# SWEDRES2005

## A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine

STRAMA

The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents

SMITTSKYDDSINSTITUTET

*Swedish Institute for Infectious Disease Control*

SMITTSKYDDSINSTITUTET
*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**
The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents

STRAMA – The Swedish Strategic Programme for the Rational use of Antimicrobial Agents, was founded in 1995 and is supported by the Swedish Government since year 2000. A national steering committee with members from all relevant authorities and organisations collaborates with regional expert groups in every county.

PUBLISHERS:
The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA), and the Swedish Institute for Infectious Disease Control

EDITORS:
Otto Cars and Barbro Olsson Liljequist

ADDRESS:
Swedish Institute for Infectious Disease Control
SE 171 82 Solna, Sweden
Phone: +46 8 457 23 00
Fax:+46 8 30 06 26
E-mail: smi@smi.ki.se
www.smittskyddsinstitutet.se
www.strama.se

LAYOUT:
Björn Lundquist AB, Malmö

PRINT:
Edita Västra Aros AB

ISSN 1400-3473

SMI-tryck 156-2006

# 1. Preface

SWEDRES/SVARM presents data on antibiotic utilisation and antimicrobial resistance in both human and veterinary medicine. In the human field Sweden has for the last ten years systematically followed and registered trends regarding antibiotic prescribing and resistant bacteria. Sales statistics on antibiotics have regularly been presented and commented by the Strama network. With the support of all laboratories of clinical microbiology the Swedish Institute for Infectious Disease Control have collected data on antibiotic resistant bacteria. These surveillance systems have been useful to detect trends in antibiotic use, geographical differences and levels of resistance. The Swedish Government recently approved a National Strategy for coordinated efforts to prevent antibiotic resistance. The Strategy emphasises that coordinated work is required in several areas. The measures proposed concern the use of antibiotics for humans and animals and the use of antibiotics in food and environmental sectors. To prevent the spread of healthcare-associated infections, a number of legislative amendments are proposed. The implementation of this National Strategy is essential to preserve the favourable situation that still is the case in Sweden in an international comparison.

# 1.2 Contributors


**Anders Blaxhult**, Department of Epidemiology, Swedish Institute for Infectious Disease Control, anders.blaxhult@smi.ki.se

**Otto Cars**, Strama, otto.cars@smi.ki.se

**Charlotta Edlund**, Medical Products Agency, charlotta.edlund@mpa.se

**Victor Fernandez**, Department of Parasitology, Mycology and Environmental Microbiology, Swedish Institute for Infectious Disease Control, victor.fernandez@smi.ki.se

**Hans Fredlund**, Communicable Disease Control, Örebro University Hospital, hans.fredlund@orebroll.se

**Patricia Geli**, Department of Epidemiology, Swedish Institute for Infectious Disease Control, patricia.geli@smi.ki.se

**Birgitta Henriques Normark**, Department of Bacteriology, Swedish Institute for Infectious Disease Control, birgitta.henriques@smi.ki.se

**Sven Hoffner**, Department of Bacteriology, Swedish Institute for Infectious Diseases Control, sven.hoffner@smi.ki.se

**Gunnar Kahlmeter**, Department of Clinical Microbiology, Växjö Hospital, gunnar.kahlmeter@ltkronoberg.se

**Charlotte Kristiansson**, IHCAR, Karolinska Institutet, charlotte.kristiansson@ki.se

**Sharon Kühlmann Berenzon**, Department of Epidemiology, Swedish Institute for Infectious Disease Control, sharon.kuhlmann@smi.ki.se

**Kerstin Mannerquist**, Department of Bacteriology, Swedish Institute for Infectious Disease Control, kerstin.mannerquist@smi.ki.se

**Christer Norman**, Strama, christer.norman@smi.ki.se

**Per Olcén**, Department of Clinical Microbiology, Örebro University Hospital, per.olcen@orebroll.se

**Barbro Olsson-Liljequist**, Department of Bacteriology, Swedish Institute for Infectious Disease Control, barbro.liljequist@smi.ki.se

**Victoria Romanus**, Department of Epidemiology, Swedish Institute for Infectious Disease Control, victoria.romanus@smi.ki.se

**Gunilla Skoog**, Strama, gunilla.skoog@smi.ki.se

**Gunilla Stridh**, Strama, gunilla.stridh@smi.ki.se

**Cecilia Stålsby Lundborg**, The National Corporation of Swedish Pharmacies, cecilia.stalsby.lundborg@phs.ki.se

**Erik Torell**, Department of Infectious Diseases, Akademiska University Hospital, erik.torell@akademiska.se

**Magnus Unemo**, Department of Clinical Microbiology, Örebro University Hospital, magnus.unemo@orebroll.se

**Mats Walder**, Department of Clinical Microbiology, Malmö University Hospital, mats.walder@mikrobiol.mas.lu.se

**Åke Örtqvist**, Communicable Disease Control, Karolinska University Hospital, ake.ortqvist@sll.se


## Acknowledgement:


The national surveillance of antibiotic resistance would not have been possible without the active support from all laboratories of Clinical Microbiology.

# 2.1 Summary

### Use of antibiotics

The total use of antibiotics (methenamine excluded) in Sweden, measured in defined daily doses (DDD), decreased by 6% during the years 2001 – 2004. However, during the last year, the use has increased by 0.4 DDD/1000/Day. Approximately 90% of the total use of antibiotics took place in out-patient care, where the most common substances were phenoxymethylpenicillin and tetracyclines.

There were seasonal variations in the use of tetracyclines with a higher use during the winter and a lower during the summer. One major indication for tetracyclines is respiratory tract infections. This might be one of the reasons why the use varies during the year, since this type of infection is more common during the winter. Another explanation to the decrease in use during the summer might be that treatment with tetracyclines may give rise to photosensibility. Younger patients received longer periods of treatment and/or higher doses than older patients. One explanation is probably that acne is often treated during long periods of time and is more common in younger patinents.

The most common fluoroquinolones in out-patient care during the last few years were norfloxacin and ciprofloxacin. The use of ciprofloxacin has increased and the use of norfloxacin has decreased at approximately the same rate. A number of generic ciprofloxacin products have become available on the Swedish market, resulting in lower prices. This might be one of the reasons why the use of this substance has increased.

During 2000-2005 the antibiotic use in hospital care increased by 13% measured in DDD/1000 inhabitants and day. Measured in DDD/100 patient days the increase was 42% in 1994-2004. This may partly be explained by the fact that the number of beds in Swedish hospitals and the mean period of hospital stay have both decreased during the same period. In the last year, the most common classes of antibiotics in hospital care were cephalosporins, penicillins, tetracyclines and fluoroquinolones.

### Antibiotic resistance

Compared to many other European countries, the prevalence of MRSA in Sweden is still low. However, during 2005 a total of 975 cases were reported, representing an increase of 37% compared to 2004. Fifty five percent of the cases has acquired MRSA in Sweden, 23% acquired it abroad and for 22% the place of acquisition was unknown or not reported. Invasive isolates of MRSA has now reached 1% of all invasive *Staphylococcus aureus*, as seen in the European surveillance network EARSS.

Most of the Swedish counties have experienced an increasing incidence of MRSA cases. The most dramatic increase in numbers of MRSA cases in 2005 was seen in Östergötland county, where two hospital-related outbreaks contributed to the highest incidence noted during the investigation period, 24/100 000 inhabitants. In Stockholm county the trend has shifted, and the number of patients infected or colonised in the health care setting is only 9%, compared to 51% in 2003. On the other hand community acquired MRSA has increased and is now 30% compared to 15% in 2003. A DNA-based method has been used for typing of all MRSA isolates since the year 2000. Isolates identical or related to internationally recognized clones are still dominating, but previously unknown types are sometimes imported. The prevalence of MRSA with PVL toxin is increasing.

During the period 1997-2002 the annual incidence of *Streptococcus pneumoniae* with reduced susceptibility to penicillin (PRP) decreased from 10.1 to 5.9 cases per 100 000 inhabitants but has increased to 7.3 in 2005. Most cases were identified through nasopharyngeal culture. Fifty nine percent of the cases reported with PRP were below 5 years of age. In 30 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 accounting for 30-50% of the isolates. The most common serotypes/groups found were types 9, 14, 19, 23, 6 and 35.

Enterococci, and more specifically vancomycin resistant enterococci (VRE), have become important causes of nosocomial outbreaks in many parts of the world, usually involving high-risk populations such as immunosuppressed and intensive care patients. Like MRSA, VRE were made a notifiable pathogen in Sweden in the year 2000 according to the Communicable Disease Act. The numbers of reported cases have varied between 18 and 47 in 2000-2005. Four counties have been responsible for the vast majority of cases, and these are Stockholm (2000-2003), Västerbotten (2000), Skåne (2003-2005) and Örebro (2003). The median age for all cases reported in 2005 was 69 years compared to 60 in 2002, 67 in 2003 and 74 in 2004. The majority of VRE reported according to the Communicable Disease Act 2000-2005 were *Enterococcus faecium* carrying the *vanB* gene.

*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 and has increased from 17 to 26% during this period. More alarmingly, the level of resistance to third generation cephalosporins among blood isolates has increased to 1.3 %, and in the majority of these the resistance was caused by plasmid-mediated ESBLs. ESBLs of CTX-M type were most frequently found, and 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 10% in 2005. The rates were the same in blood and in urine isolates.

Also other Gram-negative bacteria have been monitored in the RSQC programme and/or in EARSS. *Klebsiella pneumoniae* was included in the 2005 RSQC programme for the first time since 1994, and in the EARSS programme from July 2005. Data on *K. pneumoniae* was also available through voluntary reporting of resistant organisms. Notifications of ESBL-producing strains have appeared in all these surveillance programmes. During 2005 there has been a high number of ESBL-containing and multi-resistant isolates of *K. pneumoniae* in Uppsala county, both hospital- and community-related.

In *Pseudomonas aeruginosa*, surveyed both in the RSQC programme and from July 2005 also in EARSS, the most alarming feature is the high prevalence of carbapenem resistance (17.5% resistance to imipenem). Resistance to fluoroquinolones (ciprofloxacin) remained at 9%.

Respiratory isolates of *Haemophilus influenzae* were included in the RSQC programme on antibiotic resistance in 2005 after a three-year pause. The average level of beta-lactam resistance has not increased during the last four years, but the range between individual laboratories and counties was 5-27%. An average increase in strains resistant to trimethoprim-sulfamethoxazole was seen in 2005, but again with a wide range between individual laboratories (4-18%).

*Helicobacter pylori* has been monitored locally at a few laboratories. Resistance to clarithromycin is increasing and has locally at one laboratory reached over 10% for two years in a row.

Gonorrhoea is a notifiable disease, and in 2005 691 clinical cases of the disease were reported. Isolates from 486 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 70% of the notified cases. During the last three years approximately 25% of the isolates were beta-lactamase producing and ampicillin resistant, and almost 50% were resistant to ciprofloxacin.

Between 2004 and 2005 there was an increase in the total number of new cases of TB, from 465 to 575. Resistant TB was reported in 8.7% of the Swedish born patients and 10.7% of those foreign born. Resistance to isoniazid was most common, reported in 10.3% of the patients, followed by pyrazinamide 1.3%, rifampicin 1.1% and ethambutol 0.7%.

### National and regional intervention projects

Strama and SMI have conducted several studies in different areas. Personnel at day care centres have indicated a need for more knowledge about how to handle children's infections. To meet this wish Strama has produced a film called "Why didn't Teo get penicillin?". In the film causes, symptoms and treatment of common colds are discussed and the difference between virus and bacteria is explained. The film has been distributed to more than 300 day care centres, free of charge. Educational material has also been developed for school children, 10 years of age. The material consists of a teacher's guide, overhead pictures and a cartoon book with message about correct treatment of common colds, rational use of antibiotics and antibiotic resistance. More than 200 schools all over Sweden have used the package.

For the third time a one-week diagnosis-prescribing survey was conducted in 2005. The diagnosis pattern was more or less similar to previous studies. In total an antibiotic was prescribed in 60.1, 59.1 and 47.1% of the cases in 2000, 2002 and 2005 respectively. It is interesting to note and increases the validity of the studies that the diagnosis pattern has been relatively stable over the years despite the inclusion of two new counties in the last study.

Ethanol hand rub rather than hand washing has since the 1970s been the recommended standard for preventing nosocomial spread of microorganisms in Swedish hospitals. To estimate the compliance with these recommendations volumes of ethanol used normally and during optimal conditions was studied. Dispensers were weighed on day 1 and 2 and the amount of ethanol used was converted to ml/patient/24h and ml/staff member/24 h. Actual ml/patient/24h data for calculation of compliance rates were based on the annual volume of ethanol for hand disinfection used per ward in 2004. The mean compliance rates (local data vs gold standard) were 51% for ICUs, 36% for surgical wards and 40% for medical wards.

Another study investigated whether the current Swedish surveillance system can detect yearly changes in the level of resistance or if data of resistance can be related to outpatient use of antibiotics. The study included data on *E. coli* resistance to each of the antibiotics ampicillin, cefadroxil, mecillinam, nitrofurantoin, norfloxacin and trimethoprim. The findings showed that resistance levels to antibiotics between and within the laboratories varied considerably. There were also differences regarding the trend in resistance at individual laboratories. The data available was not sufficient to analyse the correlation between antibiotic use and resistance.

# 2.1 Sammanfattning

### Antibiotikaförbrukning

Den totala förbrukningen av antibiotika (exklusive metenamin) i Sverige mätt i antalet definierade dygnsdoser (DDD) minskade med 6 % under åren 2001-2004. Under det senaste året har förbrukningen dock ökat med 0,4 DDD/1000/dag. Cirka 90 % av förbrukningen skedde i öppenvården, där de vanligaste antibiotikasubstanserna var penicillin V (fenoximetylpenicillin) och tetracykliner.

I användningen av tetracykliner fanns tydliga säsongsbundna variationer med högre förbrukning under vintern och lägre under sommaren. Tetracykliner förskrivs bland annat mot luftvägsinfektioner, vilket skulle kunna vara en bidragande orsak till variationen eftersom denna typ av infektioner är vanligare under vintrarna. En annan orsak till en låg förbrukning under sommaren kan vara att behandling med tetracykliner kan ge upphov till fotosensibilisering och därför undviks under sommarperioden. Yngre patienter fick i genomsnitt längre tetracyklinkurer än äldre. En förklaring till detta är troligtvis att akne ofta behandlas under långa perioder och är vanligare hos yngre patienter.

De vanligaste kinolonerna inom öppenvården har de senaste åren varit norfloxacin och ciprofloxacin. Förbrukningen av ciprofloxacin har ökat och av norfloxacin har den minskat i ungefär samma takt. Detta kan bero på att ett antal generiska ciprofloxacinpreparat blivit tillgängliga på marknaden och att priserna därmed har sjunkit.

Under 2000-2005 ökade användningen i sluten vård med 13 % mätt i DDD/1000 invånare och dag. Mätt i DDD/100 vårddagar var ökningen 42 % under 1996-2004. En bidragande förklaring till detta är att både antalet vårdplatser och medelvårdtiden på svenska sjukhus minskade under denna period. Under det senaste året var de vanligaste antibiotikagrupperna inom slutenvården cefalosporiner, penicilliner, tetracykliner och kinoloner.

### Antibiotikaresistens

Jämfört med övriga länder i Europa är förekomsten av MRSA låg i Sverige. Likväl rapporterades 975 fall 2005, en ökning med 37 % jämfört med 2004. Femtiofem procent av fallen hade smittats med MRSA i Sverige, 23 % hade smittats utomlands och för 22 % av fallen var smittorten okänd eller ej rapporterad. Invasiva isolat av MRSA har nu nått nivån 1 % av alla invasiva *Staphylococcus aureus* enligt rapportering till den europeiska resistensövervakningen EARSS.

I de flesta län/regioner sågs en ökad incidens av MRSA-fall. Den mest dramatiska ökningen av MRSA-fall noterades i Östergötland, där två sjukvårdsrelaterade utbrott bidrog till den högsta incidensen per 100 000 invånare och län under hela perioden, 24 / 100 000 invånare. I Stockholms län har trenden vänt, och antalet patienter som blev infekterade eller koloniserade i sjukvården var bara 9 %, jämfört med 51 % 2003. Andelen fall av samhällsförvärvad MRSA hade å andra sidan ökat till 30 % jämfört med 15 % 2003. En DNA-baserad metod har använts för att typa alla MRSA isolat sedan 2000. Isolat med PFGE-mönster som var identiska eller snarlika de hos internationellt spridda kloner dominerar fortfarande, men även nya typer av MRSA förekommer som importfall. Förekomsten av MRSA med PVL-toxin ökar.

Den årliga incidensen per 100 000 invånare av *Streptococcus pneumoniae* med minskad känslighet för penicillin (PRP) har minskat under perioden 1997-2002 från 10,1 to 5,9 men har sedan ökat till 7,3 under 2005. De flesta fallen identifierades genom nasofarynxodling. Femtionio procent av PRP-fallen var 5 år eller yngre. I 30 fall (5 %) påvisades PRP från blod och/eller spinalvätska. Multiresistens (resistens mot penicillin och minst två ytterligare antibiotika) var vanligt hos PRP och noterades 30-50 % av isolaten. De vanligast förekommande serotyperna/grupperna var typ 9, 14, 19, 23, 6 and 35.

Enterokocker, särskilt de med resistens mot vankomycin (VRE), har ökat i betydelse vid sjukvårdsrelaterade utbrott i många delar av världen och ofta omfattat riskpatienter, t ex immunosupprimerade och intensivvårdspatienter. Liksom MRSA blev VRE anmälningspliktiga patogener i Sverige 2000. Antalet rapporterade fall per år har dock bara varit mellan 18 och 47 under 2000-2005. Fyra län har bidragit med majoriteten av fall, och de är Stockholm (2000-2003), Västerbotten (2000), Skåne (2003-2005) och Örebro (2003). Medianåldern för fallen under 2005 var 69 år jämfört med 60 år 2002, 67 år 2003 och 74 år 2004. Majoriteten av rapporterade VRE under perioden 2000-2005 var Enterococcus faecium med vanB-gen.

*Escherichia coli*, huvudsakligen från urinvägsinfektioner, har övervakats enligt det nationella programmet (via ResNet) sedan 1996, och blodisolat har inkluderats i EARSS sedan 2001. Ampicillinresistens, orsakad av plasmidmedierad betalaktamasproduktion av TEM-typ var lika hög bland blodisolat som bland urinisolat och har visat en stadig ökning från 17 till 26 %. Alarmerande är att förekomsten av blodisolat med resistens mot 3:e generationens cefalosporiner har ökat till 1,3 %, och att hos majoriteten av dessa var resistensen orsakad av plasmidmedierade ESBL. ESBL av CTX-M-typ (s k cefotaximaser) var vanligast, och denna resistens var ofta åtföljd av resistens mot många andra antibiotika som t ex aminoglycosider och kinoloner. Resistens som sådan mot kinoloner har ökat årligen och närmade sig 10 % 2005, oberoende av om isolaten kom från blod eller urin.

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. Kunskap har också erhållits genom frivillig rapportering av resistenta bakterier. Hos *K.*

*pneumoniae* har ett litet antal ESBL-producerande isolat noterats I alla övervaknings-systemen. Under 2005 har ett stort antal ESBL-producerande och multiresistenta isolat av *K. pneumoniae* påvisats i Uppsala län, både i slutenvård och öppenvård. Hos *P. aeruginosa* är den mest alarmerande egenskapen den höga förekomsten av karbapenemresistens (17,5 % av blodisolaten var resistenta mot imipenem). Resistens mot kinoloner (ciprofloxacin) låg kvar på 9 %.

Luftvägsisolat av *Haemophilus influenzae* inkluderades i övervakningen 2005 efter ett uppehåll på tre år. Medelvärdet av andelen beta-laktamasproducerande isolat hade inte ökat de senaste fyra åren, men skillnaden mellan enskilda laboratorier och län var stor (5-27 %). En ökning av andelen isolat som var resistenta mot trimetoprim-sulfonamid hade inträffat under samma period, men återigen sågs en stor variation mellan länen (4-18 %).

*Helicobacter pylori* har övervakats vid några laboratorier. Resistens mot klaritromycin ökar och har lokalt vid ett laboratorium legat över 10 % två år i rad.

Gonorré är en anmälningspliktig sjukdom och 2005 rapporterades 691 kliniska fall. Isolat från 486 av dessa, 70 % av de anmälda fallen, har undersökts antingen vid det svenska referenslaboratoriet i Örebro eller vid laboratoriet för klinisk bakteriologi, Karolinska Universitetssjukhuset Huddinge, Stockholm. Under de senaste tre åren var ungefär 25 % av isolaten beta-laktamasproducerande och ampicillinresistenta, och nästan 50 % var resistenta mot ciprofloxacin.

Under 2005 ökade antalet nya fall av *Mycobacterium tuberculosis* med 24 % jämfört med 2004, från 465 to 575. Resistent tuberkulos rapporterades i 8,7 % av de svenskfödda fallen och i 10,7 % av de utländskt födda. Resistens mot isoniazid var vanligast (10,3 % av fallen), följt av pyrazinamid (1,3 %), rifampicin (1,1 %) och etambutol (0,7 %).

### Nationella och regionala interventionsprojekt

Under 2005 har Strama och SMI genomfört ett flertal studier. Personal inom förskolan har uttalat ett behov av att få ökade kunskaper om infektioner hos små barn. För att tillmötesgå denna önskan har Strama producerat en film ”Varför fick inte Teo penicillin?”. I filmen diskuteras orsaker, symtom och behandling av vanliga förkylningar och skillnaden mellan virus och bakterier förklaras. Filmen som är gratis, har spridits till mer än 300 förskolor. Utbildningsmaterial har också tagits fram till skolelever i årskurs fyra. Materialet består av lärarhandledning, OH-bilder och en serietidning med information om hur förkylning ska behandlas, antibiotikaanvändning och antibiotikaresistens. Mer än 200 skolor har rekvirerat materialet.

För tredje gången genomfördes 2005 en diagnos-receptundersökning. Diagnosmönstret överensstämde med de tidigare studierna och totalt förskrevs antibiotika i 60,1, 59,1 och 47,1 procent av fallen under åren 2000, 2002 och 2005. Det är intressant att notera det samstämmiga diagnosmönstret vilket ökar trovärdigheten i studierna trots att två län tillkommit i den sista studien.

För att förhindra spridning av mikroorganismer på sjukhus har etanol sprit istället för handtvätt rekommenderats sedan 1970-talet. För att ta reda på följsamheten till denna rekommendation mättes den aktuella och den optimala användningen av etanol. Behållarna vägdes dag 1 och 2 och mängden använd etanol räknades om till ml/patient/24h och ml/personal/24h. Årsvolymen använd etanol per avdelning 2004 användes vid beräkning av följsamhet. Medianen för följsamhet var 51 % inom IVA, 36 % på kirurgavdelningar och 40 % på medicinkliniker.

En annan studie undersökte om det nuvarande svenska övervakningssystemet kan spåra årliga ändringar i resistensförekomst eller om resistensdata kan relateras till användningen av antibiotika inom öppen vård. I studien ingick data över resistens hos *E. coli* för ampicillin, cefadroxil, mecillinam, nitrofurantoin, norfloxacin och trimetoprim. Resultaten visade att resistensnivåerna för antibiotika varierar kraftigt mellan laboratorierna. Man fann också skillnader i resistenstrender mellan laboratorierna. Tillgängliga data möjliggör inte en analys av korrelationen antibiotikaanvändning och resistens.

# 3. Use of antimicrobials

## 3.1 Use of antibiotics

### Total antibiotic use

The total use of antibiotics in Sweden, expressed as Defined Daily Doses/1000 inhabitants and day, DDD/1000/day, is shown in Table 3.1.1.

**Table 3.1.1. Total use of antibacterial drugs for systemic use in Sweden 2000-2005, DDD/1000/day.**

| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|
| J01 excl methenamine | 15.2 | 15.3 | 14.8 | 14.6 | 14.4 | 14.8 |
| Methenamine | 1.55 | 1.54 | 1.64 | 1.72 | 1.86 | 1.88 |
| Total J01 | 16.8 | 16.8 | 16.4 | 16.3 | 16.2 | 16.6 |

There has been no major change in the total amount of antibiotics used during the last six years. The use of methenamine, however, has increased by 21%. This substance is an antiseptic and therefore of no interest regarding antibiotic resistance, even though the WHO Collaborating Centre for Drug Statistics methodology classifies it as an antibacterial drug.

### Out-patient care

The total use of antibiotics in out-patient care in 2000-2005 is shown in Table 3.1.2. As for the total amount of antibiotics used in Sweden, there has been no major change during this period.

**Table 3.1.2. Total use of antibacterial drugs for systemic use in out-patient care 2000-2005, DDD/1000/day.**

| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|
| J01 excl methenamine | 13.7 | 13.8 | 13.3 | 13.0 | 12.8 | 13.1 |
| Methenamine | 1.48 | 1.49 | 1.60 | 1.67 | 1.78 | 1.80 |
| Total J01 | 15.2 | 15.3 | 14.9 | 14.7 | 14.6 | 14.9 |

The most common antibiotics in out-patient care in 2005 were penicillins and tetracyclines. The total distribution between different antibiotic classes is shown in Figure 3.1.1.

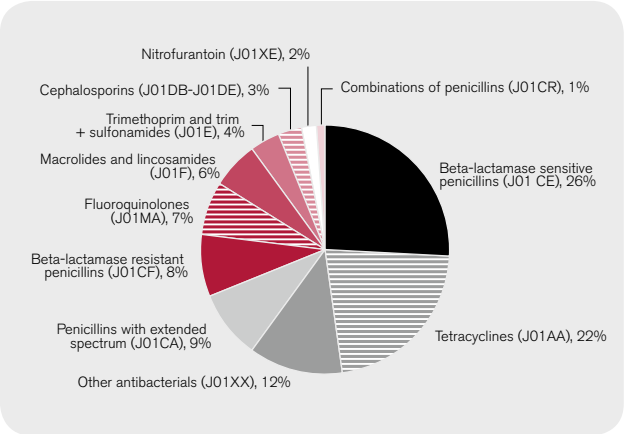


**Figure 3.1.1. Antibiotics in out-patient care 2005, percent of total DDD/1000/day.**

Figure 3.1.2 presents the use of antibiotics in 2005 compared to the average yearly use during the period 2000-2004. Calculated as a percentage, there has been a large increase in the use of nitrofurantoin and a decrease in the use of cephalosporins.

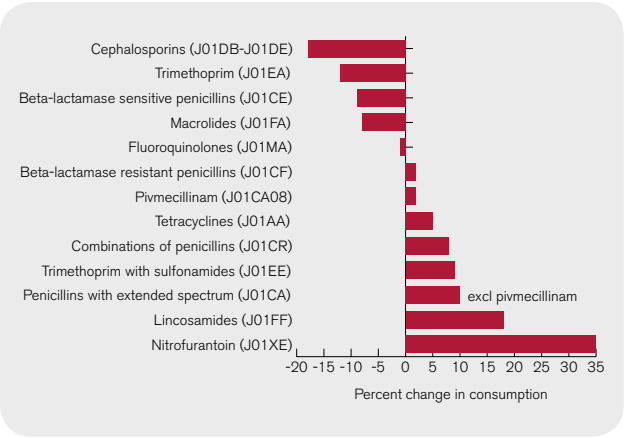


**Figure 3.1.2. Antibiotics in out-patient care, change in comsumption measured in DDD/1000/day (%), 2005 compared to the average yearly consumption 2000-2004.**

In Table 3.1.3 figures for different groups of antibiotics and age groups are presented in DDD/1000/day as well as in prescriptions/1000 inhabitants and year.

**Table 3.1.3. Antibiotics, out-patient care, different groups of antibiotics and different age-groups, 2001-2005, DDD/1000/day and prescriptions/1000/year respectively. Unfortunately, data for cephalosporins (J01DA-J01DE) were incorrect in Swedres 2004.**

| | DDD/1000/day | | | | | Prescriptions/1000/year | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group (years) | 2001 | 2002 | 2003 | 2004 | 2005 | 2001 | 2002 | 2003 | 2004 | 2005 |
| Tetracyclines (J01AA) | | | | | | | | | | |
| 0-6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0 | 0 | 0 | 0 | 0 |
| 7-19 | 2.1 | 2.1 | 2.3 | 2.4 | 2.7 | 25 | 24 | 25 | 25 | 29 |
| 20-59 | 3.6 | 3.4 | 3.3 | 3.4 | 3.5 | 75 | 68 | 64 | 63 | 67 |
| 60-79 | 3.9 | 3.7 | 3.8 | 3.9 | 4.2 | 95 | 90 | 91 | 92 | 100 |
| 80- | 3.0 | 2.9 | 2.9 | 2.8 | 3.0 | 83 | 78 | 78 | 76 | 83 |
| All age groups | 3.2 | 3.0 | 3.0 | 3.1 | 3.3 | 66 | 61 | 59 | 59 | 63 |
| Penicillins with extended spectrum (J01CA) | | | | | | | | | | |
| 0-6 | 1.5 | 1.4 | 1.3 | 1.3 | 1.4 | 99 | 97 | 91 | 85 | 85 |
| 7-19 | 0.6 | 0.5 | 0.5 | 0.5 | 0.5 | 23 | 22 | 20 | 18 | 21 |
| 20-59 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 33 | 33 | 32 | 32 | 35 |
| 60-79 | 1.9 | 2.0 | 2.0 | 2.1 | 2.3 | 67 | 69 | 70 | 73 | 77 |
| 80- | 3.5 | 3.6 | 3.6 | 3.7 | 3.7 | 141 | 141 | 140 | 143 | 148 |
| All age groups | 1.3 | 1.3 | 1.3 | 1.3 | 1.4 | 49 | 49 | 48 | 48 | 51 |
| Beta-lactamase sensitive penicillins (J01CE) | | | | | | | | | | |
| 0-6 | 4.5 | 4.1 | 3.8 | 3.3 | 3.4 | 407 | 377 | 347 | 308 | 310 |
| 7-19 | 4.4 | 3.9 | 3.5 | 2.9 | 3.0 | 195 | 170 | 150 | 121 | 122 |
| 20-59 | 5.0 | 4.6 | 4.3 | 4.2 | 4.2 | 129 | 119 | 111 | 106 | 105 |
| 60-79 | 4.0 | 4.0 | 4.1 | 4.3 | 4.3 | 97 | 97 | 100 | 105 | 103 |
| 80- | 3.6 | 3.5 | 3.4 | 3.3 | 3.4 | 103 | 94 | 90 | 87 | 87 |
| All age groups | 4.6 | 4.3 | 4.1 | 3.9 | 3.9 | 155 | 143 | 133 | 123 | 122 |
| Beta-lactamase resistant penicillins (J01CF) | | | | | | | | | | |
| 0-6 | 0.2 | 0.4 | 0.4 | 0.3 | 0.3 | 24 | 36 | 38 | 34 | 32 |
| 7-19 | 0.6 | 0.7 | 0.7 | 0.7 | 0.7 | 28 | 35 | 36 | 32 | 31 |
| 20-59 | 0.8 | 0.9 | 0.9 | 0.9 | 0.9 | 30 | 32 | 32 | 32 | 32 |
| 60-79 | 1.9 | 2.0 | 2.0 | 1.9 | 1.9 | 53 | 56 | 55 | 54 | 54 |
| 80- | 4.5 | 4.7 | 4.6 | 4.5 | 4.4 | 130 | 132 | 129 | 124 | 122 |
| All age groups | 1.1 | 1.2 | 1.2 | 1.2 | 1.2 | 38 | 42 | 43 | 41 | 41 |
| Combinations of penicillins (J01CR) | | | | | | | | | | |
| 0-6 | 0.8 | 0.8 | 0.8 | 0.7 | 0.7 | 64 | 61 | 55 | 49 | 52 |
| 7-19 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 9 | 8 | 6 | 5 | 6 |
| 20-59 | 0.2 | 0.2 | 0.1 | 0.1 | 0.2 | 4 | 4 | 3 | 3 | 4 |
| 60-79 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 3 | 3 | 3 | 3 | 4 |
| 80- | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 3 | 3 | 2 | 2 | 3 |
| All age groups | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 9 | 9 | 8 | 7 | 8 |
| Cephalosporins (J01DB-J01DE) | | | | | | | | | | |
| 0-6 | 0.6 | 0.6 | 0.6 | 0.5 | 0.5 | 53 | 54 | 56 | 50 | 46 |
| 7-19 | 0.4 | 0.4 | 0.4 | 0.3 | 0.3 | 25 | 25 | 24 | 21 | 20 |
| 20-59 | 0.4 | 0.3 | 0.3 | 0.3 | 0.3 | 20 | 19 | 18 | 17 | 17 |
| 60-79 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 26 | 25 | 24 | 24 | 23 |
| 80- | 0.9 | 0.9 | 0.9 | 0.8 | 0.8 | 51 | 48 | 46 | 43 | 42 |
| All age groups | 0.5 | 0.5 | 0.4 | 0.4 | 0.4 | 28 | 27 | 26 | 23 | 22 |
| Trimethoprim (J01EA) | | | | | | | | | | |
| 0-6 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 15 | 15 | 16 | 16 | 15 |
| 7-19 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 13 | 13 | 13 | 12 | 12 |
| 20-59 | 0.4 | 0.4 | 0.4 | 0.4 | 0.3 | 21 | 21 | 20 | 19 | 17 |
| 60-79 | 1.0 | 1.0 | 1.0 | 0.9 | 0.9 | 49 | 48 | 48 | 45 | 42 |
| 80- | 2.8 | 2.7 | 2.6 | 2.5 | 2.3 | 155 | 151 | 146 | 136 | 126 |
| All age groups | 0.6 | 0.6 | 0.6 | 0.5 | 0.5 | 31 | 30 | 30 | 28 | 26 |

| | DDD/1000/day | | | | | Prescriptions/1000/year | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age group (years) | 2001 | 2002 | 2003 | 2004 | 2005 | 2001 | 2002 | 2003 | 2004 | 2005 |
| Trimethoprim with sulfonamides (J01EE) | | | | | | | | | | |
| 0-6 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 23 | 21 | 20 | 18 | 18 |
| 7-19 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 5 | 5 | 4 | 4 | 4 |
| 20-59 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 3 | 3 | 3 | 3 | 3 |
| 60-79 | 0.2 | 0.3 | 0.3 | 0.3 | 0.3 | 7 | 7 | 7 | 8 | 8 |
| 80- | 0.3 | 0.3 | 0.3 | 0.4 | 0.3 | 11 | 11 | 11 | 12 | 12 |
| All age groups | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 6 | 6 | 6 | 6 | 6 |
| Macrolides (J01FA) | | | | | | | | | | |
| 0-6 | 1.1 | 0.9 | 0.8 | 0.7 | 0.8 | 50 | 44 | 36 | 35 | 37 |
| 7-19 | 0.9 | 0.8 | 0.6 | 0.6 | 0.7 | 30 | 24 | 20 | 18 | 21 |
| 20-59 | 0.7 | 0.6 | 0.6 | 0.5 | 0.6 | 22 | 20 | 17 | 16 | 17 |
| 60-79 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 16 | 15 | 14 | 14 | 15 |
| 80- | 0.4 | 0.4 | 0.3 | 0.3 | 0.3 | 12 | 11 | 10 | 10 | 10 |
| All age groups | 0.7 | 0.6 | 0.6 | 0.6 | 0.6 | 24 | 21 | 18 | 17 | 18 |
| Lincosamides (J01FF) | | | | | | | | | | |
| 0-6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4 | 5 | 5 | 4 | 4 |
| 7-19 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 6 | 7 | 7 | 6 | 7 |
| 20-59 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 10 | 11 | 12 | 13 | 13 |
| 60-79 | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 | 16 | 17 | 20 | 21 | 22 |
| 80- | 0.6 | 0.6 | 0.7 | 0.7 | 0.8 | 26 | 27 | 30 | 30 | 32 |
| All age groups | 0.2 | 0.2 | 0.3 | 0.3 | 0.3 | 11 | 12 | 13 | 14 | 14 |
| Fluoroquinolones (J01MA) | | | | | | | | | | |
| 0-6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1 | 1 | 1 | 1 | 1 |
| 7-19 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 7 | 6 | 6 | 6 | 6 |
| 20-59 | 0.8 | 0.8 | 0.8 | 0.8 | 0.8 | 38 | 37 | 35 | 33 | 32 |
| 60-79 | 2.1 | 2.0 | 2.1 | 2.1 | 2.1 | 96 | 94 | 92 | 88 | 85 |
| 80- | 3.6 | 3.4 | 3.3 | 3.1 | 3.1 | 201 | 188 | 173 | 158 | 149 |
| All age groups | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 48 | 47 | 45 | 42 | 41 |
| Nitrofurantoin (J01XE) | | | | | | | | | | |
| 0-6 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 7 | 7 | 7 | 7 | 6 |
| 7-19 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 4 | 4 | 4 | 5 | 5 |
| 20-59 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 5 | 6 | 7 | 7 | 8 |
| 60-79 | 0.2 | 0.2 | 0.2 | 0.3 | 0.3 | 7 | 8 | 9 | 12 | 14 |
| 80- | 0.5 | 0.5 | 0.6 | 0.7 | 0.8 | 20 | 24 | 27 | 31 | 37 |
| All age groups | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 6 | 7 | 8 | 9 | 10 |
| All agents (J01 excl methenamine) | | | | | | | | | | |
| 0-6 | 9.1 | 8.7 | 8.1 | 7.2 | 7.5 | 748 | 719 | 674 | 606 | 609 |
| 7-19 | 9.8 | 9.3 | 8.9 | 8.1 | 8.8 | 370 | 344 | 315 | 274 | 283 |
| 20-59 | 13.3 | 12.7 | 12.3 | 12.1 | 12.4 | 392 | 373 | 356 | 344 | 351 |
| 60-79 | 16.9 | 16.8 | 17.2 | 17.7 | 18.0 | 537 | 533 | 537 | 541 | 550 |
| 80- | 24.0 | 23.7 | 23.3 | 23.0 | 23.2 | 944 | 915 | 886 | 856 | 854 |
| All age groups | 13.8 | 13.3 | 13.0 | 12.8 | 13.1 | 476 | 456 | 438 | 418 | 426 |

### *Tetracyclines*

The seasonal variation in the use of tetracyclines during the period 2000-2005 is shown in Figure 3.1.3.

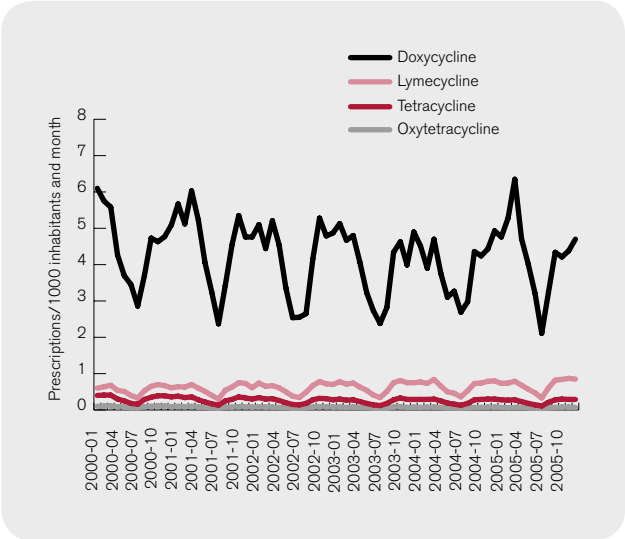


**Figure 3.1.3. Seasonal variation of tetracyclines, out-patient care 2000-2005. Prescriptions/1000 inhabitants and month.**

The use of tetracyclines decreases during the summer. The most commonly used tetracycline when measured in prescriptions/1000 inhabitants and month is doxycycline. This substance is mainly used in the treatment of respiratory tract infections, which may be one of the reasons why it is mostly used during the winter. Lymecycline, tetracycline and oxytetracycline are substances often used in the treatment of acne.

Treatment with tetracyclines may give rise to photosensibility. The intention to avoid skin damage caused by this may be one of the explanations to the decrease in use of all tetracyclines during the summer.

During the years 2003-2005 women received more medication with tetracyclines than men did, measured in DDD/1000/day as well as in prescriptions/1000/year (Table 3.1.4). However, men received longer periods of treatment and/or higher doses, indicated in Figure 3.1.4, which presents DDD/prescription for men and women in different age groups. The high value for young patients may be explained by the treatment of acne, where long periods of tetracyclines are often prescribed.

**Table 3.1.4. Tetracyclines in out-patient care 2003-2005, by gender.**

| | DDD/1000/day | | | Prescriptions/1000/year | | |
|---|---|---|---|---|---|---|
| | 2003 | 2004 | 2005 | 2003 | 2004 | 2005 |
| Men | 2.6 | 2.7 | 2.9 | 48.5 | 48.4 | 52.8 |
| Women | 3.3 | 3.3 | 3.5 | 67.2 | 66.4 | 71.5 |

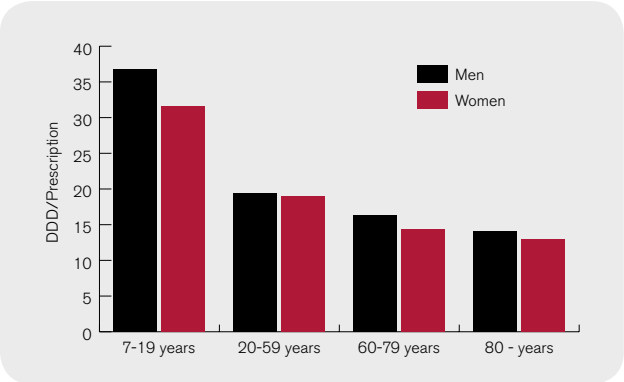


**Figure 3.1.4. Tetracyclines, out-patient care 2005, DDD/Prescription, men and women in different age groups.**

Figure 3.1.5 presents the difference in use of tetracyclines in the 21 counties of Sweden in 2005, measured in DDD/1000/day. Doxycycline is the substance largest in use in all counties, except for Örebro where the use of lymecycline is slightly larger. In this county, the drug committee recommends this substance in the treatment of acne. In Kalmar, on the other hand, the local drug committee recommends oxytetracycline for acne, which may be one of the reasons why the use of this substance is relatively large.

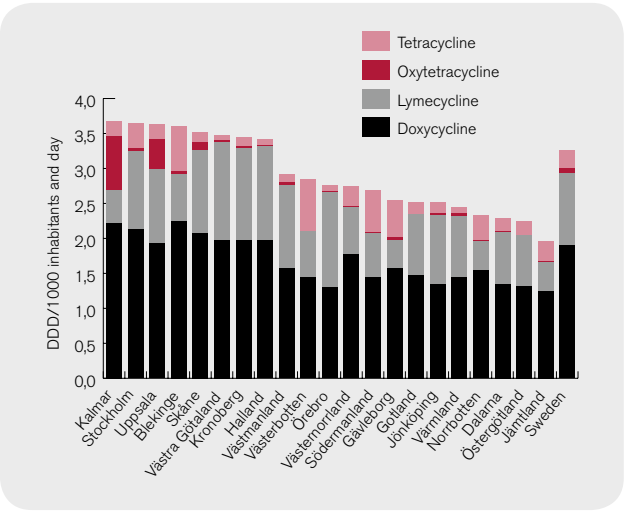


**Figure 3.1.5. Tetracyclines, out-patient care 2005 per county, DDD/1000/day.**

### *Fluoroquinolones*

The most commonly used fluoroquinolones in out-patient care during the period 2000-2005 were ciprofloxacin and norfloxacin (Figure 3.1.6). During the last few years, a number of generic ciprofloxacin products have become available on the Swedish market, resulting in lower prices. This may be one of the reasons why the use of ciprofloxacin has increased. The use of norfloxacin has decreased at approximately the same rate.

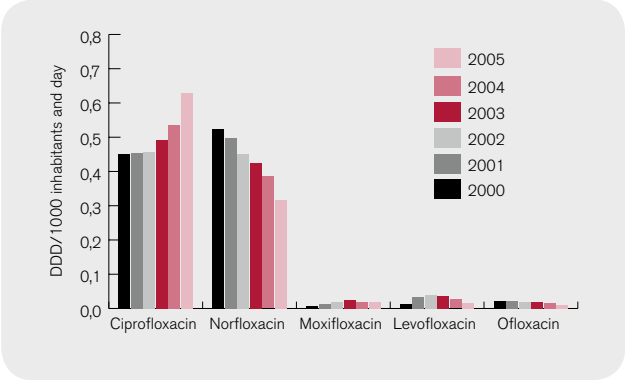


**Figure 3.1.6. Fluoroquinolones, out-patient care 2000-2005, DDD/1000/day.**

Figure 3.1.7 presents the variation in use of fluoroquinolones in the 21 counties of Sweden during the last year. In all counties ciprofloxacin is the largest in use, followed by norfloxacin.

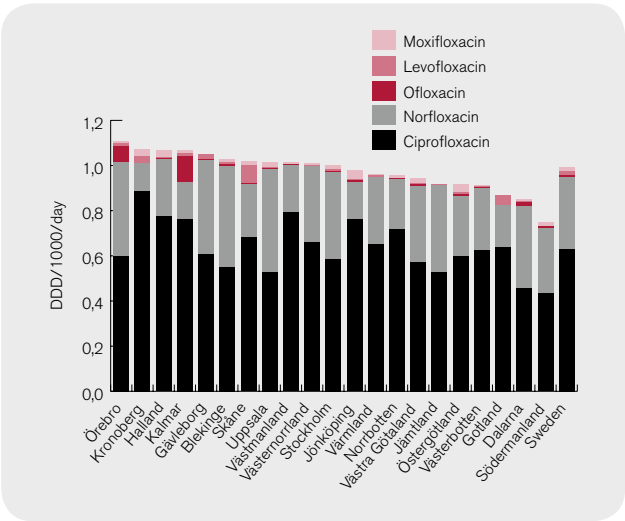


**Figure 3.1.7. Fluoroquinolones, out-patient care 2005 per county, DDD/1000/day.**

In 2005, the use of fluoroquinolones was most common in the treatment of older patients (Figure 3.1.8). Young women were treated more often than young men but among older patients the use was much higher in males.

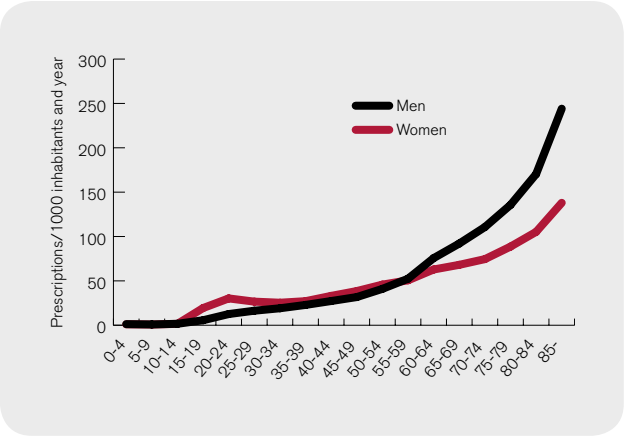


**Figure 3.1.8. Fluoroquinolones, out-patient care 2005, men and women in different age groups. Prescriptions/1000/year.**

Fluoroquinolones are still commonly used in the treatment of urinary tract infections. However, during the last six years their use has decreased and the use of pivmecillinam and nitrofurantoin has increased. (Figure 3.1.9) This reflects national and local recommendations to restrict the use of fluoroquinolones in the treatment of lower urinary tract infections in women.

**Gunilla Skoog, Gunilla Stridh**

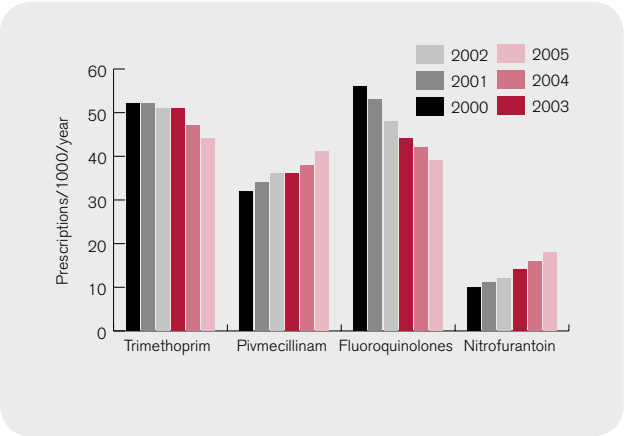


**Figure 3.1.9. Antibiotics mostly used against urinary tract infections, out-patient care 2000-2005. Women, prescriptions/1000/year.**

### *Antibiotic related adverse events*

Spontaneously reported adverse events are continuously registered in SWEDIS, a national database administered by the Swedish Medical Products Agency. The reports originate from medical personnel and the events are categorised as probably- or not probably drug-related. The frequencies of antibiotic related adverse events, judged as probably drug-related, during the last five years (2001-2005) were analysed for various groups of agents in order to monitor possible trends as a consequence of altered prescribing policies.

The five most commonly reported categories of adverse events, judged as probably related to the use of systemic

antibiotic drugs (J01), during the period 2001-2005 were skin- and subcutaneous tissue disorders (n= 361), hepatobiliary disorders (n=205), musculoskeletal disorders (n=179), gastrointestinal disorders (n=164) and general disorders (n=152). The majority of the reports (60%) were from female patients. The 10 antibiotic substances most commonly associated with adverse events, unadjusted for the consumption and regardless of the cause of the report, during the last 5 years were ciprofloxacin, flucloxacillin, trimethoprim, levofloxacin, nitrofurantoin, phenoxymethylpenicillin, clindamycin, doxycycline, norfloxacin and sulphamethotrexate plus trimethoprim.

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. In contrast, for nitrofurantoin that has been increasingly prescribed during the last 5 years, there are some indications of increased numbers of reported adverse events during this period (Table 3.1.5). 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.

No significant trends could be identified for frequencies of adverse events reported for beta-lactamase-sensitive penicillins (J01CE), beta-lactamase resistant penicillins (J01CF), tertacyclines (J01A), cephalosporins (J01D), trimethoprim +/- sulfonamides (J01E), macrolides (J01FA) or lincosamides (J01FF), in spite of altered consumption during the present period.

**Charlotta Edlund**

**Table 3.1.5. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2001–2005.**

| | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|
| **Fluoroquinolones** | | | | | |
| Total adverse events | 100 | 100 | 84 | 75 | 77 |
| Musculoskeletal | 20 | 38 | 22 | 34 | 24 |
| tendinitis | 11 | 23 | 14 | 15 | 13 |
| tendon rupture | 5 | 9 | 5 | 12 | 5 |
| Skin- and subcutaneous tissue | 16 | 11 | 16 | 7 | 11 |
| Psychiatric disorders | 7 | 6 | 9 | 4 | 10 |
| **Nitrofurantoin** | | | | | |
| Total adverse events | 13 | 17 | 32 | 48 | 26 |
| Respiratory system | 3 | 5 | 10 | 10 | 8 |
| dyspnoea | 1 | 1 | 4 | 3 | 2 |
| interstitial pneumonia | - | - | 4 | 2 | 2 |
| Skin- and subcutaneous tissue | 1 | 6 | 5 | 7 | 1 |
| General disorders | 5 | 3 | 9 | 11 | 7 |
| fever | 2 | 3 | 5 | 6 | 6 |

## Hospital care

Compared to the use in hospital care, the amount of antibiotics used in out-patient care is approximately ten-fold. The total systemic use of antibiotics in hospital care in 2000-2005 is shown in Table 3.1.6. The table shows an increase in the use of antibacterial drugs during this period, especially the use of methenamine, which has increased by 118%. As mentioned above, this substance is an antiseptic and therefore of no interest regarding antibiotic resistance.

**Table 3.1.6. Total use of antibacterial drugs for systemic use in hospital care 2000-2005, DDD/1000/day.**

| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
|---|---|---|---|---|---|---|
| J01 excl methenamine | 1.26 | 1.26 | 1.27 | 1.33 | 1.37 | 1.43 |
| Methenamine | 0.032 | 0.031 | 0.028 | 0.050 | 0.070 | 0.070 |
| Total J01 | 1.30 | 1.29 | 1.30 | 1.38 | 1.44 | 1.50 |

The distribution between different classes of antibiotics used in hospital care in 2005 is shown in Figure 3.1.10. There has been no major change since year 2004.

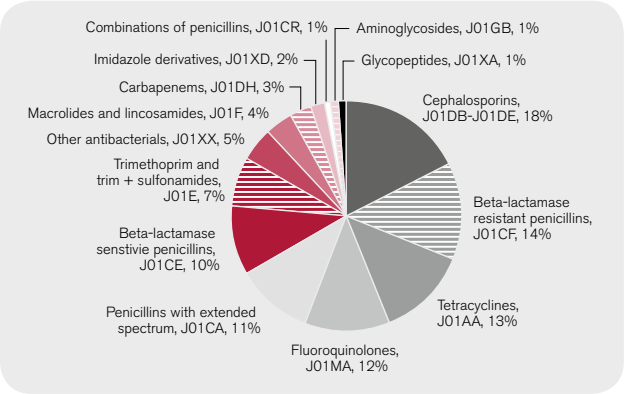


**Figure 3.1.10. Antibiotics in hospital care 2005, percent of total DDD/1000/day.**

Figure 3.1.11 presents the use of antibiotics in 2005 compared to the average yearly consumption during the period 2000-2004. The largest relative increase has been in the use of trimethoprim and combinations of penicillins. Both of these classes of antibiotics have been used more during the last three years than in 2000-2002.

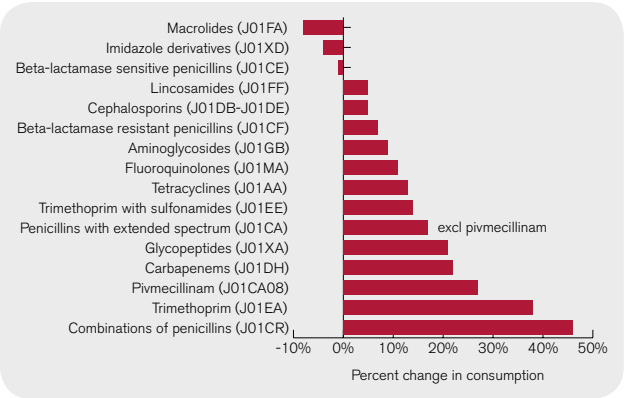


**Figure 3.1.11. Antibiotics in hospital care, change in comsumption measured in DDD/1000/day (%), 2005 compared to the average yearly consumption 2000-2004.**

The total use of the different classes of antibiotics in hospital care during the period 2003-2005 is shown in Figure 3.1.12.

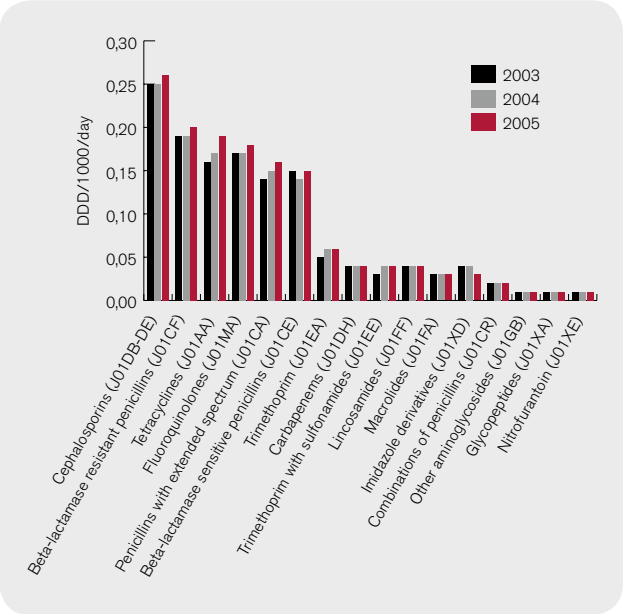


**Figure 3.1.12. Antibiotics in hospital care 2003-2005, DDD/1000/day.**

The number of hospital beds and the mean length of stay have decreased in Sweden during the period 1994-2004 (Figure 3.1.13).

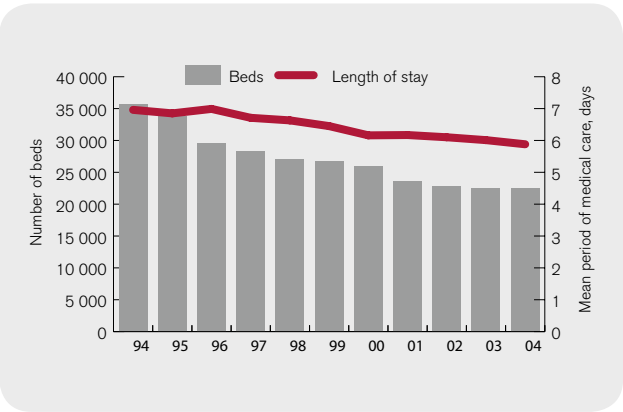


**Figure 3.1.13. Number of beds and mean length of stay in Swedish hospitals, somatic medical care, 1994-2004.**

In Tables 3.1.7 and 3.1.8 the use of antibiotics in hospital care during the period 1996-2004 is presented in terms of DDD/100 admissions and DDD/100 patient-days, respectively. Since 1996 the use of antibiotics has increased, especially in terms of DDD/100 patient-days (42%), but also in terms of DDD/100 admissions (19%).

The most commonly used classes of antibiotics in hospital care are cephalosporins, penicillins, tetracyclines and fluoroquinolones. The use of these drugs during the period 1996-2004 is shown in Figure 3.1.14. The figure shows an increase in the use of all these classes except for beta-lactamase sensitive penicillins.

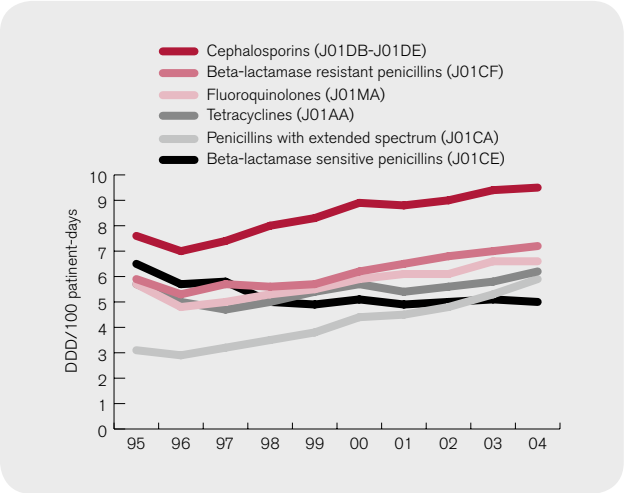


**Figure 3.1.14. Antibiotics, hospital care, 1996-2004, DDD/100 patient-days.**

Vancomycin, teicoplanin and linezolid are antibiotics used in the treatment of infections with MRSA, enterococci and multiresistant coagulase-negative staphylococci. The use of these substances in hospital care has increased during the last six years (Figure 3.1.15).

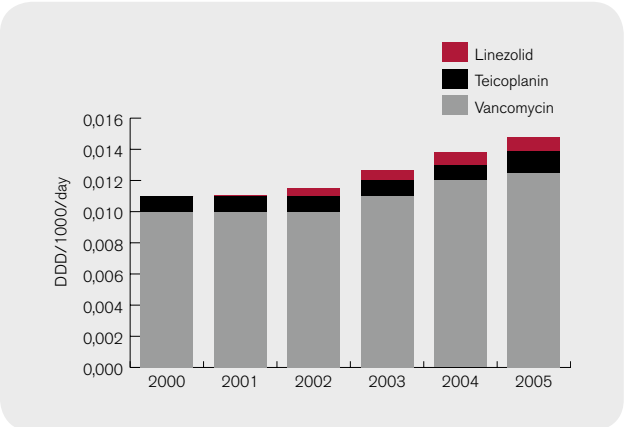


**Figure 3.1.15. Vancomycin, teicoplanin and linezolid in hospital care 2000-2005, DDD/1000/day.**

The use of linezoid in Sweden is still limited but increasing, especially in out patient care (Figure 3.1.16)

Sources: Data on numbers of patient-days, admissions, beds and mean period of medical care: The Swedish Association of Local Authorities and Regions. Sales statistics on antibiotics: The National Corporation of Swedish Pharmacies.

**Gunilla Skoog, Gunilla Stridh**

Table 3.1.7. Antibiotics in hospital care 1996-2004, DDD/100 admissions.

| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 |
|---|---|---|---|---|---|---|---|---|---|
| Tetracyclines (J01AA) | 34.7 | 31.8 | 33.1 | 34.9 | 34.8 | 33.6 | 34.3 | 34.9 | 36.4 |
| Penicillins with extended spectrum (J01CA) | 20.4 | 21.6 | 22.9 | 24.8 | 26.8 | 28.0 | 29.3 | 31.8 | 34.7 |
| Beta-lactamase sensitive penicillins (J01CE) | 39.5 | 38.8 | 33.1 | 31.9 | 31.7 | 30.5 | 30.4 | 30.7 | 29.5 |
| Beta-lactamase resistant penicillins (J01CF) | 37.1 | 37.9 | 36.9 | 36.9 | 37.9 | 40.2 | 41.4 | 42.3 | 42.5 |
| Combinations of penicillins (J01CR) | 1.6 | 1.9 | 2.1 | 2.3 | 2.8 | 2.8 | 3.2 | 4.0 | 4.7 |
| Cephalosporins (J01DB-E) | 49.2 | 49.8 | 52.7 | 53.4 | 54.6 | 54.0 | 55.0 | 56.4 | 55.6 |
| Carbapenems (J01DH) | 4.7 | 5.2 | 6.1 | 6.5 | 7.0 | 7.1 | 7.4 | 8.2 | 8.7 |
| Trimethoprim (J01EA) | 6.0 | 6.8 | 6.5 | 7.0 | 7.4 | 7.7 | 8.5 | 10.0 | 10.4 |
| Trimethoprim with sulfonamides (J01EE) | 5.8 | 5.9 | 6.0 | 6.1 | 6.6 | 6.6 | 6.9 | 7.2 | 7.7 |
| Macrolides (J01FA) | 6.6 | 6.5 | 6.4 | 6.5 | 6.3 | 6.3 | 5.9 | 5.5 | 5.4 |
| Lincosamides (J01FF) | 4.7 | 5.3 | 6.1 | 6.1 | 7.0 | 7.6 | 7.1 | 8.2 | 8.1 |
| Aminoglycosides (J01GB) | 3.0 | 2.9 | 2.8 | 2.9 | 3.1 | 3.0 | 2.9 | 3.0 | 3.2 |
| Fluoroquinolones (J01MA) | 33.7 | 33.5 | 34.9 | 35.5 | 36.5 | 37.4 | 37.1 | 39.4 | 38.9 |
| Glycopeptides (J01XA) | 1.8 | 1.9 | 2.3 | 2.2 | 2.3 | 2.5 | 2.5 | 2.8 | 3.0 |
| Imidazole derivatives (J01XD) | 6.7 | 7.0 | 7.4 | 7.6 | 8.1 | 8.1 | 8.5 | 8.3 | 8.1 |
| Methenamine (J01XX05) | 6.5 | 5.8 | 7.3 | 8.0 | 7.1 | 6.9 | 6.4 | 10.0 | 14.6 |
| Linezolid (J01XX08) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.2 | 0.2 |
| All agents (J01) | 264 | 264 | 269 | 275 | 282 | 285 | 289 | 305 | 315 |

Table 3.1.8. Antibiotics in hospital care 1996-2004, DDD/100 patient-days.

| | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 |
|---|---|---|---|---|---|---|---|---|---|
| Tetracyclines (J01AA) | 5.0 | 4.7 | 5.0 | 5.4 | 5.7 | 5.4 | 5.6 | 5.8 | 6.2 |
| Penicillins with extended spectrum (J01CA) | 2.9 | 3.2 | 3.5 | 3.8 | 4.4 | 4.5 | 4.8 | 5.3 | 5.9 |
| Beta-lactamase sensitive penicillins (J01CE) | 5.7 | 5.8 | 5.0 | 4.9 | 5.1 | 4.9 | 5.0 | 5.1 | 5.0 |
| Beta-lactamase resistant penicillins (J01CF) | 5.3 | 5.7 | 5.6 | 5.7 | 6.2 | 6.5 | 6.8 | 7.0 | 7.2 |
| Combinations of penicillins (J01CR) | 0.2 | 0.3 | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.7 | 0.8 |
| Cephalosporins (J01DB-E) | 7.0 | 7.4 | 8.0 | 8.3 | 8.9 | 8.8 | 9.0 | 9.4 | 9.5 |
| Carbapenems (J01DH) | 0.7 | 0.8 | 0.9 | 1.0 | 1.1 | 1.2 | 1.2 | 1.4 | 1.5 |
| Trimethoprim (J01EA) | 0.9 | 1.0 | 1.0 | 1.1 | 1.2 | 1.3 | 1.4 | 1.7 | 1.8 |
| Trimethoprim with sulfonamides (J01EE) | 0.8 | 0.9 | 0.9 | 1.0 | 1.1 | 1.1 | 1.1 | 1.2 | 1.3 |
| Macrolides (J01FA) | 0.9 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 0.9 | 0.9 |
| Lincosamides (J01FF) | 0.7 | 0.8 | 0.9 | 0.9 | 1.1 | 1.2 | 1.2 | 1.4 | 1.4 |
| Aminoglycosides (J01GB) | 0.4 | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Fluoroquinolones (J01MA) | 4.8 | 5.0 | 5.3 | 5.5 | 5.9 | 6.1 | 6.1 | 6.6 | 6.6 |
| Glycopeptides (J01XA) | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 |
| Imidazole derivatives (J01XD) | 1.0 | 1.0 | 1.1 | 1.2 | 1.3 | 1.3 | 1.4 | 1.4 | 1.4 |
| Methenamine (J01XX05) | 0.9 | 0.9 | 1.1 | 1.2 | 1.2 | 1.1 | 1.0 | 1.7 | 2.5 |
| Linezolid (J01XX08) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| All agents (J01) | 37.7 | 39.4 | 40.5 | 42.6 | 45.8 | 46.1 | 47.4 | 50.8 | 53.5 |

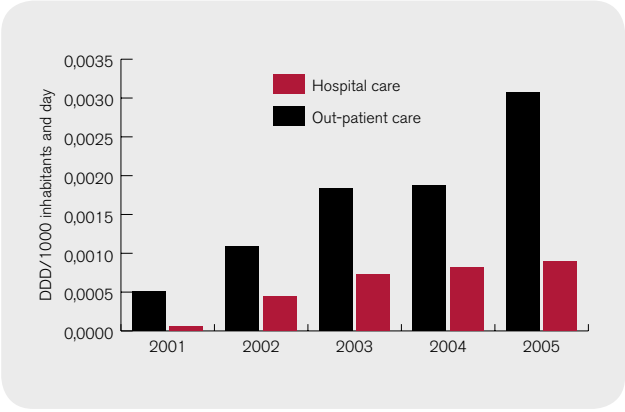


Figure 3.1.16. Linezolid, out-patient care and hospital care 2001–2005, DDD/1000/day.

**Indicators to detect underprescribing of antibiotics.**
During the last 15 years the number of prescriptions of antibiotics has been reduced by approximately 50% among children. Because of this, it is important to find out if there are any signs of under prescribing of antibiotics.

The number of prescriptions/1000 children and year for different age-groups from the pharmaceutical register at the National Board of Health and Welfare was followed during the period 1987-2004. From the national registry of diagnosis in hospital care, data on the number of patients with acute rhinosinusitis, quinsy and acute mastoiditis was obtained for different age-groups from 1987-2004 (Figure 3.1.17).

There were about 100 hospital admissions for mastoiditis and 300 for rhinosinusitits every year in children 0-14

years old. Between 1987 and 2004 hospital admissions for acute mastoiditis, acute rhinosinusitis and quinsy in children decreased. The total number of acute mastoiditis decreased in children 0-14 years from approximately 10 to 8 cases per 100 000 inhabitants.

This survey of hospital admissions for certain infectious diagnoses that may be related to too low antibiotic use, shows that these selected diagnoses have been stable or declining despite the reduction in antibiotic prescribing to children. Thus, there are so far no signs of underprescribing. However to fully secure that a further reduction in antibiotic use does not increase the number of complications or give prolonged periods of illness, more sensitive systems for surveillance of treatment effects are necessary.

**Christer Norman**


**Figure 3.1.17. Prescriptions of antibiotics per 1000 children 1987-2004 and hospital admissions for mastoiditis, quinsy and rhinosinusitis in children at different age groups**

### ESAC

Sweden is participating in the project European Surveillance of Antimicrobial Consumption, ESAC. Sales data of antibiotic use have been collected since 2001, retrospectively from 1997. 34 countries participated in 2005. The out-patient use of fluoroquinolones in 25 countries in 2003 is shown in figure 3.1.18. Substances other than those mentioned in the figure are used to an extent less than 1%. The use of fluoroquinolones in Portugal is 12 times higher than in Denmark. Sweden has a relatively high use of fluoroquinolones compared to the other Nordic countries.

**Gunilla Skoog**

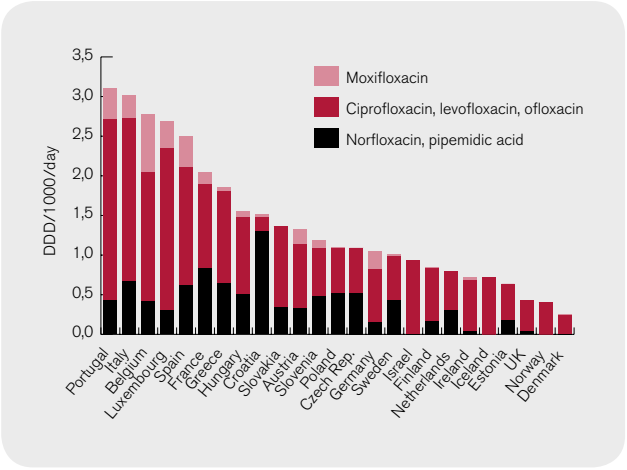


**Figure 3.1.18. Out-patient consumption of fluoroquinolones in 25 European countries 2003, ESAC project.**

## 3.2.Use of antifungals in hospital care

The use of systemic antifungals within hospital care has not increased significantly the last few years. Two new substances, voriconazole and caspofungin introduced on the market in 2002, have however increased slightly. The dominating antifungal in Sweden, fluconazole, also continues to increase. On the other hand the use of amphotericin and itraconazole have decreased (Figure 3.2.1). About 20% of fluconazole and 15% of voriconazole is given parenterally.

**Gunilla Skoog**

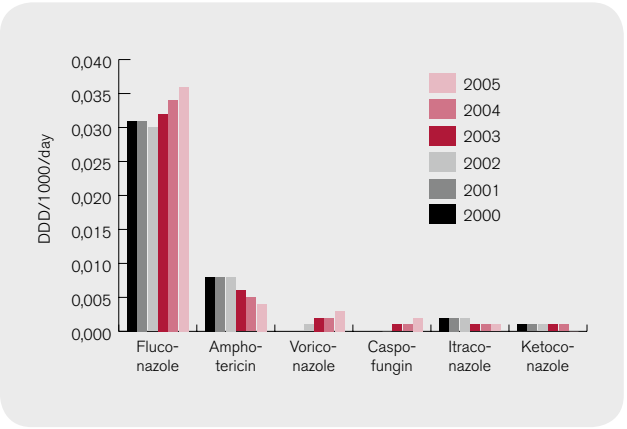


**Figure 3.2.1. Use of antifungals in hospital care, 2000-2005, DDD/1000/day.**

# 4. Antimicrobial resistance

In Sweden, routine susceptibility testing of clinical isolates is performed using standardized methods (Appendix 4). According to the national programme for surveillance of resistance that has been in place for more than five years (Appendix 5), well-characterised data on many bacterial pathogens are now available.

## *Staphylococcus aureus*

### Background

Compared to many other European countries, the prevalence of MRSA in Sweden is still low. Policies for screening high-risk patients for multiresistant bacteria and continuous surveillance have been of importance to prevent spread of the organism. The decision to include infection as well as colonisation/carriage with MRSA in the Communicable Disease Act in the year 2000 was caused by an increasing alertness, responding to the situation seen in many other European countries, where MRSA now represents an increasing proportion of staphylococcal infections in hospital settings, often exceeding 50%.

### Notifications of MRSA according to the Communicable Disease Act

During 2005 a total of 975 cases were notified to the Swedish Institute for Infectious Disease Control, (Table 4.1 and Figure 4.1). This represents an increase of 37% compared to 2004 and is a continuation of the trend seen since the beginning of mandatory notifications in 2000. Most of the Swedish counties have experienced an increasing incidence of MRSA cases. All age groups and both sexes were affected, with incidence rising with age. Fifty five percent of the cases were acquired MRSA in Sweden, 23% acquired it abroad and for 22% the place of acquisition was unknown or not reported. From the notifications, information on patient characteristics (infection or colonisation) and acquisition of MRSA (health care related or community acquired) is often incomplete or missing. Only the situation in Stockholm can be described in more detail.

In Stockholm county the number of patients infected or colonised in the health care setting was only 9%, compared to 51% in 2003. Community acquired MRSA has increased and is now 30% compared to 15% in 2003. Patients infected abroad have increased from 40 in 2003 to 100 in 2005.

**Table 4.1. MRSA notified in 2000–2005 by county according to the Communicable Disease Act.**

| | 2000 | | 2001 | | 2002 | | 2003 | | 2004 | | 2005 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **County** | **No** | **Inc*** | **No** | **Inc*** | **No** | **Inc*** | **No** | **Inc*** | **No** | **Inc*** | **No** | **Inc*** |
| Stockholm | 96 | 5.2 | 166 | 9.0 | 205 | 11.1 | 229 | 12.3 | 277 | 14.8 | 315 | 17.1 |
| Uppsala | 18 | 6.1 | 17 | 5.7 | 10 | 3.3 | 12 | 4.0 | 25 | 8.2 | 28 | 9.2 |
| Södermanland | 2 | 0.7 | 1 | 0.3 | 4 | 1.5 | 2 | 0.7 | 8 | 3.0 | 11 | 3.8 |
| Östergötland | 2 | 0.4 | 7 | 1.6 | 7 | 1.6 | 14 | 3.3 | 14 | 3.3 | 101 | 24.3 |
| Jönköping | 7 | 2.1 | 6 | 1.8 | 5 | 1.5 | 24 | 7.3 | 14 | 4.2 | 40 | 12.1 |
| Kronoberg | 1 | 0.5 | 0 | 0 | 4 | 2.2 | 5 | 2.8 | 17 | 9.5 | 11 | 6.1 |
| Kalmar | 3 | 1.2 | 2 | 0.8 | 5 | 2.1 | 6 | 2.5 | 16 | 6.8 | 23 | 9.7 |
| Gotland | 1 | 1.7 | 10 | 17.3 | 3 | 5.2 | 3 | 5.2 | 1 | 1.7 | 10 | 17.3 |
| Blekinge | 5 | 3.3 | 1 | 0.6 | 3 | 1.9 | 2 | 1.3 | 3 | 1.9 | 9 | 5.9 |
| Skåne | 21 | 1.8 | 75 | 6.6 | 68 | 5.9 | 99 | 8.6 | 131 | 11.3 | 162 | 13.9 |
| Halland | 10 | 3.6 | 25 | 9.0 | 13 | 4.6 | 13 | 4.6 | 4 | 1.4 | 21 | 7.4 |
| Västra Götaland | 106 | 7.1 | 52 | 3.4 | 47 | 3.1 | 61 | 4.0 | 116 | 7.6 | 125 | 8.1 |
| Värmland | 9 | 3.2 | 7 | 2.5 | 5 | 1.8 | 11 | 4.0 | 18 | 6.5 | 9 | 3.2 |
| Örebro | 8 | 2.9 | 6 | 2.1 | 16 | 5.8 | 8 | 2.9 | 12 | 4.3 | 16 | 5.8 |
| Västmanland | 3 | 1.1 | 8 | 3.1 | 7 | 2.7 | 11 | 4.2 | 12 | 4.6 | 35 | 13.4 |
| Dalarna | 0 | 0 | 4 | 1.4 | 2 | 0.7 | 2 | 0.7 | 3 | 1.0 | 6 | 2.1 |
| Gävleborg | 2 | 0.7 | 1 | 0.3 | 13 | 4.6 | 5 | 1.8 | 5 | 1.8 | 24 | 8.6 |
| Västernorrland | 14 | 5.6 | 12 | 4.8 | 7 | 2.8 | 10 | 4.0 | 5 | 2.0 | 4 | 1.6 |
| Jämtland | 0 | 0 | 0 | 0 | 2 | 1.5 | 5 | 3.9 | 1 | 0.7 | 8 | 6.2 |
| Västerbotten | 3 | 1.1 | 18 | 7.0 | 10 | 3.9 | 13 | 5.0 | 16 | 6.2 | 10 | 3.8 |
| Norrbotten | 3 | 1.1 | 5 | 1.9 | 6 | 2.3 | 9 | 3.5 | 7 | 2.7 | 8 | 3.1 |
| **Total** | **314** | **3.5** | **423** | **4.7** | **442** | **4.9** | **544** | **6.0** | **705** | **7.8** | **975** | **10.8** |

* Inc = Incidence/100 000 inhabitants.

Transmission of MRSA is also reported in homes for the elderly, often found through contact tracing.

The most dramatic increase in numbers of MRSA cases in 2005 was seen in Östergötland county, where two hospital-related outbreaks contributed to the highest incidence per 100 000 inhabitants and county noted during the investigation period, 24/100 000 inhabitants (Table 4.1). Other counties with high incidence figures were Stockholm, Jönköping, Gotland, Skåne and Västmanland.

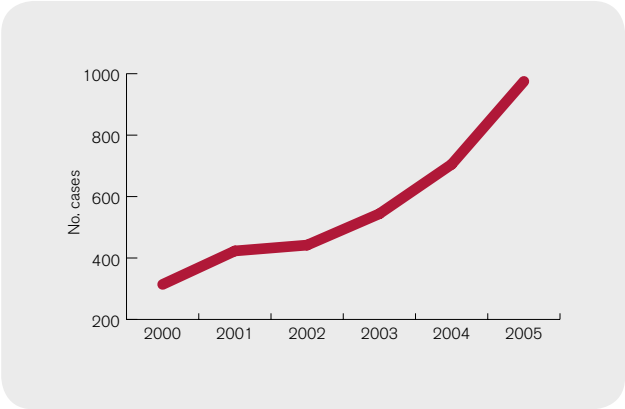


**Figure 4.1. Number of reported cases of MRSA per year, Sweden 2000-2005.**

## Typing of MRSA

A DNA-based method has been used for typing of all MRSA isolates since the year 2000 (pulsed field gel electrophoresis, PFGE). PFGE patterns of the Swedish isolates were compared with international reference strains (epidemic MRSA from European countries, the Harmony project) and were included in a database (Table 4.2). Awaiting international consensus on nomenclature, names were adopted from the Harmony project for patterns identical to one of the reference strains (e.g. UK E15). Other patterns, when found in isolates from at least two patients, were given Swedish designations including the year of isolation (e.g. SE97-3). These patterns could be either related or unrelated to a reference strain. As a link to recent proposals on nomenclature of MRSA, the sequence types (ST) of reference strains, using a sequence-based method (MLST, see www.mlst.net), are also shown in Table 4.2.

Isolates with PFGE patterns identical to or related to UK E15 (ST22) were the most frequently seen each year since 2001, but they were less dominating during the last two years depending on the more favourable situation in the Stockholm area . The second most common group of isolates were those with patterns identical or related to DK E97-1. They were found in all Swedish counties although predominantly in the Skåne and Västra Götaland regions. These isolates are often referred to as community acquired, and they are always PVL-positive. In 2005, MRSA with PFGE patterns identical to or related toBel EC-3a (ST5) were the second most common, largely due to the hospital epidemic of type SE01-9 in Östergötland. Isolates with Berlin IV like PFGE patterns (ST45) are continuously found in all parts of Sweden. Isolates with UK E1 related PFGE patterns are 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 the genes coding for the Panton-Valentine leucocidin (PVL). All isolates of the DK E97-1 group were found positive, one clone each among the UK E16 and Fra B groups, (SE00-3 and SE00-7, respectively), and also isolates with the patterns SE01-3, SE02-18 and SE03-5.

## 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 oxacillin (from 2004 cefoxitin has replaced oxacillin as the screening 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 4.2.

**Table 4.2. PFGE patterns of MRSA isolated in Sweden 2000–2005.**

| PFGE pattern | ST of reference patterns | No. of isolates with identical or related patterns (% of total per year) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 |
| UK E15 | 22 | 22 (6.9) | 76 (18.4) | 107 (24.4) | 119 (21.9) | 103 (16.7) | 124 (15.9) |
| DK E97–1 | 80 | 38 (16.9) | 54 (13.1) | 73 (16.7) | 80 (14.7) | 89 (14.5) | 116 (14.9) |
| Berlin IV | 45 | 24 (7.5) | 52 (12.6) | 14 (3.2) | 63 (11.6) | 67 (10.9) | 99 (12.7) |
| Bel EC-3a | 5 | 11 (3.4) | 19 (4.6) | 32 (7.3) | 46 (8.8) | 45 (7.3) | 121 (15.5) |
| UK E16 | 36 | 79 (24.7) | 48 (11.6) | 41 (9.4) | 34 (6.3) | 47 (7.6) | 54 (6.9) |
| UK E1/Spa E1/Gr-1 | 239, 241 | 46 (14.4) | 41 (9.9) | 45 (10.3) | 39 (7.2) | 51 (8.3) | 67 (8.6) |
| Fra A | 8 | 29 (9.1) | 31 (7.5) | 34 (7.8) | 33 (6.1) | 17 (2.8) | 10 (3.1) |
| Fra B | 8 | 3 (0.9) | 18 (4.4) | 16 (3.7) | 31 (5.7) | 45 (7.3) | 50 (6.4) |
| UK E3 | 5 | 5 (1.6) | 10 (2.4) | 13 (3.0) | 15 (2.8) | 29 (4.7) | 14 (1.8) |
| S German II | 228 | 4 (1.3) | 5 (1.2) | 8 (1.8) | 7 (1.3) | 6 (1.0) | 6 (0.8) |
| Unrelated SE-patterns and unique | Not tested | 43 (13.4) | 59 (14.3) | 55 (12.6) | 75 (13.8) | 116 (18.9) | 118 (15.1) |
| **Total** | | **320** | **413** | **438** | **544** | **615** | **779** |

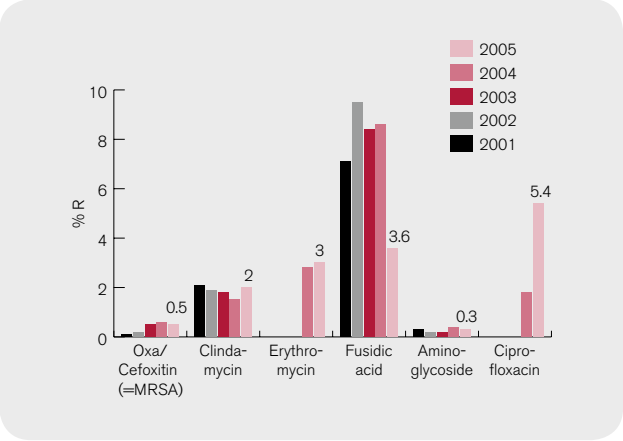


**Figure 4.2.. Resistance rates for *Staphylococcus aureus* 2001–2005 (data from the annual RSQC programme, approximately 3000 isolates per year).**

In 2005 resistance rates were recorded in *S.aureus* isolated from wounds and secretions from elderly people (> 65 years). This might be one of the reasons for the trends in these point prevalence resistance rates. MRSA in wound infections, detected by the oxacillin and from 2004 the cefoxitin screening disks, did not continue to increase in 2005. An increasing number of screening cultures taken might explain this decrease. The high rates of fusidic acid resistance in wound infections from 2001-2004 were not seen in 2005, probably because the fusidic acid resistant clone (MIC of fusidic acid 4 mg/L) causing impetigo in young children had not affected the elderly population. On the other hand the rate of ciprofloxacin resistance had increased markedly, and this may implicate overuse of fluoroquinolones in patients with wound infections.

## Data from 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 2005, 1.0% of the invasive *S. aureus* isolates were MRSA (identified by the cefoxitin screen disk test and confirmed by the detection of the *mecA* gene). Swedish data from the previous five years indicated a low rate of MRSA among invasive isolates (Table 4.3). Comparative data for Europe are given in Figure 4.3.

**Anders Blaxhult, Barbro Olsson-Liljequist, Åke Örtqvist**

**Table 4.3. *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%) |

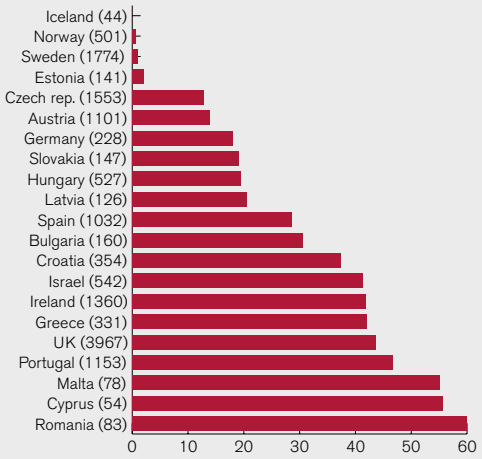


**Figure 4.3. MRSA in Europe 2005. Data from EARSS (www.ears.rivm.nl 2006-04-20).**

## *Streptococcus pneumoniae*

### Background

Infection and carriage due to *S. pneumoniae* with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (henceforth designated PRP) has been notifiable according to the Communicable Disease Act since 1996.

### Notifications according to the Communicable Disease Act Surveillance

During the time period 1997 to 2002 the number of PRP cases decreased from 896 to 525, but since then increased to 653 in 2004 and 654 in 2005. Most cases were identified through nasopharyngeal culture. Even though we observe fluctuations in the annual incidence rate per 100 000 population, the incidence decreased during 1997 to 2005 from 10.1 to 7.3 (Figure 4.4). Previous analysis has indicated that the declining incidence is related to a concurrent decrease in nasopharyngeal culturing propensity. Also, 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. Due to this, comparison of regional data will probably not reflect true differences in the incidence rates. In 2005 the incidence per 100 000 of males and females, respectively was 7.6 versus 6.9 (ratio 1.1). Also, 59% of the cases reported with PRP were below 5 years of age. In 30 cases (5%) the PRP isolates came from invasive sites, i e blood and/or spinal fluid.

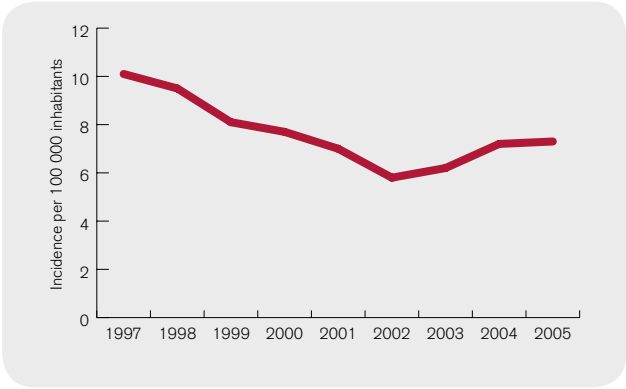


**Figure 4.4. Annual PRP incidence 1997-2005.**

Multiresistance was common among PRP. During 1997 to 2003 approximately 80% of PRP were resistant to trimethoprim with sulfonamides, and 30% resistant to tetracycline or erythromycin. Reduced susceptibility to penicillin alone decreased from 21% in 1997 to 6% in 2003.

All pneumococci with a reduced susceptibility to penicillin (MIC PcG ≥ 0,5 mg/L) have been collected to Swedish Institute for Infectious Disease Control from the Microbiological laboratories in Sweden since Spring 1998. The most common serotypes/groups found are type 9, 14, 19, 23, 6 och 35. Serogroup 9 has been the predominating type for many years, but serotypes 14 and 19 have increased lately (see Figure 4.5).

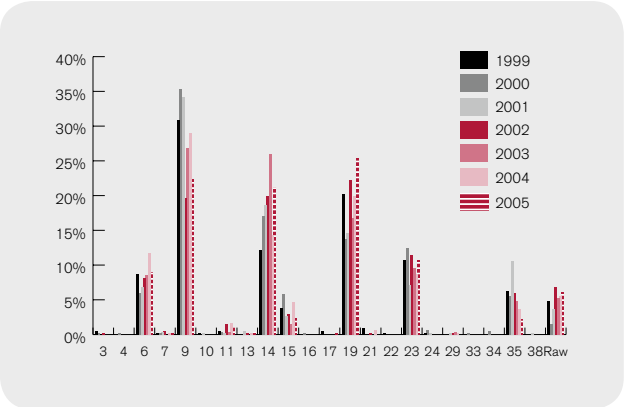


**Figure 4.5. *Streptococcus pneumoniae* penicillin MIC ≥ 0,5mg/L 1999-2005 in Sweden**

### Annual Resistance Surveillance and Quality Control (RSQC) programme

Pneumococci have been one of the target pathogens for the annual Resistance Surveillance and Quality Control (RSQC) programme since 1994. In these studies, approximately 3000 consecutive clinical isolates of *S. pneumoniae*, i.e. 100 isolates from each of all clinical microbiology laboratories, have been tested for susceptibility to penicillin (by means of oxacillin 1 µg screen disk test), erythromycin, tetracycline, and the combination of sulfonamide and trimethoprim, using the disk diffusion method. The national overview of these studies is given in Figure 4.6. A trend of increasing resistance is seen for all four groups of antibiotics.

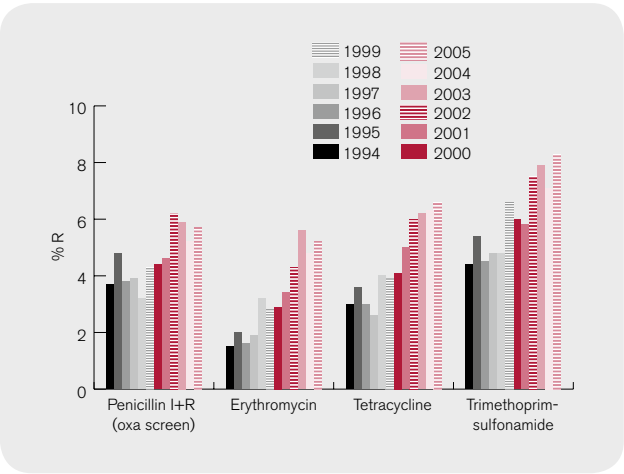


**Figure 4.6. National resistance rates of *S. pneumoniae* (resistant isolates in percent of all pneumococcal isolates) for four different antibiotics 1994–2005 (data from the annual RSQC programme, approximately 3000 isolates per year).**

### Data from 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 (European Antimicrobial Resistance Surveillance System), enabling comparisons with other European countries (Figure 4.7).

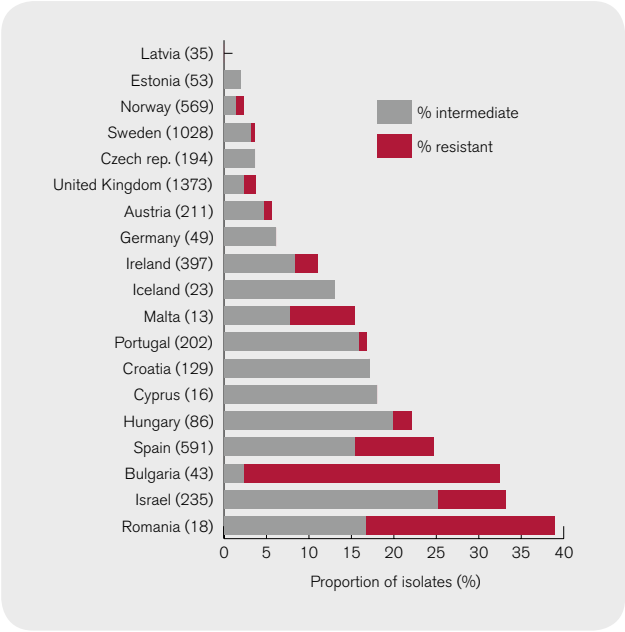


**Figure 4.7. Frequencies of reduced susceptibility to penicillin among invasive isolates of *Streptococcus pneumoniae* in Europe 2005. Data from EARSS (www.earss.rivm.nl 2005-04-20).**

The Swedish data on susceptibility to penicillin and erythromycin for the last five years is given in Table 4.8. Overall levels of resistance have been lower in invasive isolates than in the nasopharyngeal isolates from the RSQC programme. This could partly be explained by a lower proportion of samples from children among the invasive isolates. It should be noted that MIC breakpoints for EARSS reporting (penicillin G MIC > 0.12 mg/L – PNSP) and notification by the Communicable Disease Act (MIC > 0.5 mg/L – PRP) differ, and the figures from the different reporting systems are therefore not directly comparable.

**Birgitta Henriques Normark, Barbro Olsson-Liljequist, Victoria Romanus**

**Table 4.8. Invasive isolates of *Streptococcus pneumoniae* reported to EARSS.**

| | Penicillin* | | | |
|---|---|---|---|---|
| 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 |
| | 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 |

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

# *Enterococcus faecium* and *faecalis*

## Background

Enterococci, and more specifically vancomycin resistant enterococci (VRE), have become important causes of nosocomial outbreaks in many parts of the world, usually involving high-risk populations such as immunosuppressed and intensive care patients. Like MRSA, VRE were first made a notifiable pathogen in Sweden in the year 2000 according to the Communicable Disease Act and is since 2004 classified as mandatorily notifiable.

## Notifications of VRE according to the Communicable Disease Act

From 2000 to 2004 the number of reported cases of VRE were between 18 and 47. In 2005 there were 33 cases (Figure 4.8). Four counties have been responsible for the vast majority of cases, and these are Stockholm (2000-2003), Västerbotten (2000), Skåne (2003-2005) and Örebro (2003). In 2005 there were 19 cases reported from Skåne. Of these there were at least14 patients and one staff originating from the same surgical ward. The 14 patients had a median age of 84 years.

The median age for all cases reported in 2005 was 69 years compared to 60 in 2002, 67 in 2003 and 74 in 2004.

The majority of VRE reported according to the Communicable Disease Act 2000 – 2005 were *Enterococcus faecium* carrying the *vanB* gene (n=148), whereas 8 were *Enterococcus faecium* with *vanA*-gene, 3 *Enterococcus faecalis* with *vanA* and 1 *Enterococcus faecalis* with *vanB*.

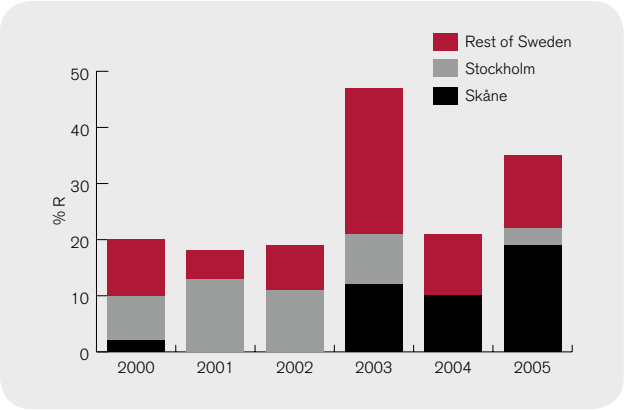


**Figure 4.8. Annual number of VRE cases reported in Sweden.**

## Annual Resistance Surveillance and Quality Control (RSQC) programme

There are no data in the RSQC programme on antibiotic resistance in *Enterococcus faecalis* and *Enterococcus faecium* for 2005.

## Data from 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

Table 4.9.Susceptibility of invasive isolates of *Enterococcus faecalis* in Sweden 2001-2005.

| | 2001 Total (%R) | 2002 Total (%R) | 2003 Total (%R) | 2004 Total (%R) | 2005 Total (%R) |
|---|---|---|---|---|---|
| Ampicillin | 479 (0) | 453 (0) | 612 (0) | 590 (0.3) | 570 (0) |
| Amino-glycosides | 212 (12.7) | 235 (17) | 440 (17.5) | 533 (15.4) | 492 (18.7) |
| Vanco-mycin | 395 (0) | 430 (0) | 593 (0) | 592 (0) | 567 (0) |

Table 4.10. Susceptibility of invasive isolates of *Enterococcus faecium* in Sweden 2001-2005.

| | 2001 Total (%R) | 2002 Total (%R) | 2003 Total (%R) | 2004 Total (%R) | 2005 Total (%R) |
|---|---|---|---|---|---|
| Ampicillin | 196 (71) | 167 (72) | 241 (76.3) | 260 (78.1) | 253 (72.3) |
| Amino-glycosides | 99 (9.1) | 96 (6.3) | 170 (11.2) | 227 (7.0) | 211 (4.3) |
| Vanco-mycin | 169 (0) | 181 (0) | 231 (2.2) | 260 (1.2) | 253 (0) |

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 vancomycin-resistant invasive isolates of *Enterococcus faecium* were reported, and in 2004 3 isolates were found, representing 1.2% (Tables 4.9 and 4.10). High-level aminoglycoside resistance was more prevalent in *Enterococcus faecalis* (13-18%) than in *Enterococcus faecium* (6-11%) during this period.

**Anders Blaxhult, Barbro Olsson-Liljequist**

# *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 (Figure 4.9). The average resistance rates to ampicillin have increased yearly, from 17 to 24%. The same is true for trimethoprim with an average increase from 10 to15%. Fluoroquinolone resistance, detected by the screening disk nalidixic acid since 2002, has shown a slight increase during this period and reached an average of 9.3% in 2005.

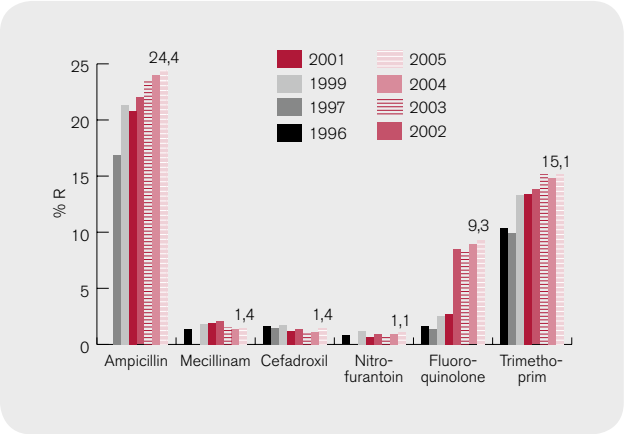


Figure 4.9. Resistance rates (resistant isolates in percent of all *Escherichia coli* isolates) for six antibiotics 1996-2005. *Between 1996-2001 fluoroquinolone resistance was detected with Norfloxacin, from 2002 with Nalidixic acid.

## Data from the EARSS network

*Escherichia coli* derived from invasive infections (blood isolates) have been part of the European Antimicrobial Resistance Surveillance System (EARSS) since the year 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 to fluoroquinolones.

Twenty-one Swedish laboratories have taken part in this surveillance and have delivered data on more than 3200 blood isolates in 2005. Results for 2001–2005 are presented in Table 4.11. 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 tested in the RSQC programme (see Figure 4.9.), yet these figures are low compared to most other countries in Europe. The level of resistance to third generation cefalosporins among blood isolates has increased to 1.3%, and in the majority (0.9%) this resistance was attributed to the presence of ESBLs. ESBLs of CTX-M type were most frequently found. Aminoglycoside resistance in *Escherichia coli* is still

extremely rare in Sweden. Resistance to fluoroquinolones has increased every year and exceeded 10% in 2004. Taking into account both resistant (R) and intermediate (I) isolates, the rates are almost the same in blood as in urine isolates. Data on fluoroquinolone resistance from other European countries 2005 are presented in Figure 4.10.

**Barbro Olsson-Liljequist, Gunnar Kahlmeter**

**Table 4.11. *E. coli* from blood in Sweden 2001–2005, reported to EARSS.**

| | 2001 Total (%R) | 2002 Total (%R) | 2003 Total (%R) | 2004 Total (%R) | 2005 Total (%R) |
|---|---|---|---|---|---|
| Ampicillin | 1513 (26.5) | 1753 (24.9) | 1953 (28.5) | 2019 (23.0) | 1918 (26.0) |
| Cefotaxime (3rd gen cef /ESBL) | 2627 (0.5) | 3062 (0.5) | 3300 (0.4) | 3290 (0.6/0.5) | 3212 (0.4/0.9) |
| Aminogly-cosides* | 1241 (1.0) | 1585 (0.6) | 2819 (1.0) | 3313 (1.5) | 3202 (1.5) |
| Fluoroqui-nolones (Cip I/R) ** | 2273 (1.8/3.7) | 2414 (2.0/5.1) | 3120 (1.7/6.6) | 3336 (3.5/7.6) | 3049 (2.6/6.3) |

*gentamicin, tobramycin, ** cip = ciprofloxacin

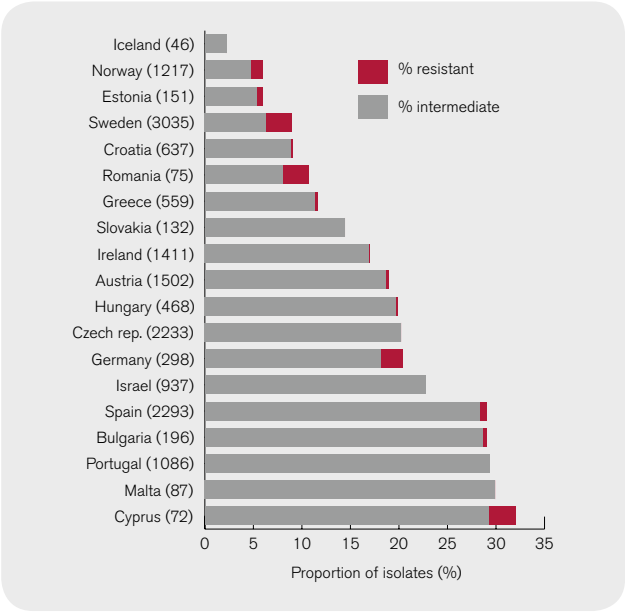


**Figure 4.10. Resistance rates (% R and I) to fluoroquinolones in *Escherichia coli* in Europe 2005. Data from EARSS (www.earss.rivm.nl 2006–04–20).**

# *Klebsiella pneumoniae*

## Annual Resistance Surveillance and Quality Control (RSQC) programme

*Klebsiella pneumoniae* was included in the 2005 RSQC programme for the first time since 1994. There are two reasons for this, one that *Klebsiella pneumoniae* is one of the most important bacterial species from a hospital infection control point of view, and another that this species has also been 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 4.11).

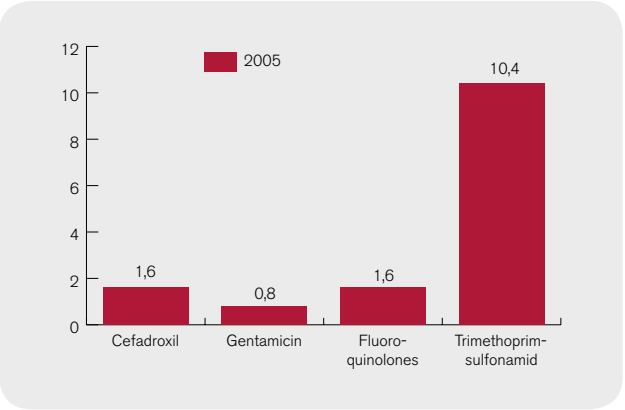


**Figure 4.11. Resistance rates (resistant isolates in percent of all *Klebsiella pneumoniae* Isolates) for four different antibiotics 2005. *Nalidixic acid.**

## Data from EARSS

From 1 July 2005, participants in the EARSS network have been asked to contribute with data on blood isolates of *Klebsiella pneumoniae*. From Sweden a total of 281 isolates from 20 laboratories have been tested, and the results are shown in Table 4.12.

**Table 4.12. *Klebsiella pneumoniae* from blood in Sweden 2005, reported to EARSS.**

| | 2005 Total (%R) |
|---|---|
| Cefotaxime (3rd gen cef/ESBL) | 281 (0.7/0.7) |
| Aminoglycosides* | 279 (1.4) |
| Fluoroquinolones (Cip I/R) ** | 265 (5.3/4.5) |

* gentamicin, tobramycin, ** cip = ciprofloxacin

## Voluntary reporting of resistant isolates

Rare cases of both *Klebsiella pneumoniae* and *Klebsiella oxytoca*, exhibiting high-level resistance to third generation cefalosporins, often caused by ESBLs, are found. 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. During 2005 there has

been a high number of ESBL-containing and multi-resistant isolates of *Klebsiella pneumoniae* in Uppsala county, both hospital- and community-related, which accentuates the importance of basic hygiene procedures.

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.

**Barbro Olsson-Liljequist**

## *Pseudomonas aeruginosa*

### Annual Resistance Surveillance and Quality Control (RSQC) programme

There are no new data in the RSQC programme on *Pseudomonas aeruginosa* for 2005, but new data will be collected in 2006.

### Data from EARSS

From 1 July 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 have been tested, and the results are shown in Table 4.13.

**Barbro Olsson-Liljequist**

**Table 4.13. *Pseudomonas aeruginosa* from blood in Sweden 2005, reported to EARSS.**

| | 2005 Total (%R) |
|---|---|
| Ceftazidime | 149 (4.7) |
| Imipenem | 57 (17.5 |
| Aminoglycosides* | 149 (0.0) |
| Fluoroquinolones (Cip I/R) ** | 133 (3.0/6.0) |

* = gentamicin, tobramycin, ** cip = ciprofloxacin

## *Haemophilus influenzae*

### Notifications according to the Communicable Disease Act

All invasive *Haemophilus influenzae* infections became notifiable according to the Communicable disease act of 2004. During 2005, a total of 118 cases were notified.

### Annual Resistance Surveillance and Quality Control (RSQC) programme

Respiratory isolates of *Haemophilus influenzae* were included in the RSQC programme on antibiotic resistance in 2005 after a three-year pause. Aapproximately 3000 clinical isolates of *Haemophilus influenzae* (100 consecutive isolates from each of the clinical microbiology laboratories) have been tested for resistance to beta-lactam drugs (beta-lactamase production and non-beta-lactamase mediated penicillin/cephalosporin resistance, so called BLNAR, best detected by loracarbef), tetracycline, and the combination of sulfonamide and trimethoprim, using the disk diffusion method. The national overview of these data is given in Figure 4.12. The average level of beta-lactam resistance has not increased during the last four years, but the range between individual laboratories and counties was 5-27%. An average increase in strains resistant to trimethoprim-sulfamethoxazole was seen in 2005, but again with a wide range between individual laboratories (4-18%).

**Barbro Olsson-Liljequist**

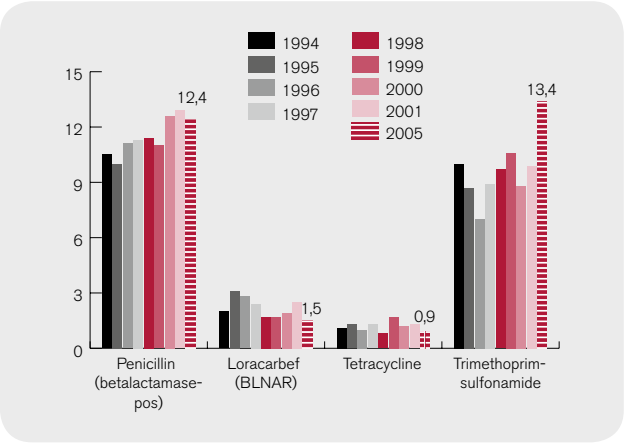


**Figure 4.12. Resistance rates for *Haemophilus influenzae* 1994–2001 and 2005 (data from the annual RSQC programme) for four different antibiotics. (BLNAR = Beta-lactamase Negative, Ampicillin Resistance).**

## *Streptococcus pyogenes*

### Notifications according to the Communicable Disease Act

Invasive *Streptococcus pyogenes* infections became mandatorily notifiable diseases according to the Communicable disease act of 2004. During 2005, a total of 252 cases were notified.

### Annual Resistance Surveillance and Quality Control (RSQC) programme

There are no data in the RSQC programme on antibiotic resistance in *Streptococcus pyogenes* for 2004-2005, but new data will be collected in 2006.

## *Helicobacter pylori*

### Annual Resistance Surveillance and Quality Control (QCRS) programme

*Helicobacter pylori* derived from gastric biopsies has not until 2001 been included in the annual RSQC programme but 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 (3%) but is increasing and has locally at one laboratory reached over 10% for two years in a row. Resistance to tetracycline is less than 1% and resistance to amoxicillin has only been described in a few strains and only outside Scandinavia. Frequencies of resistance to clarithromycin and metronidazole in clinical isolates from southwest of Sweden are presented in Table 4.13, representing a population of approximately 300 000.

**Mats Walder**

**Table 4.13.** ***Helicobacter pylori*****, University Hospital MAS, Malmö Sweden 1994-2005, %R.**

| Year | Total number | Clarithromycin | Metronidazole |
|---|---|---|---|
| 1994 | 536 | 1.0 | 29.0 |
| 1995 | 588 | 2.9 | 32.1 |
| 1996 | 381 | 3.9 | 35.2 |
| 1997 | 331 | 7.7 | 39.8 |
| 1998 | 116 | 6.7 | 34.3 |
| 1999 | 149 | 6.1 | 33.1 |
| 2000 | 216 | 7.8 | 30.5 |
| 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 |

## *Salmonella and Shigella spp.*

### Annual Resistance Surveillance and Quality Control (QCRS) programme

*Salmonella* spp. and *Shigella* spp. derived from faecal cultures have not been included in the annual RSQC programme until 2002 but 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 tourists returning home, 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.

**Mats Walder**

## *Campylobacter spp*

### Annual Resistance Surveillance and Quality Control (QCRS) programme

*Campylobacter* spp. derived from patients with diarrhoea has not until 2001 been included in the annual RSQC programme but 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 fluoroquinolone resistance among *Campylobacter* isolates noticed a few years ago has now regained the former level of about 50%, (Table 4.13). 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 4.13.** ***Campylobacter jejuni/coli*****, University Hospital MAS, Malmö, Sweden 1992-2005, %R.**

| Year | Nalidixic acid | Ciprofloxacin | Tetracycline | Erythromycin |
|---|---|---|---|---|
| 1995 | | 22 | 27 | 4 |
| 1997 | | 23 | 30 | 3 |
| 1998 | | 34 | 33 | 2 |
| 1999 | | 45 | 35 | 1 |
| 2000 | | 55 | 45 | 1 |
| 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 |

## *Neisseria gonorrhoeae*

### Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable disease, and in 2005 691 clinical cases of the disease 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 2005, isolates from 486 of the notified clinical cases were completely characterised at these laboratories, representing 70% of the notified cases. In total, 497 different *Neisseria gonorrhoeae* strains were cultured from these cases (n=486).

Susceptibility testing was performed according to standardized methodology using Etest for MIC determination of ampicillin, cefixime, ceftriaxone, azithromycin, ciprofloxacin, and spectinomycin. Production of beta-lactamase was examined by using nitrocefin discs. Results for 2005 are compared with those from 1998, and 2000-2004 in Table 4.14.

**Magnus Unemo, Hans Fredlund**

## *Neisseria meningitidis*

### Notifications according to the Communicable Disease Act

Invasive meningococcal disease is a notifiable disease. In 2005 58 clinical cases of the disease were reported. A total of 48 clinical isolates from blood or cerebrospinal fluid were analysed at the Swedish Reference Laboratory for pathogenic Neisseria, Department of Clinical Microbiology, University Hospital Örebro.

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), phenoxymethylpenicillin (pcV), cefotaxime, ciprofloxacin, chloramphenicol and rifampicin. Production of beta-lactamase was examined by nitrocefin discs.

None of the isolates produced beta-lactamase. Eleven isolates (23%) had reduced susceptibility to pcG (MIC>0.064 mg/L). The MIC for pcV is normally 5-10 times higher and eight isolates had MIC ≥0.5 mg/L. All the isolates had cefotaxime – MIC ≤0.008 and ciprofloxacin – MIC ≤0.012. Chloramphenicol – MIC varied between 0.25 and 1.5 and rifampicin was not higher than 0.25 mg/L.

The MIC breakpoints in the SIR-system (as determined by SRGA) are for pcG 0.25/1, pcV 1/1, cefotaxime 0.06/1, ciprofloxacin 0.03/0.06, chloramphenicol 2/8 and rifampicin 1/1.

**Per Olcén**

**Table 4.14. Antibiotic resistance rates (%) and ß-lactamase production of Swedish *Neisseria gonorrhoeae* strains in 1998, and 2000–2005.**

| | 1998 (n=348) | 2000 (n=131) | 2001 (n=141) | 2002 (n=120) | 2003 (n=130) | 2004 (n=149) | 2005 (n=497)** |
|---|---|---|---|---|---|---|---|
| Beta-lactamase positive | 24 | 37 | 37 | 39 | 22 | 26 | 23 |
| Penicillin G | 32 | 42 | 38 | 48 | - | - | - |
| Ampicillin | 24 | 37 | 37 | 39 | 22 | 26 | 23 |
| Cefuroxime | 0 | 2 | 0 | 4 | - | - | - |
| Cefixime | - | - | - | 0 | 0 | 0* | 0 |
| Ceftriaxone | 0 | - | - | 0 | 0 | 0 | 0 |
| Azithromycin | 0 | - | - | 0 | <1 | 0* | 0 |
| Tetracycline | 32 | 52 | 56 | 54 | - | - | - |
| Ciprofloxacin | 10 | 28 | 43 | 48 | 52 | 48 | 46 |
| Spectinomycin | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

- = not analysed

* *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).

** 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. Previous years (1998 and 2000–2004), only data from the Swedish Reference Laboratory were reported.

## *Mycobacterium tuberculosis*

During 2005 there was a 24% increase in the total number of new cases of TB compared to 2004, from 465 to 575. In 2005, resistance against at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamide) was reported in 52 patients i.e. 11.6% of the 448 patients with culture confirmed *M. tuberculosis* or *M. africanum*. This proportion is the same as in 2004, (Table 4.15). Resistant TB was reported in 8.7% of the Swedish born patients and 10.7% of those foreign born. Among 15 patients with a previous history of TB after 1949, there were 3 patients with resistant TB (20%).

Resistance to isoniazid was most common, reported in 10.3% of the patients, followed by pyrazinamide 1.3%, rifampicin in 1.1% and ethambutol in 0.7%. Single resistance to rifampicin was reported in one patient and MDR-TB in another four patients, all of them born abroad.

By means of genetic typing with RFLP (restriction fragment length polymorphism) of all resistant strains of *Mycobacterium tuberculosis* a big cluster of patients with identical fingerprint pattern has been identified. During the period from 1996 up to March 2006 in total 99 patients were identified, 20 of them were diagnosed during 2005. One of these patients worked in a day care centre. Contact tracing identified in total 17 children 1-5 years of age with active but not culture confirmed tuberculosis. In addition a number of children received prophylactic treatment for latent infection. All but seven of the 99 patients live in the county of Stockholm. This outbreak indicates ongoing spread of isoniazid resistant tuberculosis in Sweden.

In 2005 routine testing of resistance to the drug streptomycin was discontinued in three of five laboratories, due to the lack of clinical relevance of resistance to this drug. Thus resistance against streptomycin is no longer included in the results. In order to get comparable data from previous years the results, from 2000 through 2005, were recalculated for testing just against the four drugs included in standard treatment i.e. isoniazid, rifampicin, ethambutol and pyrazinamid.

Comments on some other methodological changes that took place in 2004 and which might affect the epidemiological report of drug resistant tuberculosis:

- In order to harmonise with European standards it was decided to reduce the breakpoint concentration of isoniazid from 0.2 to 0.1 mg/L.
- The test assay is not as uniform as before when all laboratories used the radiometric Bactec 460 method from Becton & Dickinson. Today some laboratories still use this technique, while others have changed to more modern broth base test assays as MGIT (Becton & Dickinson) or BacTalert (BioMeriuex).
- It was agreed that all identified cases of drug resistance strains of *M. tuberculosis* identified in Sweden should be verified at the SMI reference laboratory.

**Sven Hoffner, Victoria Romanus**

**Table 4.15. Drug resistant tuberculosis in Sweden. Resistance among initial isolates of *Mycobacterium tuberculosis* or *africanum* to at least one of the four drugs: isoniazid, rifampicin, ethambutol or pyrazinamid.**

| Year of diagnosis | 2001 | 2002 | 2003 | 2004 | 2004 |
|---|---|---|---|---|---|
| Culture confirmed *M. tuberculosis* or *M.africanum* (N=) | 354 | 346 | 345 | 368 | 448 |
| Any resistance Total (%) | 10.7 | 10.4 | 6.4 | 11.7 | 11.6 |
| Isoniazid | 8.8 | 9.8 | 7.5 | 9.5 | 10.3 |
| Rifampicin | 1.7 | 1.2 | 2.9 | 1.6 | 1.1 |
| Ethambutol | 0.8 | 0.3 | 1.4 | 0.8 | 0.7 |
| Pyrazinamid | 1.7 | 1.2 | 2.0 | 3.3 | 1.3 |
| Isoniazid + rifampicin (MDR) | 1.1 | 1.2 | 2.3 | 1.4 | 0.9 |

## 4.2. Antifungal resistance

An increasing incidence of invasive fungal infections has been reported from different parts of the world in the last two decades. One major reason for this increase is the expansion of the immunocompromised patient population. Organisms of the genus *Candida* are the most common cause of invasive mycosis, including nosocomial bloodstream infections. In Sweden, no infection due to fungal pathogens with normal or reduced susceptibility to antifungals is notifiable according to the Communicable Disease Act. In consequence, annual incidence data on fungal infections has not been available. The Swedish Institute for Infectious Disease Control initiated in 2003 a programme for surveillance of invasive *Candida* infections. This programme also comprises surveillance of resistance to the antifungals most frequently used for systemic prophylaxis and treatment.

### *Candida* species

Susceptibility data was obtained for 221 consecutive clinical isolates received from twenty-nine clinical microbiology laboratories in the first nationwide survey of *Candida* species causing bloodstream infections. Frequencies of resistance or decreased susceptibility in *C. albicans*, which was the cause of infection in 65% of the cases, were 2.1% for fluconazole, 2.9% for itraconazole and 4.3% for flucytosine (Table 4.2.1). One isolate displayed resistance to voriconazole and none to amphotericin B. Commonly, wild type populations of *C. albicans* are clinically susceptible to azole and polyene drugs. Secondary resistance can develop in previously susceptible isolates. Some of the best-documented examples of acquired resistance in *C. albicans* concern oropharyngeal candidiasis in HIV-infected patients receiving multiple courses of azole antifungal therapy. Resistance to amphotericin B remains uncommon among *C. albicans* isolates despite the widespread use of this polyene compound since its introduction in the 1950s.

*Candida glabrata* and *C. krusei* are inherently less susceptible or resistant to fluconazole and other azole compounds with the exception of voriconazole. Comparatively, *C. parapsilosis* is uniformly sensitive to most systemic antifungals. In this survey, the overall prevalence of *C. glabrata* was 23%, increasing with patient age from 0% in neonates to 30% in patients >65 years. Rates of resistance or decreased susceptibility in *C. glabrata* were 43% for fluconazole, 92% for itraconazole, 2.0% for amphotericin B and 0% for flucytosine. Two *C. glabrata* isolates were resistant to voriconazole. The three sepsis isolates identified as *C. krusei* were resistant or displayed reduced susceptibility to fluconazole and itraconazole. Two of these isolates were resistant to amphotericin B. *Candida parapsilosis* isolates represented 6.4% of the total received. No isolate of this species displayed in vitro resistance to the antifungals tested. On the whole, *Candida* non-albicans comprised 95% of the azole-resistant isolates, a finding that is in line with results from numerous studies at various locations in the world.

In conclusion, rates of susceptibility to azole compounds are high among *C. albicans* isolated from blood in Sweden. Simultaneously, *C. glabrata* seems to emerge as a cause of bloodstream infections, with a frequency ranking among the highest in Europe. It remains to be clarified whether this apparent change in epidemiology is a result of the extensive use of fluconazole for the prophylaxis and treatment of *Candida* infections since the early 1990s.

### Aspergillus species and other molds

Development of antifungal resistance in fungi other than yeasts remains poorly studied. Primary resistance is known to occur in certain species of molds. One example is the innate resistance of Pseudallescheria boydii (*Scedosporium apiospermum*), *Fusarium* spp. and *Aspergillus terreus* to amphotericin B. The lack of activity of fluconazol against *Aspergillus* spp. is also well established.

**Victor Fernandez**

**Table 4.2.1. Rates of resistance or reduced susceptibility to antifungals among invasive yeast isolates. Data from first nationwide survey of candidemia in Sweden.**

| | Percentage of isolates with reduced susceptibility or resistant | | | | |
|---|---|---|---|---|---|
| Species (no. of isolates) | Fluconazole | Itraconazole | Voriconazole | Flucytosine | Amphotericin B |
| *C. albicans* (143) | 2.1 | 2.9 | 0.7 | 4.3 | 0 |
| *C. glabrata* (49) | 43.0 | 91.8 | 2.0 | 0 | 6.1 |
| *C. parapsilosis* (14) | 0 | 7.1 | 0 | 0 | 0 |
| Other yeast [1] (13) | 30.8 | 79.2 | 0 | 7.7 | 23.1 |
| *C.* non-albicans (76) | 35.5 | 72.4 | 1.3 | 1.3 | 7.9 |

[1] Including *C. lusitaniae* (4 isolates). *C. tropicalis* (3 isolates). *C. krusei* (3 isolates). *C. dubliniensis* (2 isolates) and *S. cerevisiae* (1 isolate).

# 5. National and regional intervention projects

## Why didn't Teo get penicillin?

Although virus is the cause of 90 percent of all respiratory tract infections, RTIs, this is the most common reason why young children seek health care. It is also known that RTIs among young children is the most common reason for antibiotic treatment. In a former Strama study it was exposed that parents as well as personnel at day care centres want to learn more about how to handle young children's infections. Therefore Strama has supported the production of a film called "Why didn't Teo get penicillin?". An otolaryngologist, also participating in the film, wrote the manuscript of the film, in which causes, symptoms and treatment of common colds are discussed and the difference between virus and bacteria is explained. There is also information regarding when to seek a doctor and the benefits and disadvantages about antibiotic treatment. The film has been distributed to more than 300 day care centres, free of charge. Strama believes that this is a pedagogic way to explain medical facts that indirectly can lead to that unnecessary antibiotic treatment can be avoided.

## The Strama diagnosis-prescribing survey 2000, 2002 and 2005

Strama has three times 2000, 2002 and 2005, each year during one week in November, conducted diagnosis-prescribing surveys. The two first years the studies were conducted in five counties and in 2005 in seven counties. In all three studies doctors in primary care completed forms for all patient seeking care for an infectious complaint irrespective if an antibiotic was prescribed or not. On each form the set diagnosis, diagnostic tools used and the antibiotic prescribed if any and the length of treatment was noted by the physician in connection with the consultation.

The overall pattern of diagnoses is shown in Table 5.1. Respiratory tract infections were dominating all three years although the last year a shift can be seen towards other diagnoses.

The diagnosis pattern was more or less similar the three years. The most common diagnoses are shown in Table 5.2.

**Table 5.1 The overall pattern of diagnoses groups in the diagnosis prescribing survey 2000, 2002 and 2005**

| Diagnosis group | 2000 n (%) | 2002 n (%) | 2005 n (%) |
|---|---|---|---|
| Respiratory tract infections | 4383 (70.6) | 3795 (70.3) | 4887 (65.2) |
| Urinary tract infections | 869 (14.0) | 699 (13.0) | 1022 (13.6) |
| Skin infections | 607 (9.8) | 525 (9.7) | 658 (8.8) |
| Other infections | 312 (5.0) | 325 (6.0) | 792 (10.6) |
| No diagnosis given | 36 (0.6) | 51 (0.9) | 139 (1.9) |
| **Total** | **6207 (100)** | **5395 (100)** | **7498 (100)** |

**Table 5.2. The most common diagnoses in the diagnosis prescribing survey 2000, 2002 and 2005.**

| Diagnosis | Number (%) 2000 | Number (%) 2002 | Number (%) 2005 |
|---|---|---|---|
| Upper respiratory tract infection | 023 (16.5) | 1263 (23.4) | 1681 (22.4) |
| Lower UTI | 643 (10.4) | 520 (9.6) | 784 (10.5) |
| Streptococcal tonsillitis | 704 (11.3) | 475 (8.8) | 486 (6.5) |
| Acute otitis media | 492 (7.9) | 476 (8.8) | 483 (6.4) |
| Acute sinusitis | 347 (5.6) | 463 (8.6) | 348 (4.6) |
| Acute bronchitis | 384 (6.2) | 272 (5.0) | 506 (6.7) |
| | **3593 (57.9)** | **3469 (64.3)** | **4288 (57.2)** |

In total an antibiotic was prescribed in 60.1, 59.1 and 47.1% of the cases in 2000, 2002 and 2005 respectively. The percentage of those treated with an antibiotic that received penicillin V was 43.7 42.4 and 41.8 respectively in the three years.

For lower urinary tract infections a shift in antibiotic choice was noted, see Table 5.3.

**Table 5.3. Choice of antibiotics for lower urinary tract infections in the diagnosis prescribing survey 2000, 2002 and 2005**

| Drug | 2000 n (%) | 2002 n (%) | 2005 n (%) |
|---|---|---|---|
| Trimethoprim | 224 (34.8) | 199 (38.2) | 162 (20.7) |
| Pivmecillinam | 183 (28.5) | 154 (29.6) | 323 (41.1) |
| Fluoroquinolones | 137 (21.3) | 83 (16.0) | 116 (14.8) |
| Nitrofurantoin | 19 (3.0) | 32 (6.2) | 112 (14.3) |
| Other drugs or combinations | 35 (5.4) | 37 (7.1) | 36 (4.6) |
| No drug | 45 (7.0) | 15 (2.9) | 35 (4.5) |
| | **643 (100)** | **520 (100)** | **784 (100)** |

It is interesting to note and increases the validity of the studies that the diagnosis pattern has been relatively stable over the years despite the inclusion of two new counties in the last study. A trend towards more upper respiratory tract diagnoses and fewer diagnoses of streptococcal tonsillitis, acute otitis media and acute bronchitis may be seen. The most notable shift is however for lower urinary tract infections where nitrofuratoin has doubled between each of the studies.

**Cecilia Stålsby Lundborg**

## Prevention of spread of bacteria between patients in hospitals

Ethanol hand rub rather than hand washing has since the 1970s been the recommended standard for preventing nosocomial spread of microorganisms in Swedish hospitals. During 2005 a Strama study was performed with the aim to estimate the compliance with these recommenda-

tions by studying the volumes of ethanol used normally and during optimal conditions. In this study, ICUs (n=11), wards of orthopaedic/general surgery (n=16) and internal medicine (n=17) in primary (n= 12), secondary (n= 9) and tertiary (n=5) hospitals took part in a 24h measurement of the volume of ethanol used for hand disinfection during "100% compliance". Staff members served as observers. Dispensers were weighed at 08 AM on day 1 and 2 and the amount of ethanol used was converted to ml/patient/24h and ml/staff member/24h. Actual ml/patient/24h data for calculation of compliance rates were based on the annual volume of ethanol for hand disinfection used per ward in 2004.

The median ethanol usage rate for ICUs were 221 ml/patient/24h (95% CI 186–313) and 175ml/staff member/24h (107–185) compared to 79 (51–120) and 143 (114–217) for surgery, and 61 (39–119) and 184 (86–225) for medicine. As hand rub requires 2ml both before and after patient contact the above rates were divided by 4 for estimation of the number of patient contacts based on hand disinfectant usage. The mean compliance rates (local data vs gold standard) were 51% (1.3–119) for ICUs, 36% (range 25–70) for surgical wards, and 40% (23–95) for medical wards.

In conclusion, this "gold standard" method for calculation of compliance yielded data that can be used for feedback to staff in order to increase compliance with hand-hygiene guidelines.

**Kerstin Mannerquist, Erik Torell**

## Ten years surveillance of resistance in Sweden: what can it tell us about the relationship between resistance and outpatient antimicrobial use?

In Sweden the Swedish Reference Group of Antibiotics subcommittee on susceptibility testing and the Swedish Institute for Infectious Diseases in collaboration with the Swedish clinical microbiology laboratories have performed systematic surveillance of resistance development and testing proficiency for many years. Each of the 28 laboratories in the 21 counties in Sweden collects at least 100 isolates each year during a specified period. The objective of this study was to

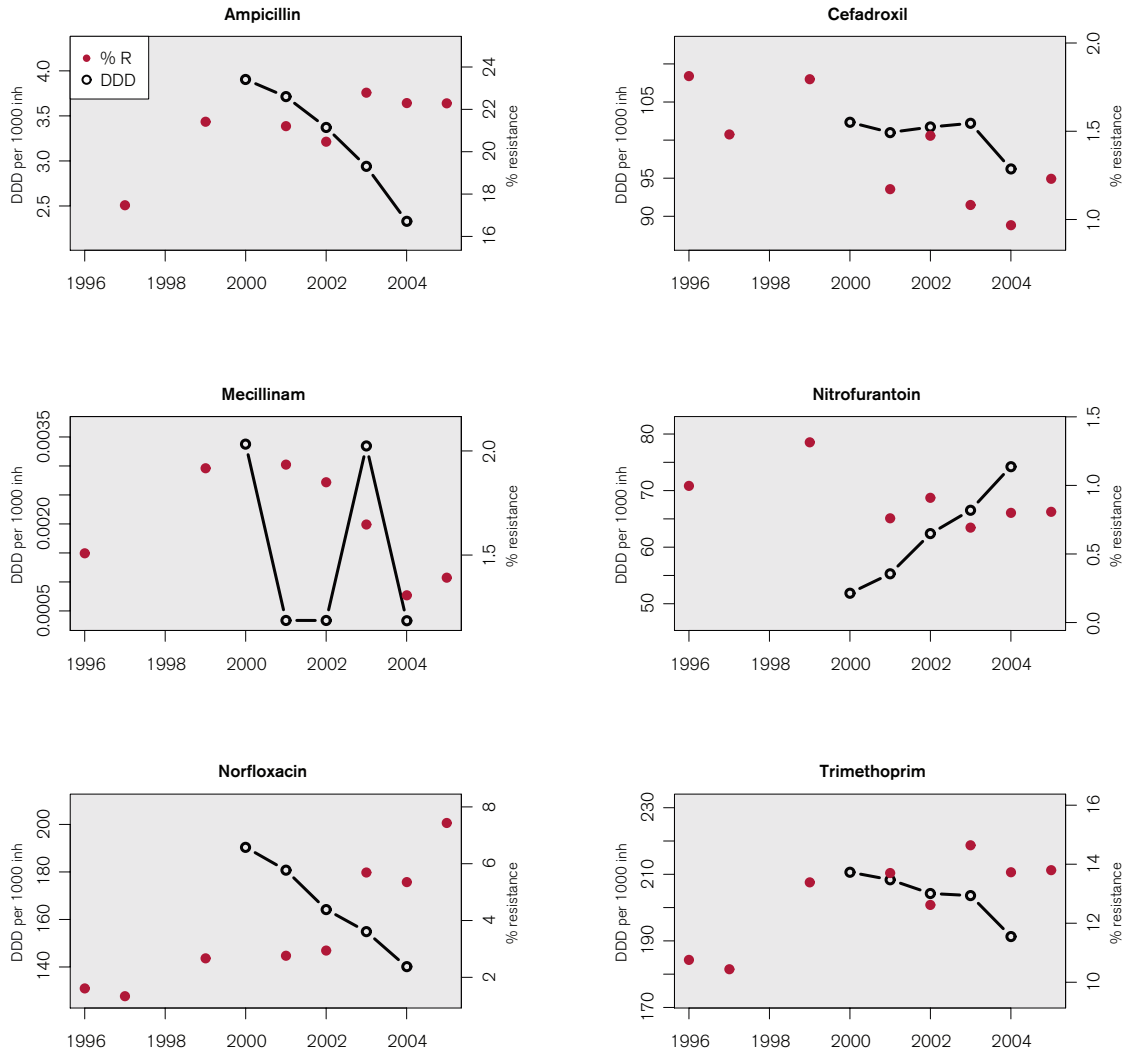


Fig 5.1. Antibiotic use in out patient care and resistance rate in Sweden 1996-2004.

i) investigate whether the current surveillance system could detect yearly changes in the level of resistance; ii) investigate whether the surveillance system could detect increasing or decreasing trends in resistance; and iii) assess whether the surveillance data of resistance could be related to outpatient use of antibiotic.

The study includes data on *Escherichia coli* resistance to each of the antibiotics ampicillin, cefadroxil, mecillinam, nitrofurantoin, norfloxacin and trimethoprim per year and laboratory. Consumption data included the total outpatient use of each antibiotic per year and county. To test the annual trend for the resistance, we used a logistic regression for the proportion of resistant isolates, and we calculated correlations between antibiotic resistance and antibiotic use using Spearman's coefficient for non-linear correlations.

Our findings showed that resistance levels to the antibiotics between and within the laboratories varied considerably. There were also differences regarding the trend in resistance at individual laboratories. Only a few cases with significant increasing or decreasing trend were found. Furthermore, given the current mean levels of resistance, the guideline of 100 isolates was determined not to be sufficient for finding changes from one year to another within a laboratory.

The data available was not sufficient to analyse the correlation between antibiotic use and resistance and in addition take the lagged effects into account. Nevertheless, we found that although the use of ampicillin, norfloxacin, and trimethoprim has decreased since 2000, the *E. coli* resistance to these antibiotics has increased over the period. On the other hand, for cefadroxil it was possible to observe a decrease in resistance concurrent with a stable low use of this antibiotic; no trend was found in the resistance of mecillinam or nitrofurantoin.

**Patricia Geli, Sharon Kühlmann Berenzon**

## Educational material for school children

Strama has supported the development and production of an educational material addressing the topics of antibiotic resistance and common cold. The target group of the material is school children in the age of 10 years and it is meant to be used by teachers as an integrated part of the ordinary education in schools. The material consists of a teacher's guide, overhead pictures and a cartoon book where a message about correct treatment of common colds, rational use of antibiotics and antibiotic resistance is woven into an entertaining story that is told with photos and cartoons.

The materials ability to improve knowledge among the children was pre-tested in a controlled study. The material was during 2005 distributed and used in more than 200 schools all over Sweden. A number of teachers were interviewed regarding their opinion about the design and usefulness of the material and a questionnaire addressing the same topics was sent to 100 of the schools.

Generally the teachers were satisfied with the material, they considered the material comprehensive and easy to use. The texts in the teachers guide were understandable and not too long and the material could be used directly, without too much of preparation, a crucial point for many of the teachers. Teachers stated "it was so nice with a material that was complete" and "it was a positive surprise that the material was both entertaining and educational". The cartoon book with the entertaining story functioned well and was well received by the children as it "concerned children in their own age and situations that they surely have been in".

Several of the teachers had used the material itself in their teaching and in addition used the extra assignments listed in the back of the teacher's guide. They have made projects in the class room where the children were assigned health ambassadors and took on the task of informing younger children as well as writing songs and making paintings on the theme of antibiotic use and resistance. Most teachers judged the information given in the teachers guide as sufficient, if not they sought additional information on internet. However, some teachers chose to pass on the material to the teacher responsible for nature science or to cooperate with the school nurse.

**Charlotte Kristiansson**

# Appendix 1 – Abbreviations

**AST** – Antibiotic susceptibility testing
**ATC** – The Anatomical Therapeutic Chemical classification system
**CCDC** – Centre of Communicable Disease Control
**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
**RSQC** – Resistance Surveillance and Quality Control Programme
**SRGA-M** – The Swedish Reference Group of Antibiotics- subcommittee on Methodology
**ST** – Sequence type
**STRAMA** – Swedish Strategic programme for the Rational use of Antimicrobial Agents and Surveillence of 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 2003–2005 (the numbers represents the population on December 31st the previous year).**

| | 2003 | 2004 | 2005 |
|---|---|---|---|
| Population | 8 940 744 | 8 975 669 | 9 011 391 |

Table App 2.3. Denominator data from the microbiological laboratories. NA = data not available

| | Number of analyses 2005 | | | | | | | Number of positive cultures 2005 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | 11 515 | 150 | 2 913 | 4 488 | 6 415 | 1 190 | 6 525 | 3 912 | 761 | 790 | 6 837 |
| Capio Eskilstuna | 6 663 | 135 | 5 396 | 4 745 | 7 334 | 1 518 | 4 543 | 3 158 | 882 | 650 | 6 374 |
| Falun | 9 853 | 235 | 2 207 | 1 861 | 8 380 | 1 209 | 4 305 | 3 361 | 420 | 555 | 6 320 |
| Gävle | 7 960 | 167 | 1 950 | 1 260 | 6 400 | 3 125 | 3 300 | 3 159 | 379 | 199 | 5 559 |
| Göteborg | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Halmstad | 7 628 | 153 | 2 865 | 3 096 | 8 174 | 8 647 | 6 080 | 2 839 | 541 | 585 | 6 230 |
| KU, Huddinge | 25 411 | 2 136 | 15 058 | 5 862 | 29 222 | 57 501 | 10 650 | 11 436 | 2 442 | 1 506 | 17 755 |
| Jönköping | 10 500 | 198 | 2 880 | 4 040 | 10 470 | 5 990 | 6 390 | 4 400 | 580 | 680 | 8 500 |
| Kalmar | 7 295 | 290 | 3 843 | 2 756 | 7 421 | 10 975 | 4 281 | 4 032 | 720 | 340 | 6 990 |
| Karlskrona | 3 641 | 50 | 1 219 | 1 823 | 5 074 | 2 298 | 3 024 | 2 007 | 302 | 198 | 3 898 |
| Karlstad | 12 364 | 213 | 960 | 1 887 | 10 794 | 3 729 | 4 087 | 5 058 | 257 | 435 | 6 574 |
| Kristianstad | 7 699 | 107 | 5 879 | 5 064 | 10 114 | 5 716 | 6 378 | 5 128 | 1 093 | 639 | 7 860 |
| KU Solna | 24 050 | 1 964 | 23 849 | 9 815 | 35 864 | 65 000 | 11 164 | 10 462 | 3 019 | 1 567 | 17 807 |
| Linköping | 13 005 | 686 | 4 722 | 2 948 | 15 327 | 31 172 | 7 280 | 6 362 | 758 | 602 | 7 938 |
| Lund | 19 401 | 1 364 | 10 316 | 6 540 | 21 255 | 13 188 | 13 202 | 9 511 | 2 275 | 1 409 | 1 7693 |
| Malmö | 16 297 | 265 | 6 662 | 6 372 | 18 557 | 8 933 | 14 205 | 6 839 | 2 106 | 1 196 | 13 101 |
| Medilab | - | - | 11 455 | 5 041 | 6 329 | 9 294 | 7 776 | 3 535 | 1 449 | 950 | 8 457 |
| Capio St Göran | 5 036 | 163 | 5 306 | 3 768 | 13 308 | 26 465 | 7 287 | 4 332 | 811 | 796 | 8 957 |
| Capio Skövde | 10 638 | 79 | 2 544 | 2 125 | 6 157 | 3 778 | 4 954 | 3 607 | 465 | 590 | 9 489 |
| Sunderby (Luleå)* | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Sundsvall | 7 682 | 97 | 3 139 | 2 414 | 7 800 | 3 216 | 4 483 | 3 324 | 676 | 455 | 7 648 |
| Uddevalla | 13 056 | 198 | 1 752 | 3 039 | 7 616 | 2 293 | 5 364 | 3 749 | 405 | 507 | 9 255 |
| Umeå | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Uppsala | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Visby | 2 700 | 8 | 2 941 | 899 | 3 047 | 0 | 1 162 | 1 335 | 419 | 187 | 2 237 |
| Västerås | 7 932 | 182 | 2 851 | 2 471 | 8 504 | 4 509 | 5 952 | 3 476 | 557 | 461 | 6 795 |
| Växjö | 4 062 | 92 | 1 614 | 2 643 | 5 507 | 2 967 | 2 570 | 2 330 | 344 | 602 | 4 681 |
| Örebro | 11 957 | 188 | 7 303 | 1 813 | 12 144 | 3 498 | 4 554 | 5 724 | 1 151 | 384 | 6 769 |
| Östersund | 4 941 | 72 | 2 044 | 1 618 | 6 379 | 1 245 | 2 032 | 2 458 | 461 | 278 | 5 056 |

# Appendix 3 – Surveillance of antibiotic consumption

**The ATC classification system and defined daily doses (DDD)**
Since 1988, the Anatomical Therapeutic Chemical (ATC) classification system is used in Sweden for national drug statistics. The WHO recommends the system.

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 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 medicines 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 read with caution.

**Swedish national statistics on drug utilisation**
Since 1975, the National Corporation of Swedish Pharmacies (Apoteket AB) regularly produces sales statistics on medicines, for the country as a whole and for individual counties. The sales are registered as number of DDD, cash value and number of packages.

Out-patient care data includes information on the sales of medicines 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 medicines 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.

# 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; in previous nomenclature 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 1988:1472). With the exception of certain sexually transmitted infection (STI), 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 and to the Swedish Institute for Infectious Disease Control (SMI). Some diseases, mainly gastrointestinal infections, should also be notified to the municipal environmental health office. 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. Penicillin-resistant *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 requested to supplement the information. As an important complement to the notifications, the MRSA and PRP strains are sent to the SMI for epidemiological typing, using pulsed-field gel electrophoresis (PFGE) and other molecular epidemiological methods.

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

The feed back of notification data is done monthly on the SMI Internet homepage (http://www.smittskyddsinstitutet.se) and yearly in "Communicable Diseases in Sweden – the Yearly Report of the Department of Epidemiology" 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.

### Voluntary laboratory reporting

A system for individual, anonymised case reporting of certain very rare (or not yet identified) pathogen-resistance combinations is under construction. The pathogens are so selected that each finding should trigger some action (either confirmation testing or infection control measures). To make the system exhaustive, the identification and reporting of these pathogens from the local laboratory computer systems to the SmiNet must be automated.

### 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 30 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 30 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 4 and 6.

Originally data were sent on paper (1994–1997) to be entered in spreadsheet (Excel)-format at the reference laboratory. Between 1998 and 2001 the laboratories have sent their data in Excel-format for a central semi-automatic work-up with "on-paper" feedback in the mail and in yearly workshops on AST methodology and resistance development.

From 2002 a web-based newly developed 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). Recently the software has been updated to display also the 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/E. faecium*, and monitors variations in antimicrobial resistance over time and place. Two new pathogens are added from 1 Juli, 2005, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

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 website (www.earss.rivm.nl).

Data collected by EARSS should be routinely generated quantitative data (MICs or inhibition zones), but the data presented are only in the format of susceptibility cathegories (SIR). External quality assurance exercises have been carried out by EARSS in cooperation with UK-NEQAS and the EARSS Advisory Board in 2000, 2001, 2002 and 2003. 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 twentyone 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 *Helicobacter 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) 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 dispaying in ResNet.

# Appendix 6 – Recent publications

### 3.1 Use of antibiotics


**André M, Eriksson M, Mölstad S, Stålby Lundborg C, Jakobsson A, Odenholt I** and the Swedish Study Group on Antibiotic Use. The management of infections in children in general practice in Sweden. A repeated 1-week diagnosis-prescribing study in 5 counties in 2000 and 2002. Scand J Infect Dis 2005;37:863–69.

**André M, Mölstad S, Stålsby Lundborg C, Odenholt I** and the Swedish Study Group on Antibiotic use. Management of urinary tract infections in primary care: A repeated 1-week diagnosis-prescribing study in five counties in Sweden in the years 2000 and 2002. Scand J Infect Dis 2004;36:134–38

**André M, Schwan Å, Odenholt I, the Swedish Study Group on Antibiotic Use.** The use of CRP tests in patients with respiratory tract infections in primary care in Sweden can be questioned. Scand J Infect Dis, 2004;36:192–197.

**Ganestam F, Stålsby Lundborg C, Grabowska K, Cars O, Linde A.** Weekly Antibiotic Prescribing and Influenza Activity in Sweden – A Study throughout Five Influenza Seasons. Scand J Infect Dis 2003; 35:836–42.

**Hedin K, Andre M, Mölstad S, Rodhe N, Petersson C.** Infections in families with small children – use of social insurance and health care. Accepted for publication in Scand J of Prim Health Care.

**Hedin K, Petersson C, Cars H, Beckman A, Håkansson A.** Infection prevention at day-care centres: Feasibility and possible effects of intervention. Scand J of Prim Health Care 2006;24:44-49.

**Högberg L.** Penicillin-resistant pneumococci in Sweden- epidemiology and public health response. Academic dissertation. Karolinska institutet. Stockholm 2006. ISBN 91–7140–526–7.

**Kahlmeter G, Menday P, Cars O.** Non-hospital antimicrobial usage and resistance in community-acquired *Escherichia coli* urinary tract infection. J Antimicrob Chemother. 2003; 52:1005–10.

**Melander E, Hansson HB, Mölstad S, Persson K, Ringberg H.** Limited Spread of Penicillin Nonsusceptible Pneumococci, Skåne Country, Sweden. Emerging Infectious Diseases. 2004;10:1082–7

**Svensson E, Haaijer-Ruskamp F, Stålsby Lundborg C.** Self-medication with antibiotics in a Swedish general population. Scand J Infect Dis 2004;36: 450–2.

## 4.1 Antimicrobial resistance


**Berggren-Palme I, Larsson L-O, Zedenius I, Gillman A, Bennet R.** Outrbreak of tuberculosis in a Stockholm nursery affects 35 children. Eurosurveillance Weekly 2005; 10(10); 051027

**Fang H, Lundberg C, Olsson-Liljequist B, Hedin G, Lindbäck E, Rosenberg A, Struwe J.** Molecular epidemiological analysis of *Eschericia coli* isolates producing extended-spectrum beta-lactamases for identification of nosocomial outbreaks in Stockholm, Sweden. J Clin Microbiol 2004;42(12):5917-20.

**Hanberger H, Erlandsson M, Burman LG, Cars O, Gill H, Lindgren S, Nilsson LE, Olsson-Liljequist B, Walther S., ICU-Strama Study group.** High antibiotic susceptibility among bacterial pathogens in Swedish ICUs. Report from a nation-wide surveillance program using TA90 as a novel index of susceptibility. Scand J Infect Dis 2004;36(1):24-30.

**Henriques Normark B, Christensson B, Sandgren A, Noreen B, Sylvan S, Burman LG, Olsson-Liljequist B.** Clonal analysis of *Streptococcus pneumoniae* nonsusceptible to penicillin at day-care centres with index cases, in a region with low incidence of resistance. Emergence of an invasive type 35B clone among carriers. Microb Drug Resist 2003;9(4):337-44.

**Högberg L, Ekdahl K, Sjöström K, Olsson–Liljequist B, Walder M, Melander E, Ringberg H, Henriques Normark B.** Penicillin-resistant pneumococci in Sweden 1997-2003: increased multiresistance despite stable prevalence and decreased antibiotic use. Microb Drug Resist 2006:12(1);16-22.

**Iversen A, Kuhn I, Rahman M, Franklin A, Burman LG, Olsson-Liljequist B, Torell E, Möllby R.** Evidence for transmission between humans and the environment of a nosocomial strain of *Enterococcus faecium*. Environ Microbiol 2004;6(1):55-9.

**Kahlmeter G, Brown DF, Goldstein FW, MacGowan AP, Mouton JW, Österlund A, Rodloff A, Steinbakk M, Urbaskova P, Vatopoulos A.** European harmonization of MIC breakpoints for antimicrobial susceptibility testing of bacteria. J Antimicrob Chemtoher 2003;52(2):145-8.

**Kahlmeter G, Menday P.** Cross-resistance and associated resistance in 2478 *Escherichia coli* isolates from the Pan-European ECO.SENS project surveying the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections. J Antimicrob Chemother 2003;52(1):128-31. E-pub.

**Kahlmeter G.** Prevalence and antimicrobial susceptibility of pathogens in uncomplicated cystitis in Europe. The ECO.SENS study. Int J Antimicrob Agents 2003;22: Suppl 2:49-52.

**Kronvall G, Kahlmeter G, Myhre E, Galas MF.** A new method for normalized interpretation of antimicrobial resistance from disk test results for comparative purposes. Clin Microbiol Infect 2003;9(2):120-32.

**Kronvall G, Larsson M, Boren C, Kahlmeter G, Bartoloni A, Rossolini GM, Grape M, Kristiansson C, Karlsson I.** Extended antimicrobial resistance screening of the dominant faecal *Escherichia coli* and of rare resistant clones. Int J Antimicrob Agents 2005;26(6):473-8. E-pub.

**Miklasevic E, Haeggman S, Balode A, Sanchez B, Martinson A, Olsson-Liljequist B, Dumpis U.** Report on the first PVL-positive community acquired MRSA straing in Latvia. Euro Surveill 2004;9(11):29-30.

**Murchan S, Kaufmann ME, Deplano A, de Ryck R, Struelens M, Zinn CE, Fussing V, Salmenlinna S, Vuopio-Varkila J, el Solh N, Cuny C, Witte W, Tassios PT, Legakis N, van Leeuwen W, van Belkum A, Vindel A, Laconcha I, Garaizar J, Haeggman S, Olsson-Liljequist B, Ransjö U, Coombes G, Cookson B.** Harmonization of pulsed-field gel electrophoresis protocols for epidemiological typing of strains of methicillin-resistant *Staphylococcus aureus*: a single approach developed by consensus in 10 European laboratories and its application for tracing the spread of related strains. J Clin Microbiol 2003;41(4):1574-85.

**Nilsson AI, Berg OG, Aspevall O, Kahlmeter G, Andersson DI.** Biological costs and mechanisms of fosfomycin resistance in *Escherichia coli*. Antimicrob Agents Chemother 2003;47(9):2850-8.

**Sandgren A, Sjöström K, Olsson-Liljequist B, Christensson B, Samuelsson A, Kronvall G, Henriqes Normark B.** Effect of clonal and serotype-specific properties on the invasive capacity of *Streptococcus pneumoniae*. J Infect dis 2004;189(5):785-96.

**Skov R, Smyth R, Larsen AR, Frimodt-Möller N, Kahlmeter G.** Evaluation of cefoxitin 5 and 10 microg discs for the detection of methicillin resistance in staphylococci. J Antimicrob Chemother 2005;55(2):157-61. E-pub.

**Smyth RW, Kahlmeter G.** Mannitol salt agar-cefoxitin combination as a screening medium for methicilllin-resistant *Staphylococcus aureus*. J Clin Microbiol 2005;43(8)3797-9.

**Stenhem M, Örtqvist Å, Ringberg H, Larsson L, Olsson-Liljequist B, Haeggman S, Ekdahl K, Andersson A, A von Rosen I, Ardung B, Eliasson I, Fridh G, Hedin G, Helisoja R, Isaksson B, Karlman K, Kransberg L, Lennell A, Lidblom A, Lindh G, Lundholm R, Nilsson I, Nilsson L, Nilsson P, Thollström UB, Åbom PE.** Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Sweden 2000-2003, increasing incidence and regional differences. BMC Infect Dis 2006;21:6(1):30. E-pub.

**Torell E, Kuhn I, Olsson-Liljequist B, Haeggman S, Hoffman B-M, Lindahl C, Burman LG.** Clonality among ampicillin resistant *Enterococcus faecium* isolates in Sweden and relation to ciprofloxacin resistance. Clin Microb Inf 2003;9(10):1011–19.


### Workshop

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

### Websites

www.strama.se

www.srga.org

www.srga.org/resnet_sok.htm

www.smittskyddsinstitutet.se

http://www4.smittskyddsinstitutet.se/IvaStrama/index.jsp

STRAMA

The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents

SMITTSKYDDSINSTITUTET

*Swedish Institute for Infectious Disease Control*