149	2667	1574	18284
*Linköping**	13005	686	4722	2948	15327	31172	7280	6362	758	602	7938
Lund	21350	1302	12028	7398	22605	16420	13649	9559	2729	1665	18311
Malmö	18617	365	5771	7685	22619	29076	14890	7703	1608	1519	14890
Medilab	NP	NP	11770	5339	7979	9667	8772	4012	1723	921	9068
St Göran (Capio)	5832	157	5588	4470	13924	28841	7987	4984	867	959	9263
*Skövde**	10638	79	2544	2125	6157	3778	4954	3607	465	590	9489
*Sunderby, Luleå***	7149	132	2971	3839	7428	288	3489	2997	340	534	6545
Sundsvall	8168	126	2696	1819	4637	3905	5890	2961	539	338	7002
Uddevalla	16068	245	1509	3323	7900	2389	4854	3923	381	627	9749
*Umeå****	6920	580	1710		8717	2000	4850	2968	301		6613
Uppsala	15708	677	5353	1981	13046	23211	5047	4638	645	520	6899
Visby	2772	15	2565	846	2853	0	1240	1005	323	103	2351
Västerås	8443	216	2674	3401	9681	9394	4546	3937	526	426	7313
Växjö	4500	30	1697	2185	5951	5433	3774	2522	247	302	4662
Örebro	12507	240	7198	1750	12470	6578	4633	5380	1003	494	7400
*Östersund**	4941	72	2044	1618	6379	1245	2032	2458	461	278	5056

Italics indicate that data is not available for year 2006. Data from nearest available year is presented instead.
* data available from 2005
** data available from 2003
*** data available from 2002.
MRB = multiresistant bacteria
SSYC = *Salmonella, Shigella, Yersinia* and *Campolybacter*

Appendix 3. Surveillance of antibiotic consumption

Statistical sources and units of measurement

The ATC classification system and defined daily doses (DDD)

Since 1988, the Anatomical Therapeutic Chemical (ATC) classification system recommended by the WHO is used in Sweden for national drug statistics.

To facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of the National Corporation of Swedish Pharmacies (Apoteket AB) are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway.

The sales of drugs are presented as number of DDDs per 1000 inhabitants and day (DDD/1000/day), which give an estimate of the proportion of the population daily exposed to a particular drug. This figure is a rough estimate and should be interpreted with caution.

Swedish national statistics on drug utilisation

Since 1975, the National Corporation of Swedish Pharmacies regularly produces sales statistics on drugs, for the country as a whole and for individual counties. The sales are registered as number of DDDs, cash value and number of packages.

Out-patient care data includes information on the sales of drugs dispensed on prescription by all Swedish pharmacies by the prescription survey, running since 1974. The statistical material was until 1995 built of samples of dispensed prescriptions. From 1996 all prescriptions dispensed by pharmacies are included. From 1999, ApoDos (individually packed doses of drugs often dispensed to elderly) is also included in the survey.

Recorded data are trade name, quantity, patient fee, total cost, sex and year of birth of the patient. Data can be expressed as DDD/1000/day or number of prescriptions/1000 inhabitants.

Hospital care data includes drugs delivered by all hospital pharmacies to the hospital departments. The system also produces sales statistics for each hospital department and on national and county sales to hospitals. The sales are expressed as cash value, number of packages and number of defined daily doses.

The Swedish Prescribed Drug Register

Since July 2005, the Swedish National Board of Health and Welfare supplies an individually based register on all drugs prescribed in out-patient care. This data gives 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 (Pat/1000/year). It is also possible to follow the number of purchases per person.

Appendix 4. Antibiotic Susceptibility testing

The **agar dilution method** is the reference method in Swedish susceptibility testing to which other methods are compared. Clinical microbiology in Sweden has a long tradition of using **paper disk diffusion** antibiotic susceptibility testing (AST). This method is quantitative (diameter of inhibition zones measured in mm) but results are normally interpreted to give a qualitative ”recommendation”: **S** (susceptible, sensitive), **I** (indeterminate; intermediate) and **R** (resistant).

The disk diffusion method has been successfully standardized by the Swedish clinical microbiology laboratories in collaboration with the SRGA-M. It is used as the routine method for susceptibility testing, and as a screening method which in some instances needs to be followed up by methods for gene detection (e.g. MRSA, VRE) and in other instances by MIC-determination using broth- or agar-dilution or with Etest (betalactam resistance in pneumococci, chromosomally mediated betalactam resistance in *Haemophilus influenzae*), and still in others by methods for enzyme detection (beta-lactamase detection in *Haemophilus influenzae*, *Neisseria gonorrhoeae* and others).

Phenotypic methods (disk diffusion or MIC) are performed on a basic medium for AST, ISA (IsoSensitest Agar) from Oxoid Ltd, UK. For this medium and the corresponding antibiotic paper disks, interpretive criteria for SIR-categorization are provided by the SRGA-M. The criteria are regularly updated and available through the web-site www.srga.org.

Internal and external quality assurance and quality control of susceptibility testing is performed by each laboratory. Internal quality control includes using international QC strains regularly (every day, once a week) and analysing data in relation to national guidelines. Validation of susceptibility testing can also be done by histogram analysis of consecutive clinical isolates (see www.srga.org) External quality control is often done by participation in UK-NEQAS and/or other international programs, whereas quality assurance is one of the features of the Swedish ”100-strains or RSQC programme”.

Appendix 5. National surveillance of antibiotic resistance

Surveillance regulated in the Communicable Disease Act

Statutory notifications of certain communicable diseases are regulated in the Communicable Disease Act (SFS 2004:168, SFS 2004:255). With the exception of certain sexually transmitted infection (STI), and from 2007 ESBL-producing Eenterobacteriaceae, both the clinician caring for a patient with a notifiable disease (clinical notification) and the laboratory diagnosing the pathogen causing the disease (laboratory notification) are obliged to notify. This double notification significantly enhances the sensitivity of the surveillance system.

Notification shall be done within 24 hours, in duplicate to the County Medical Officer for Communicable Disease Control (smittskyddsläkare) and to the Swedish Institute for Infectious Disease Control (SMI). Notifications, with the exception of STI, are done with full person identification. The clinical notification shall also include information on the likely source and route of infection, as well as other information of epidemiological importance.

Infections (or carriage) with four different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with Penicillin G MIC ≥ 0.5 mg/L (PRP) have been notifiable since 1996. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE) have been notifiable since 2000.

The notifications are entered into the national computerized surveillance system, SmiNet2. At the SMI, the clinical and laboratory notification for each case are merged and checked for errors. If data are missing, contact persons in the counties are asked to supplement the information. As an important complement to the notifications, the MRSA and PRP strains are sent to SMI for typing using epidemiological methods.

Tuberculosis (TB) is a notifiable disease, irrespectively of drug resistance. On a voluntary basis the TB laboratories are reporting all drug-resistant isolates of *Mycobacterium tuberculosis* and *bovis* to SMI. All resistant isolates are sent to SMI for epidemiological typing, using restriction fragment length polymorphism (RFLP).

The feed back of notification data is done monthly on SMI internet website (www.smittskyddsinstitutet.se) and yearly in "Communicable Diseases in Sweden – the Yearly Report of SMI and in this report. Data on drug-resistant TB is also annually published in "the Swedish Tuberculosis Index".

Possible epidemiological links between patients from different counties, as identified from the epidemiological typing results and the notifications, are communicated to the persons in charge of the communicable disease control actions at the county level.

Swedish combined surveillance and QC programme (RSQC surveys) further developed into ResNet 2002.

In 1994 a model for the concomitant surveillance of antimicrobial resistance and quality assurance of antimicrobial susceptibility testing was devised. In Sweden there are 29 microbiological laboratories, each covering a county (or part of county) of Sweden. The demographics of the laboratories, their geographic areas and their corresponding populations are well characterized. The antimicrobial susceptibility testing methods of the laboratories are standardized through the combined work of the SRGA-M (Swedish Reference Group of Antibiotics – subcommittee on Methodology) and the 29 laboratories (see also Appendix 4).

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100 consecutive clinical isolates of a number of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. On one or several occasions *Escherichia coli*, *Enterococcus faecalis/E. faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* and *Enterobacter* have been part of these surveys. The number of antibiotics tested for each pathogen has varied between four and six.

From 2002 a web-based software (ResNet) will receive the

data from the laboratories and, following approval of registered data by one of two web administrators, instantly displayed it in the form of resistance frequencies on the geographical areas on maps of Sweden. Behind each resistance frequency the distribution of zone diameters or MICs together with the relevant demographic data are directly accessible. The software will accept both MIC and zone distributions of well-characterized data sets. The graphs presenting the data are designed to include all necessary information in order for the graphs to be used on their own (in presentations etc). The software also has the feature of displaying aggregated, quantitative data of invasive isolates which form the Swedish part of the EARSS network (see below).

EARSS

EARSS, funded by DG SANCO of the European Commission, is an international network of national surveillance systems, collecting comparable and validated antimicrobial susceptibility data for public health action. EARSS performs on-going surveillance of antimicrobial susceptibility of invasive infections of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis/faecium*, and monitors variations in antimicrobial resistance over time and place. From 2005 invasive isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are also part of the scheme.

Participation in EARSS was initially intended for member states of the European Union, also including Norway and Iceland, but in year 2000 six countries in eastern Europe were included, and by 2003 28 countries provide susceptibility data regularly. Information about EARSS, as well as a database yielding information about the susceptibility results for each country, year and pathogen, is available through a web-site (www.earss.rivm.nl).

Data collected by EARSS should be routinely generated quantitative data (MICs or inhibition zones), but the data presented is only in the format of susceptibility cathegories (SIR). External quality assurance exercises have so far been carried out by EARSS in cooperation with UK-NEQAS and the EARSS Advisory Board in 2000, 2001, 2002, 2003 and 2004. Results of those exercises showed that participating laboratories were capable of delivering good quality susceptibility data, indicating that the overall resistance rates as monitored through EARSS are accurate.

Although not perfect, the EARSS network of networks seems to form a solid base for surveillance of resistance, yet could and should be extended and improved.

The participation from 21 laboratories in Sweden is coordinated through the SMI, where electronic data collection, validation and verification of specific resistance mechanisms is performed. Sweden, because of its well organised network of clinical laboratories and high quality of routine susceptibility testing, is so far the largest contributor of national data to EARSS.

Sentinel surveillance

Susceptibility testing of gastrointestinal pathogens such as *Salmonella, Shigella*, *Campylobacter jejuni/coli* and *Helicocobacter pylori* is not performed on a regular basis by clinical laboratories. Existing data are mainly derived from special investigations by devoted researchers / laboratories.

In order to get a national overview of the situation, the ResNet software developed by SMI (see above) is available also for data on these pathogens, as well as for national quantitative data on *Neisseria gonorrhoeae* and *N. meningitidis* performed by the reference centre in Örebro. Also collections of quantitative susceptibility data on other pathogens of general interest are suitable for entering and displaying in ResNet.

Appendix 6. Recent publications

Use of antibiotics

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Workshops

Management of rinosinuitis (in Swedish). Medical Products Agency, www.mpa.se (April 2005)

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Websites

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www.smittskyddsinstitutet.se
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Strama

Swedish Strategic Programme
against Antibiotic Resistance

SMITTSKYDDSINSTITUTET

Swedish Institute for Infectious Disease Control