SWEDRES2004

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

1.1 Preface....3
1.2 Contributors....3
2.1 Summary....4
2.2 Sammanfattning....6
3. Use of antimicrobials....8
3.1. Use of antibiotics....8
3.2. Use of antifungals....15
4. Antimicrobial resistance....16
Streptococcus pneumoniae....16
Staphylococcus aureus....17
Enterococcus faecium and *faecalis*....20
Streptococcus pyogenes....21
Haemophilus influenzae....21
Escherichia coli....21
Klebsiella species....22
Enterobacter species....23
Pseudomonas aeruginosa....23
Helicobacter pylori....23
Salmonella and *Shigella* spp.....23
Campylobacter spp....23
Neisseria gonorrhoeae....24
Neisseria meningitidis....24
Mycobacterium tuberculosis....25
5. National and regional intervention projects....26
5.1 Urinary tract infections in women - a longitudinal study of antimicrobial resistance and effect of empirical therapy in Kronoberg County, Sweden....26
5.2 Is a drastic decrease in trimethoprim consumption followed by a related decrease in trimethoprim resistance?....26
5.3 A qualitative study to describe views on resistance and treatment decisions for uncomplicated urinary tract infections....27
5.4 Infections in families with young children....27
5.5 The STRAMA Point Prevalence Study 2004 on hospital antibiotic use....28
5.6 Evaluation of antibiotic treatment of Acute Otitis Media in children – a Report from the South Swedish Otitis Trial.....29
Appendix 1 – Abbreviations....30
Appendix 2 – Demographics and denominator data....30
Appendix 3 – Surveillance of antibiotic consumption....32
Appendix 4 – Antibiotic susceptibility testing....32
Appendix 5 – National surveillance of antibiotic resistance....33
Surveillance regulated in the Communicable Disease Act....33
Voluntary laboratory reporting....33
Swedish combined surveillance and QC program (RSQC surveys) further developed into ResNet 2002....33
ResNet for surveillance and quality control....33
Appendix 6 – Recent publications....34

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.

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1.1 Preface

THIS IS THE THIRD SWEDISH REPORT combining results from the monitoring of antimicrobial resistance and antimicrobial usage in both veterinary and human medicine: SWEDRES and SVARM. It is today generally accepted that all use of antimicrobials in different sectors contributes to the development of resistance. In Sweden human and veterinary medicine have collaborated over a number of years not the least within the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). We are convinced that joint efforts between human and veterinary medicine are essential in order to counteract the threat of antimicrobial resistance in human and animal health. In both fields, changes have recently been made in the legal framework. According to the Zoonosis Directive that was implemented in the EU in 2003 surveillance of antimicrobial resistance shall not only comprise zoonotic organisms such as Salmonella and Campylobacter but should also include indicator bacteria such as *E. coli* and enterococci. The indicator bacteria constitute a reservoir of resistance genes that may be transferred to pathogenic bacteria. In Sweden a new Communicable Disease Act has been effective from July 2004. In this act, MRSA and penicillinresistant pneumococci are not only notifiable diseases but requires that patients report this when in contact with health care and also allows restrictions for patients to minimise spread.

The overall aim of a national antibiotic strategy is to contain antibiotic resistance and thereby preserve the possibility of effective antibacterial treatment when it is needed. It is thus evident that resistance rates and trends need to be measured and analysed. For the same reason monitoring antibiotic use is important. However surveillance systems alone do not solve the problem with antibiotic resistance and data must be used for action. Our hope is that this report will provide important knowledge for professional organisations, therapeutic committees and other bodies when policy decisions, guidelines, interventions and research strategies are established.

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2.1 Summary

Use of antibiotics

Between 1995 and 2004 there has been a 15% decrease in the total antibiotic consumption (methenamine excluded) in Sweden, from 17.3 to 14.6 DDD/1000/day. 90% of the total use is prescribed in out-patient care and penicillin V the most commonly used drug (27%). Penicillin V is also the substance showing the largest decline, especially among children. One reason may be a consensus report concerning acute otitis media. The report recommends "wait and see" policy for children above 2 years old with uncomplicated acute otitis media.

Tetracylines are the second biggest class of antibiotics used in out-patient care, 21%, when expressed as DDD/1000/day. Presented as prescriptions this group is smaller reflecting either high doses or, in this case more likely, long treatments. One third of the tetracyclines prescribed was lymecycline, the usual treatment against acne vulgaris.

The use of fluoroquinolones is still relatively high compared to other Nordic countries. Swedish guidelines for treatment of lower urinary tract infections among women do not recommend fluoroquinolones. Nevertheless studies reveal that they are used for this condition. In order to change this, many drug and therapeutic committees as well as local STRAMA groups have set targets to lower the use of fluoroquinolones.

An outbreak in the end of 1990's of impetigo caused by *S. aureus* resistant to fucidic acid resulted in a doubled use of flucloxacillin among children 0-6 years. During 2004 this trend was broken.

In Sweden it is posible to compare the use of antibiotics between counties. The county with the highest use in 2004 had consumption 1.5 times higher than the county with the lowest use. The reason for this is not known.

In Sweden, by tradition, cephalosporins are used generously within hospital care. Two large point prevalence studies performed in 2003 and 2004 showed that cephalosporins most commonly were used to treat community acquired pulmonary infections.

Although the prevalence of MRSA is still low in Sweden there has been a small increase in the use of vancomycin, teicoplanin and linezolid during the past three years. This increase is probably due to an increased frequency of patients infected with multiresistant coagulase-negative staphylococci in Swedish hospitals.

The total use of antifungals for systemic use has not increased even though two new substances were introduced on the market in 2002.

Antibiotic resistance

During the last 2 years there has been a minor increase in the number of PRP cases reported through the Communicable Disease Act, but the annual incidence is still lower than during the late 1990's. However, previous analysis indicates that the decrease in incidence seen during the period is closely related to a concurrent decrease in nasopharyngeal culturing propensity. Data from the year 2004 might also be affected by changes between notification systems, which could slightly overestimate the number of PRP cases. Trends of increasing resistance are seen among penicillin, erythromycin, tetracycline and the combination of sulfonamide and trimethoprim.

Compared to other European countries, the prevalence of MRSA in Sweden is still low. However during 2004 a total of 709 cases were reported, representing an increase of 30% compared to 2003. Most of the Swedish counties are experiencing an increasing incidence of MRSA infections. All age groups and both sexes are affected, with incidence rising with age. Due to an outbreak in the county of Stockholm, the screening programs were dramatically intensified. A similar intensification has probably occurred in other counties and may account for part of the increase in incidence during 2004. A DNA-based method has been used for typing all MRSA isolates since the year 2000 (pulsed field gel electrophoresis, PFGE).

In 2004 the total number of vancomycin resistant enterococci, VRE, was 23. In comparison to 51 cases reported in 2003 this is a sharp decrease. The difference can be explained by two factors: an outbreak in the county of Örebro in 2003 accounted for 15 cases and no cases were reported in 2004 from the county of Stockholm. The majority of VRE reported from 2000 to 2004 were *Enterococcus faecium* carrying the *vanB* gene.

In 2004 invasive *Streptococcus pyogenes* infections became notifiable according to The Communicable Disease Act. A collection of 50 isolates showed resistance against tetracycline but not against macrolides. In a study on 100 isolates beta-lactamase production in *Haemophilus influenzae* was 14% and trimethoprim resistance 9%.

Escherichia coli has been included in the national surveillance program since 1996. The average resistance rates to ampicillin have shown a steady increase from 17 to 24%. The same was true for trimethoprim where resistance rates increased from 10 to 15%. Fluoroquinolone resistance, detected by the screening disk nalidixic acid since 2002, has not shown any increase during this period but has remained on an average of 8%. Cephalosporin resistance was only 1%, and resistance caused by ESBL was only 0.5% in invasive isolates.

Rare cases of *Klebsiella pneumoniae* and *Klebsiella oxytoca* are found, which exhibit high-level resistance to third generation cephalosporins, often caused by ESBL.

In 2004 only isolates from wound infections of *Pseudomonas aeruginosa* were tested. Resistance to ciprofloxacin was 11%.

Helicobacter pylori has been monitored locally at a few laboratories. Resistance to clarithromycin is increasing and has locally at one laboratory reached over 10%.

Salmonella spp., *Shigella* spp. and *Campylobacter* spp. are monitored locally at a few laboratories. Too few strains are included to obtain a conclusive result, however fluoroquinolone resistance is high, between 20-25% among *Salmonella* strains. 50% of the *Campylobacter* strains are imported cases.

Gonorrhoea is a notifiable disease and 568 clinical cases were reported in 2004. Isolates from 149 patients were sent to the reference laboratory, representing 26% of the notified cases. Resistance to ciprofloxacin is still alarmingly high, 48%.

59 clinical cases of invasive meningococcal disease were reported in 2004. A total of 47 clinical isolates were analysed at the reference laboratory and none of the isolates produced beta-lactamase.

During 2004 there was a 13% increase of the total number of *Mycobacterium tuberculosis*, compared to 2003. Resistant tuberculosis was reported in 7% of the Swedish born patients and 18% of those foreign born.

National and regional intervention projects

Lower urinary tract infections in women 18-50 years are almost always treated empirically and urinary cultures are seldom performed. With antimicrobial resistance development there is a need to revaluate empirical therapy. In an ongoing study in the county of Kronoberg urinary cultures will be obtained and analysed in order to evaluate the resistance rates, susceptibility testing strategies and the choice of substance prescribed. The object in another ongoing study in the same county is to determine if, and how rapidly and to what extent, the frequency of trimethoprim resistance in *E. coli* can be decreased by a sudden and drastic reduction in trimethoprim use. From October 2004 until the end of September 2006 all physicians will substitute trimethoprim and cotrimoxazole with other antibiotics. If successful this type of intervention could be used on a larger scale to reduce the frequency of resistant bacteria. In connection to this study qualitative interviews with 20 GPs have been collected. According to an interview guide four different ways of experiencing resistance were identified. GPs that expressed greater worries considering resistance seemed more willing to follow recommendations regarding antibiotic prescribing. This offers an important insight valuable when issues on use of antibiotics are discussed and interventions are planned, since the comprehension of if and how resistance constitutes a problem, can be assumed to influence the GPs prescribing patterns.

Respiratory tract infections are most common in small children. In a study 954 families participated and noted in a diary, during one month, all symptoms of infection. In addition to this they also registered whether they had been home from day-care, school or work, if they had claimed social insurance, contact with doctor or nurse and if antibiotic was prescribed. When analysing data many symptom days with mainly mild symptoms were found. Only a small proportion of those days lead to contact with health care and antibiotic consumption. About one fourth of the days lead to absence from day-care and social insurance was claimed in just a minor proportion of the symptom days.

In 2003 a point prevalence study was conducted in 54 hospitals and the study was repeated in 2004 in 49 hospitals. Data were collected at the ward level through personal visits. A case record form was used which included demographic data as well as the amounts and indications for antimicrobial agents against bacteria and fungi. The total amount of antimicrobials used for adults was 43.1 DDD/100 admitted patients and the most frequent used drugs were cephalosporins. The observation already made in 2003 of too long duration of perioperative prophylaxis was observed also in 2004, 40% of therapies were longer than one day (47% in 2003). Analysis of different diagnoses showed over-use of broad-spectrum antimicrobials in community acquired infections and fluoroquinolones in cystitis. The performed studies in 2003 and 2004 present very similar results indicating the validity of the method.

In 2000 a consensus statement regarding the treatment of acute otitis media was introduced. In order to find out whether these recommendations are followed an open, prospective, clinical, randomised trial was performed. Children aged between 2 and 16 years, presenting with one- or double-sided acute otitis media with symptom duration of less than four days were included. The children were randomised to either standard regimen of PcV for five days or no antibiotic treatment. In addition, children/parents who did not approve of randomisation were offered a possibility to still participate after making their own treatment choice (PcV or no antibiotics). All parents were asked to register a health score and compliance on a daily basis for seven days. A total of 261 patients carried out the trial; 92 randomised to PcV, 87 to no antibiotic treatment and 82 made their own treatment choice (59 PcV, 23 no antibiotics). There was no significant difference in recovery time in either group with or without antibiotic treatment.

The study group concludes that the investigation supports the proposal from the consensus statement that it is equally safe to treat non-complicated acute otitis media without antibiotics and that antibiotics provide little benefit in otherwise healthy children aged 2-16 years. One prerequisite for this approach is a developed system for follow-up and adequate instructions to the patients and their parents in order to avoid serious complications.

2.2 Sammanfattning

Antibiotikaförbrukning

Mellan 1995 och 2004 har den totala antibiotikaförbrukningen (metenamin exkluderat) i Sverige sjunkit med 15%, från 17,3 till 14,6 DDD/1000 inv och dag. 90% av den totala användningen sker i den öppna vården och penicillin V är den substans som förskrivs oftast (27%). Det är även i denna grupp som den största minskningen skett, speciellt till barn. En anledning kan vara de nya behandlingsrekommendationer för akut öroninflammation som förordar exspektans för barn över två år vid okomplicerad akut öroninflammation.

Tetracykliner är den näst största antibiotikagruppen inom öppenvård, 21%, räknat i DDD/1000/dag. Uttryckt i antal förskrivna recept blir gruppen mindre vilket kan bero på höga doser eller, mer troligt, långa behandlingar. En tredjedel av de förskrivna tetracyklinerna utgörs av lymecyklin, den vanligaste behandlingen vid acne vulgaris.

Fluorokinolonanvändningen i Sverige är fortfarande stor i förhållande till andra nordiska länder. I svenska behandlingsrekommendationer förordas inte kinoloner vid nedre urinvägsinfektion hos kvinnor. Ändå visar studier att denna grupp används vid dessa tillstånd. Många STRAMA-grupper och läkemedelskommittéer har därför satt upp mål för att minska användningen av kinoloner vid cystit hos kvinnor.

Ett utbrott av impetigo i slutet av 90-talet, orsakad av fucidinresistenta *S. aureus*, resulterade i en fördubblad användning av flukloxacillin för barn 0-6 år. Under 2004 bröts denna uppgång.

I Sverige kan vi också följa och jämföra förbrukningen mellan de olika länen. Skåne, som ligger högst, använder cirka 1,5 gånger mer antibiotika än Dalarna, som ligger lägst.

I Sverige är av tradition användningen av cefalosporiner hög inom den slutna vården. Två punktprevalensstudier som genomfördes 2003 och 2004 visade att cefalosporiner var den vanligaste behandlingen vid samhällsförvärvad lunginflammation.

Även om förekomsten av MRSA fortfarande är låg i Sverige har det skett en liten ökning i användningen av vankomycin, teikoplanin och linezolid de senaste åren. Denna ökning beror troligen på behandling av patienter infekterade med multiresistenta koagulasnegativa stafylokocker.

Den totala användningen av svampmedel för systemisk bruk har inte ökat trots att två nya substanser introducerades 2002.

Antibiotikaresistens

Under de senaste två åren har det skett en liten ökning av antalet anmälningspliktiga PRP, men den årliga incidensen är fortfarande lägre jämfört med den under det sena 90-talet. Emellertid visar tidigare analyser att nedgången i antal fall sammanfaller med nedgången i antal nasofarynxsodlingar. Data från 2004 kan också ha påverkats av förändringen i rapporteringssystem vilket något kan ha överskattat antalet PRP. Trender för ökad resistens ses mot penicillin, erytromycin, tetracyklin och kombinationer av sulfa och trimetoprim.

Jämfört med övriga europeiska länder är förekomsten av MRSA låg i Sverige. Likväl rapporterades 709 fall under 2004, en ökning med 30% jämfört med 2003. Ökningen syns i de flesta län, inom alla åldrar, båda könen och stiger i takt med ålder. Ett utbrott i Stockholm föranledde ett dramatiskt utökat screeningprogram. Troligen har liknande insatser gjorts även i andra län och kan delvis vara förklaringen till ökningen under 2004. En DNA-baserad metod har använts för att typa MRSA isolat sedan 2000 (pulsfältselektrofores, PFGE).

2004 anmäldes 23 fall av vankomycinresistenta enterokocker, VRE. I jämförelse med de 51 fall som rapporterades 2003 är detta en kraftig nedgång. Skillnaden kan förklaras dels med 15 fall från ett utbrott i Örebro län under 2003 och dels med att inga fall rapporterades från Stockholm 2004. Majoriteten av de VRE som har rapporterats mellan 2000 och 2004 har varit *Enterococcus faecium* med *vanB* gen.

Sedan 2004 är alla invasiva infektioner orsakade av *Streptococcus pyogenes* och *Haemophilus influenzae* anmälningspliktiga enligt Smittskyddslagen. Sverige deltar i en europeisk studie om känsligheten för makrolider hos luftvägspatogener. 50 isolat av *S. pyogenes* visade resistens mot tetracyklin men ej mot makrolider. Data för *H. influenzae* kommer att samlas in under 2005.

Escherichia coli har ingått i det nationella övervakningsprogrammet sedan 1996. Den genomsnittliga resistensen mot ampicillin har visat en stadig ökning varje år från 17 till 24%. Det samma gäller för trimetoprim med en ökning från 10 till 15%. Kinolonresistens, påvisad med nalidixinsyra sedan 2002, har inte ökat under denna period men kvarstått i genomsnitt med 8%.

Få fall av *Klebsiella pneumoniae* och *Klebsiella oxytoca* uppvisar höggradig resistens mot 3:e generationens cefalosporiner, ofta orsakad av ESBL.

Under 2004 har endast isolat från sårinfektioner med *Pseudomonas aeruginosa* testats. Resistensen mot ciprofloxacin var 11%.

Helicobacter pylori har övervakats vid några laboratorier. In vitro resistens mot metronidazol har rapporterats i 10-40%. Resistens mot klaritromycin är mindre vanlig (3%) men ökar och har lokalt på ett laboratorium nått över 10%.

Salmonella spp., *Shigella* spp. och *Campylobakter* spp. övervakas på några få laboratorier. Dock är antalet stammar för få för att slutsatser ska kunna dras men fluorokinolonresistensen är hög, mellan 20-25% för *Salmonella*. 50% av Campylobakterstammarna är importfall.

Gonorré är en anmälningspliktig sjukdom och 2004 rapporterades 568 kliniska fall. Isolat från 149 patienter, 26% av de anmälda fallen, skickades till det svenska referenslaboratoriet. Resistensen mot ciprofloxacin är fortfarande alarmerande hög, 48%.

Under 2004 rapporterades 59 fall av invasiv meningokocksjukdom. 47 kliniska isolat analyserades på referenslaboratoriet och inget fall producerade beta-lactamas.

Jämfört med 2003 ökade antalet fall av *Mycobacterium tuberculosis* med 13%. Resistent tuberkulos var rapporterad i 7% av de svenskfödda fallen och i 18% av de utländskt födda.

Nationella och regionala interventionsprojekt

Nedre urinvägsinfektioner hos kvinnor mellan 18-50 år behandlas nästan alltid med empirisk terapi och odling utförs sällan. Med en ökad resistensutveckling finns det behov av att utvärdera den empiriska terapin. I en pågående studie i Kronobergs län tas urinodlingar för att analyseras med avsikt på resistens, testmetoder och val av behandling. Målet med en annan pågående studie i samma län är att utvärdera om, hur snabbt och till vilken grad förekomsten av trimetoprimresistens hos *E. coli* kan minska vid en plötslig och drastisk nedgång i användningen av trimetoprim. Från oktober 2004 till september 2006 kommer alla förskrivare att ersätta trimetoprim och trimsulfa med andra antibiotika. Om studien ger positivt resultat skulle denna typ av intervention kunna användas i större skala för att reducera antalet fall av resistenta bakterier. I anslutning till denna studie har kvalitativa intervjuer med 20 allmänläkare genomförts. Enligt en intervjuguide identifierades fyra typer av inställning till resistens. De allmänläkare som uttryckte större oro för resistens var mer villiga att följa rekommendationer för antibiotikabehandling. Denna uppfattning bör beaktas när interventioner planeras då den kan antas påverka allmänläkarnas förskrivningsmönster.

Luftvägsinfektioner är vanligast bland små barn. 954 familjer deltog i en dagboksstudie och registrerade under en månad alla infektionssymtom. Utöver detta registrerades också om de varit hemma från förskolan, skolan eller arbetet, om de hade utnyttjat föräldraförsäkringen, kontaktat läkare eller sköterska och om antibiotika hade ordinerats. Vid analysen av data fann man många symtomdagar med mestadels lättare symtom. Endast en liten del av dagarna ledde till kontakt med sjukvården och antibiotikabruk. Ungefär en fjärdedel av dagarna ledde till frånvaro från förskolan och föräldraförsäkringen utnyttjades endast vid ett fåtal fall av symtomdagarna.

I november 2003 genomfördes en punktprevalensstudie på 54 sjukhus och studien upprepades 2004. På 49 sjukhus samlades data in på avdelningsnivå genom personliga besök. Det protokoll som användes innehöll såväl demografiska data som indikation och mängd antimikrobiella medel mot bakterier och svamp. Totala mängden antimikrobiella medel för vuxna var 43,1 DDD/100 inneliggande patienter och mest användes cefalosporiner. Erfarenheten från studien 2003 om en för lång peroperativ profylax noterades också 2004, 40% av behandlingarna var längre än en dag (47% 2003). Vid analysen av olika diagnoser sågs en överanvändning av bredspektrum vid samhällsförvärvade infektioner. Vid lunginflammation användes cefalosporiner och tetracykliner i 52% av fallen och utgjorde 46% av givna DDD. Motsvarande siffror för penicillin var 27% av behandlingarna och 34% av DDD. De båda studierna visar mycket lika resultat vilket indikerar metodens tillförlitlighet.

2000 introducerades genom ett konsensusuttalande nya behandlingsrekommendationer för akut öroninflammation. För att undersöka om dessa rekommendationer fått genomslag i praxis genomfördes 2004 en öppen, prospektiv, klinisk, randomiserad studie. I studien ingick barn mellan 2 och 16 år med en- eller dubbelsidig akut öroninflammation och med symtom i färre än fyra dagar. Barnen randomiserades till antingen standardbehandling med PcV i fem dagar eller ingen primär antibiotikabehandling. Dessutom erbjöds de barn/föräldrar som inte ville randomiseras att delta efter att själva ha valt behandlingsalternativ: PcV eller ingen behandling. Alla föräldrar ombads att registrera ett dagligt hälsoindex och följsamhet under sju dagar. Totalt 261 patienter deltog i studien: 92 randomiserades till PcV, 87 till ingen behandling och 82 valde själv behandling (59 PcV, 23 ingen behandling). Det var ingen signifikant skillnad i tiden för tillfrisknande mellan grupperna.

Studiegruppen anser att studien stödjer konsensus uttalandet om att det är lika säkert att avstå från antibiotikabehandling vid okomplicerad akut öroninflammation och att antibiotika erbjuder liten nytta till i övrigt friska barn i åldern 2-16 år. En förutsättning för denna förändring är ett utvecklat system för uppföljning med adekvata instruktioner till patienter och föräldrar för att förhindra allvarliga komplikationer.

3. Use of antimicrobials

3.1. Use of antibiotics

Total antibiotic use

The total use of antibiotics continues to decline in Sweden. The total antibiotic sale has since 1995 been reduced from 18.2 DDD/1000 inhabitants and day, DDD/1000/day, to 16.5 DDD/1000/day 2004 (9%). These data include methenamine which in year 2000 was classified as an antibacterial by the WHO Collaborating Centre for Drug Statistics methodology. During the period 1995-2004 the use of methenamine has nearly doubled from 1.0 to 1.9 DDD/1000/day. However, since methenamine is an antiseptic, this substance is of no interest regarding antibiotic resistance. The total use of antibacterial drugs, with relevance for resistance (methenamine excluded) has decreased from 17.3 to 14.6 DDD/1000/day (15%) (Table 3.1.1).

Table 3.1.1. Total use of antibacterial drugs in Sweden 1995-2004, DDD/1000/day

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
J01 excl methenamine	17,3	16,0	15,1	16,0	15,8	15,5	15,6	15,0	14,8	14,6
Methenamine	1,0	1,1	1,0	1,1	1,5	1,6	1,6	1,7	1,7	1,9
Total J01	18,2	17,1	16,1	17,0	17,3	17,1	17,2	16,7	16,6	16,5

Antibiotic use presented in this Swedres includes data from two different sources (App 3). Due to technical reasons there might be a slight difference when comparing data between the two systems.

Out-patient care

Antibiotics for systemic use in out-patient care constitute about 90% of the total use and have declined while methenamine has increased (Figure 3.1.1). The distribution between different antibiotic classes is shown in Figure 3.1.2. In Table 3.1.2 figures for different groups of antibiotics and age groups are presented in DDD/1000/day as well as in prescriptions/1000/year.

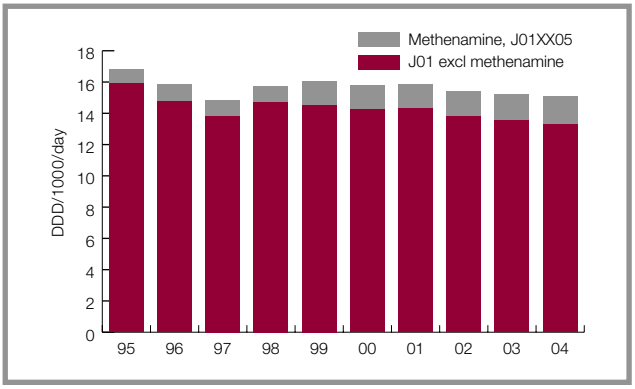

Figure 3.1.1. Antibiotics, out-patient care in Sweden 1995-2004.

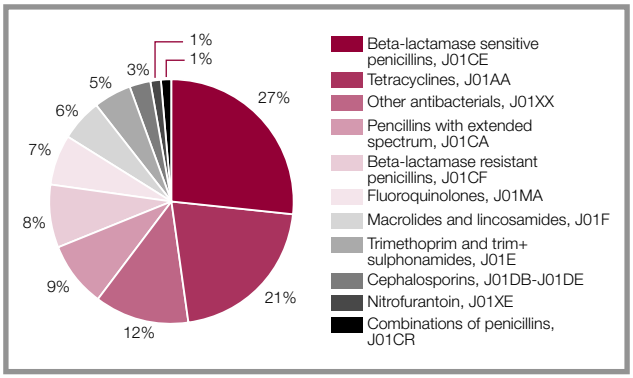

Figure 3.1.2. Distribution (DDD/1000/day, percent) of antibiotic classes used in out-patient care 2004. Group J01XX contains only methenamine.

Changes in consumption of different antibiotic classes are shown in Figures 3.1.3 and 3.1.4. The use of some antibiotics is specifically commented on below.

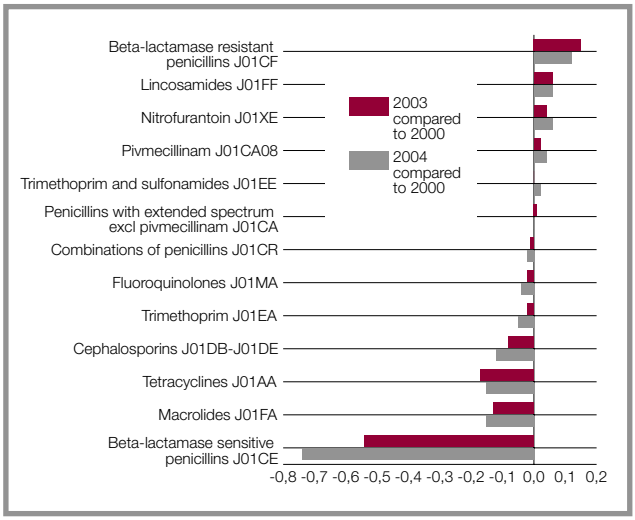

Figure 3.1.3. Out-patient care, changes in consumption 2004 and 2003 compared to 2000, DDD/1000/day.

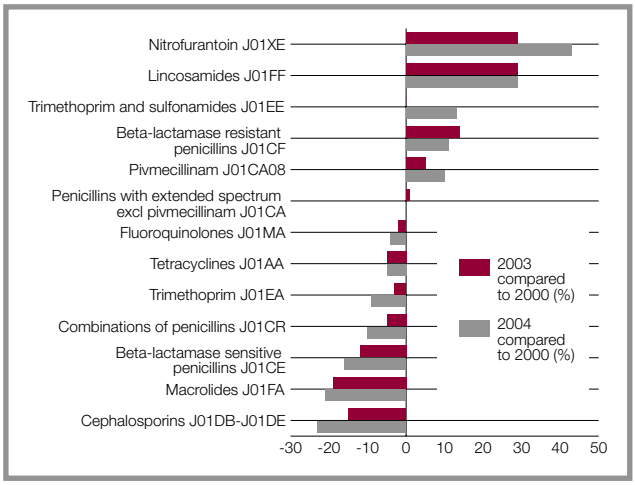

Figure 3.1.4. Out-patient care, percent change in consumption 2004 and 2003 compared to 2000. DDD/1000/day (%).

There is a difference in use of antibiotics between the 21 counties in Sweden. Generally the southern region of Sweden has a higher consumption than the northern region. Skåne, Stockholm and Västra Götaland are all counties with big cities and they all have a relatively high consumption. These three counties also dominate the figure for the whole country since they constitute about 50% of the total population. The difference between the county with the lowest use, Dalarna, and the highest use, Skåne, is about 1.5 times (Figure 3.1.5). For detailed information about consumption in the different counties, please visit the website www.strama.se.

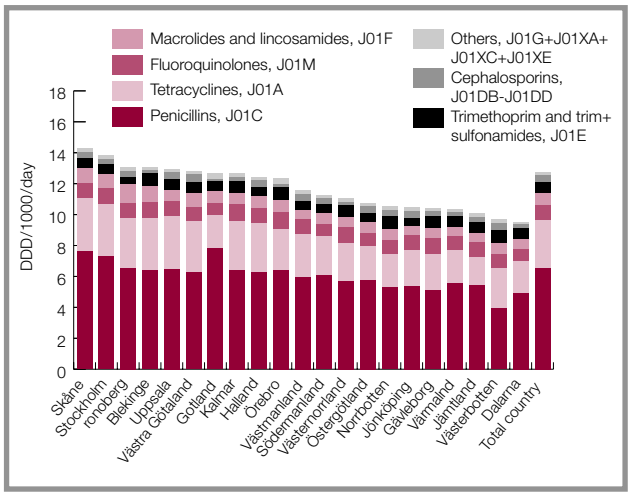

Figure 3.1.5. Antibiotics, out-patient care 2004 per county. Methenamine excluded.

Table 3.1.2. Antibiotics, out-patient care, different groups of antibiotics and different age-groups, 2000-2004, DDD/1000/day, prescriptions/1000/year respectively.

	DDD/1000/day					Prescriptions/1000/year				
Age group (years)	2000	2001	2002	2003	2004	2000	2001	2002	2003	2004
Tetracyclines (J01AA)										
0-6	0,0	0,0	0,0	0,0	0,0	0	0	0	0	0
7-19	2,3	2,1	2,1	2,3	2,4	26	25	24	25	26
20-59	3,6	3,6	3,4	3,3	3,4	74	75	68	64	63
60-79	3,9	3,9	3,7	3,8	3,9	98	95	90	91	92
80-	3,2	3,0	2,9	2,9	2,8	88	83	78	78	76
All age groups	3,2	3,2	3,0	3,0	3,1	67	66	61	59	59
Penicillins with extended spectrum (J01CA)										
0-6	1,4	1,5	1,4	1,3	1,3	98	99	97	92	85
7-19	0,5	0,6	0,5	0,5	0,5	20	23	22	20	18
20-59	1,0	1,0	1,0	1,0	1,0	32	33	33	32	32
60-79	1,9	1,9	2,0	2,0	2,1	65	67	69	70	73
80-	3,4	3,5	3,6	3,6	3,7	134	141	141	140	143
All age groups	1,2	1,3	1,3	1,3	1,3	48	49	49	48	48
Beta-lactamase sensitive penicillins (J01CE)										
0-6	4,6	4,5	4,1	3,8	3,3	412	407	377	348	308
7-19	4,1	4,4	3,9	3,5	2,9	182	195	170	150	121
20-59	5,0	5,0	4,6	4,3	4,2	130	129	119	112	106
60-79	4,1	4,0	4,0	4,1	4,3	102	97	97	100	105
80-	3,7	3,6	3,5	3,4	3,3	104	103	94	90	87
All age groups	4,6	4,6	4,3	4,1	3,9	156	155	143	133	123
Beta-lactamase resistant penicillins (J01CF)										
0-6	0,2	0,2	0,4	0,4	0,3	20	24	36	39	34
7-19	0,5	0,6	0,7	0,7	0,7	24	28	35	36	32
20-59	0,8	0,8	0,9	0,9	0,9	29	30	32	33	32
60-79	1,9	1,9	2,0	2,0	1,9	51	53	56	56	55
80-	4,2	4,5	4,7	4,6	4,5	121	130	132	130	125
All age groups	1,1	1,1	1,2	1,2	1,2	36	38	42	43	41
Combinations of penicillins (J01CR)										
0-6	0,9	0,8	0,8	0,8	0,7	74	64	61	55	49
7-19	0,2	0,2	0,2	0,2	0,2	8	9	8	7	5
20-59	0,1	0,2	0,2	0,1	0,1	4	4	4	3	3
60-79	0,1	0,1	0,2	0,2	0,2	3	3	3	3	4
80-	0,1	0,1	0,1	0,1	0,1	3	3	3	2	2
All age groups	0,2	0,2	0,2	0,2	0,2	10	9	9	8	7

Cephalosporins (J01DA-J01DE)										
0-6	0,1	0,1	0,1	0,1	0,1	11	11	11	11	10
7-19	0,1	0,1	0,1	0,1	0,1	5	5	5	5	4
20-59	0,1	0,1	0,1	0,1	0,1	4	4	4	4	3
60-79	0,1	0,1	0,1	0,1	0,1	5	5	5	5	5
80-	0,2	0,2	0,2	0,2	0,2	11	10	10	9	9
All age groups	0,1	0,1	0,1	0,1	0,1	6	6	5	5	5
Trimethoprim (J01EA)										
0-6	0,1	0,1	0,1	0,1	0,1	15	15	15	16	16
7-19	0,2	0,2	0,2	0,2	0,2	13	13	13	13	12
20-59	0,4	0,4	0,4	0,4	0,4	21	21	21	20	19
60-79	1,0	1,0	1,0	1,0	0,9	50	49	48	48	45
80-	2,9	2,8	2,7	2,6	2,5	157	155	151	147	137
All age groups	0,6	0,6	0,6	0,6	0,5	31	31	30	30	28
Trimethoprim with sulfonamides (J01EE)										
0-6	0,2	0,2	0,2	0,2	0,2	24	23	21	20	18
7-19	0,1	0,1	0,1	0,1	0,1	5	5	5	4	4
20-59	0,1	0,1	0,1	0,1	0,1	3	3	3	3	3
60-79	0,3	0,2	0,3	0,3	0,3	7	7	7	7	8
80-	0,3	0,3	0,3	0,3	0,4	11	11	11	11	12
All age groups	0,2	0,2	0,2	0,2	0,2	6	6	6	6	6
Macrolides (J01FA)										
0-6	1,0	1,1	0,9	0,8	0,7	46	50	44	36	35
7-19	0,9	0,9	0,8	0,6	0,6	27	30	24	20	18
20-59	0,7	0,7	0,6	0,6	0,5	21	22	20	17	17
60-79	0,5	0,5	0,5	0,5	0,5	16	16	15	14	14
80-	0,4	0,4	0,4	0,3	0,3	13	12	11	10	10
All age groups	0,7	0,7	0,6	0,6	0,6	23	24	21	18	18
Lincosamides (J01FF)										
0-6	0,0	0,0	0,0	0,0	0,0	4	4	5	5	4
7-19	0,1	0,1	0,1	0,1	0,1	5	6	7	7	7
20-59	0,2	0,2	0,2	0,2	0,2	9	10	11	12	13
60-79	0,4	0,4	0,4	0,5	0,5	14	16	17	20	21
80-	0,6	0,6	0,6	0,7	0,7	23	26	27	30	30
All age groups	0,2	0,2	0,2	0,3	0,3	10	11	12	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	7	6	6	6
20-59	0,8	0,8	0,8	0,8	0,8	38	38	37	35	33
60-79	2,1	2,1	2,0	2,1	2,1	98	96	94	92	89
80-	3,8	3,6	3,4	3,3	3,1	211	201	188	173	159
All age groups	1,0	1,0	1,0	1,0	1,0	49	48	47	45	43
Nitrofurantoin (J01XE)										
0-6	0,1	0,1	0,1	0,1	0,1	7	7	7	7	7
7-19	0,1	0,1	0,1	0,1	0,1	4	4	4	4	5
20-59	0,1	0,1	0,2	0,2	0,2	5	5	6	7	7
60-79	0,2	0,2	0,2	0,2	0,3	6	7	8	9	12
80-	0,4	0,5	0,5	0,6	0,7	17	20	24	27	31
All age groups	0,1	0,2	0,2	0,2	0,2	6	6	7	8	9
Alla agents (J01 excl methenamine)										
0-6	9,2	9,1	8,7	8,1	7,2	754	748	719	675	607
7-19	9,3	9,8	9,3	8,9	8,1	346	370	344	316	275
20-59	13,3	13,3	12,7	12,3	12,1	389	392	373	358	346
60-79	17,1	16,9	16,8	17,2	17,7	543	537	533	541	546
80-	24,0	24,0	23,7	23,3	23,0	946	944	915	890	861
All age groups	13,7	13,8	13,3	13,0	12,8	473	476	456	439	420

Penicillin V

Penicillin V is the most commonly used antibiotic in out-patient care but is also the antibiotic with the most prominent decrease (Figure 3.1.6). Other antibiotics against respiratory tract infections, macrolides, cephalosporins and tetracyclines, also show a slight reduction in use. The largest decrease of penicillin V is seen among children (Figure 3.1.7). The falling trend started already ten years ago but gets more evident from 2002. One possible reason may be a consensus report, released in May 2000, concerning acute otitis media. The report recommends "wait and see" policy for children >2 years old with uncomplicated acute otitis media. One study in the county of Östergötland has shown that the number of patients with the diagnosis of acute otitis media has been substantially reduced from 1999 to 2003.

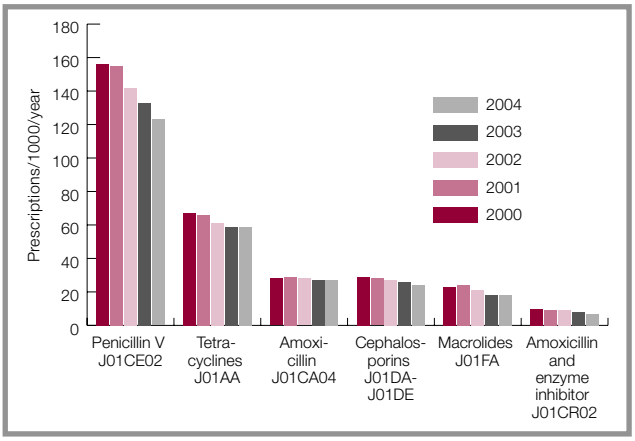

Figure 3.1.6. Antibiotics mostly used against respiratory tract infections, out-patient care 2000-2004, prescriptions/1000/year.

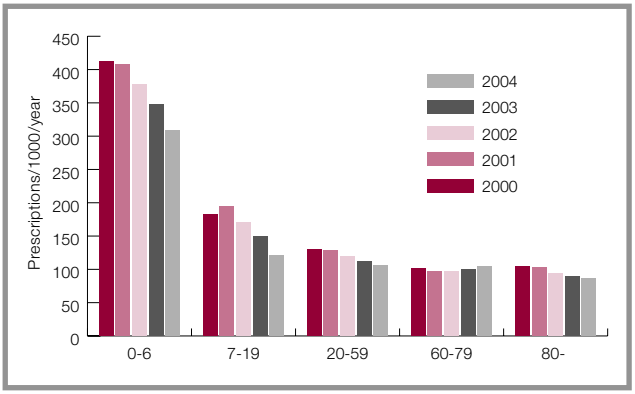

Figure 3.1.7. Penicillin V (J01CE02), out-patient care 2000-2004, different age groups, prescriptions/1000/year.

Tetracyclines

Tetracyclines are the second largest group in out-patient care when measured in DDD/1000/day (Figure 3.1.2). The proportion of prescriptions is not as large, reflecting long treatments (i.e. a high number of DDDs per prescription). Lymecycline, which is the most common treatment against acne vulgaris, constitutes about one third of the tetracyclines, in DDD:s (Table 3.1.3).

Fluoroquinolones

A diagnose-prescribing study in 2000 showed that guidelines concerning treatment of lower urinary tract infections among women were not satisfactorily followed. Fluoroquinolones, which are not recommended, were nevertheless commonly used for this indication. Many drug and therapeutic committees and local STRAMA groups have defined targets concerning lowering the use of fluoroquinolones for women with uncomplicated urinary tract infections. Comparing sales data of antibiotics that are mostly used against urinary tract infections, there is now a favourable decreasing trend among fluoroquinolone use for women between 2000 and 2004 (Figure 3.1.8). Instead the use of pivmecillinam and nitrofurantoin are increasing. Among men there has only been an insignificant change in the use of fluoroquinolones.

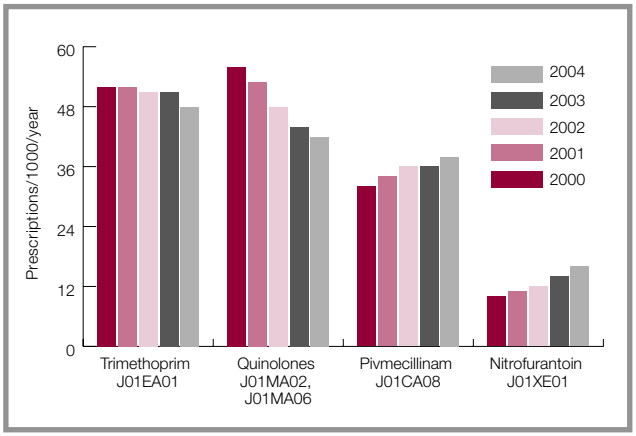

Figure 3.1.8. Antibiotics mostly used against urinary tract infections, out-patient care 2000-2004. Women, prescriptions/1000/year.

Table 3.1.3. Use of tetracyclines, out-patient care 2004, DDD/1000/day and prescriptions/1000/year respectively.

	DDD/1000/day					Prescriptions/1000/year				
	2000	2001	2002	2003	2004	2000	2001	2002	2003	2004
Doxycycline	2,0	2,0	1,8	1,8	1,8	55	55	50	48	47
Lymecycline	0,8	0,8	0,9	0,9	1,0	7	7	7	8	8
Tetracycline	0,3	0,3	0,3	0,3	0,3	4	3	3	3	3
Oxytetracycline	0,1	0,1	0,1	0,1	0,1	1	1	1	1	1
Tetracyclines total (J01AA)	3,2	3,2	3,0	3,0	3,1	67	66	61	59	59

The largest decrease of fluoroquinolone prescriptions is seen among women >80 years old (Figure 3.1.9).

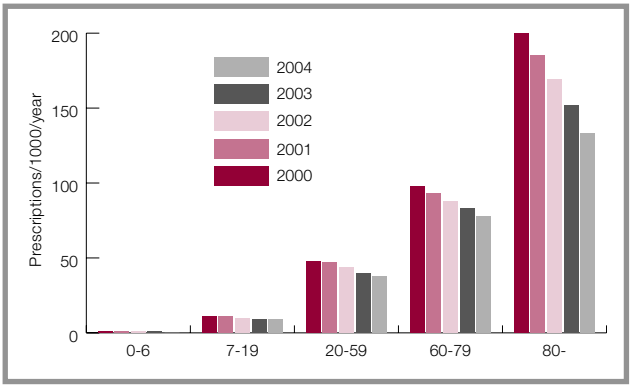

Figure 3.1.9. Fluoroquinolones (J01MA) prescribed to women in out-patient care 2000-2004, different age groups, prescriptions/1000/year.

Even if the number of prescriptions are decreasing the number of DDD/1000/day are not decreasing in the same proportion. There is a tendency of increasing DDD/prescription which may reflect longer treatments with fluoroquinolones, (Figure 3.1.10).

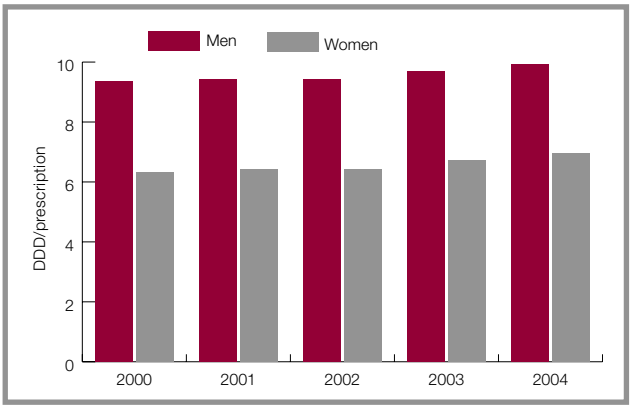

Figure 3.1.10. Fluoroquinolones, out-patient care 2000-2004, DDD/prescription.

Flucloxacillin

In the end of the 1990's an epidemic with impetigo, caused by *S. aureus* resistant to fucidic acid, started in Sweden. This epidemic resulted in a change of treatment policy from local treatment with fucidic acid ointment to systemic flucloxacillin. Mupirocin ointment was not recommended because of the risk of developing resistance in *S. aureus*. Within two to three years the use of flucloxacillin doubled among children 0-6 years and the use of fusidic acid and mupirocin decreased. Data for year 2004 indicates that the use of flucloxacillin may be declining again (Figure 3.1.11) although resistance rates imply the continuing prescence of this fusidic acid resistant clone.

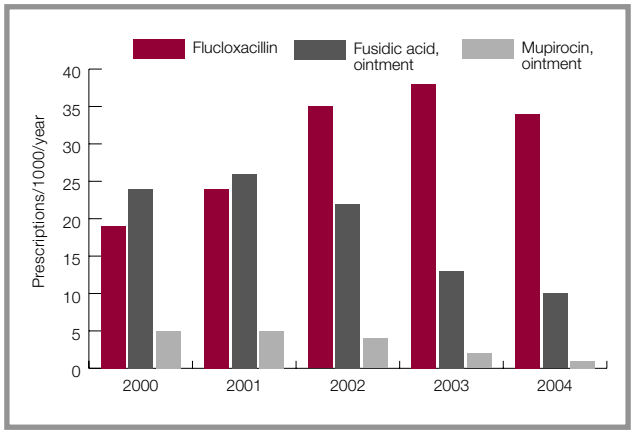

Figure 3.1.11. Flucloxacillin, fusidic acid and mupirocin, out-patient care 2000-2004, children 0-6 years, prescriptions/1000/year.

Hospital care

There has only been minor changes in the use of antibiotics within hospital care for the last 10 years, but the proportion of different groups has altered (Table 3.1.4). The distribution between different classes of antibiotics is shown in Figure 3.1.12.

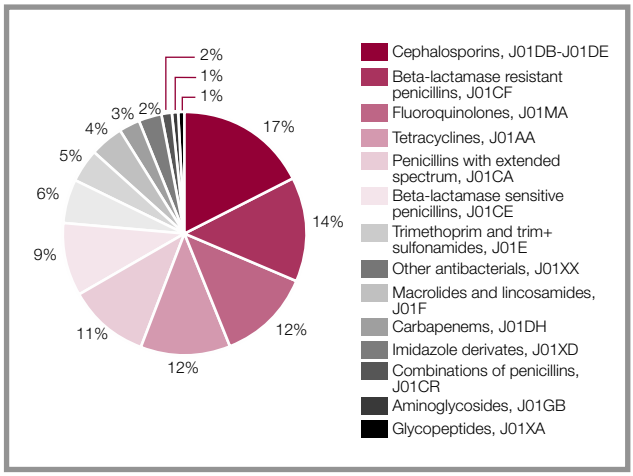

Figure 3.1.12. Antibiotics, hospital care 2004, percent of DDD/1000/day. Group J01XX constitutes 99% of methenamine.

Changes in consumption of different classes of antibiotics are shown in Figures 3.1.13 and 3.1.14.

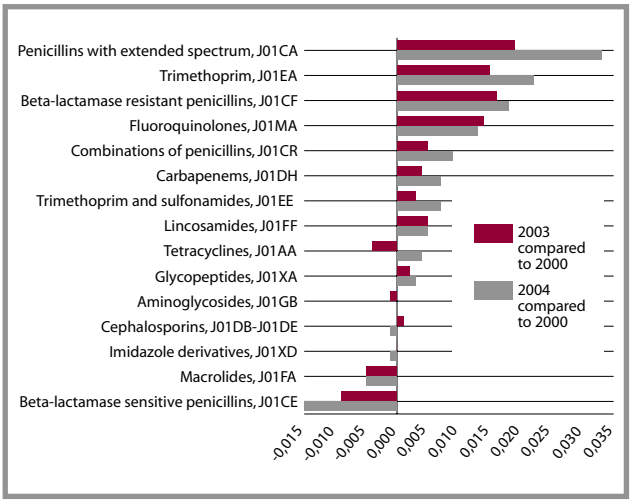

Figure 3.1.13. Antibiotics hospital care 2004 and 2003 compared to 2000, DDD/1000/day.

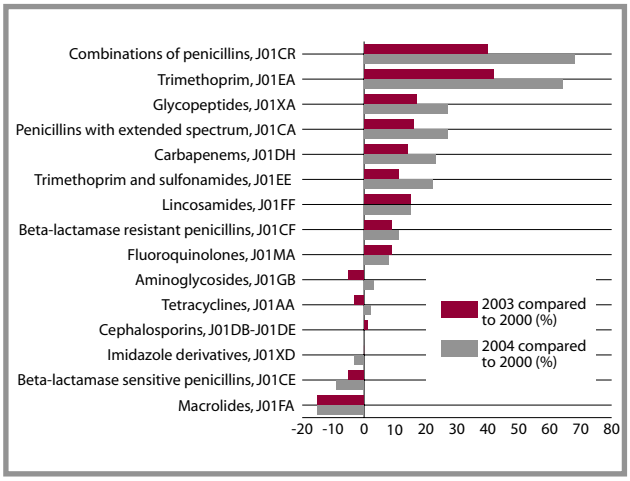

Figure 3.1.14. Antibiotics hospital care 2004 and 2003 compared to 2000, DDD/1000/day (%).

Among penicillins there has been a shift. Beta-lactamase sensitive penicillins have decreased and penicillins with extended spectrum have increased (Figure 3.1.15).

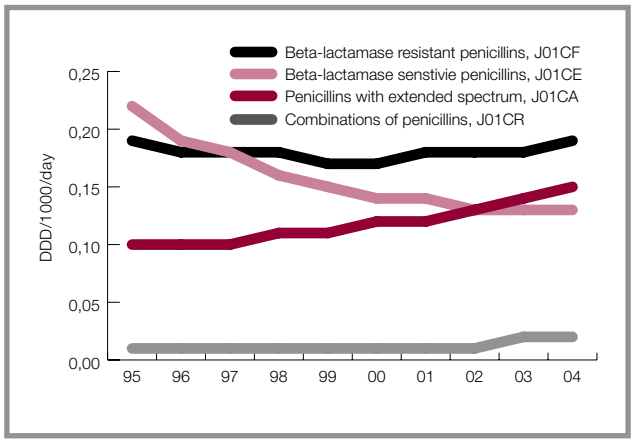

Figure 3.1.15. Penicillins, Hospital care 1995-2004, DDD/1000/day.

Table 3.1.4. Total use of antibioitics within hospital care 1995-2004, DDD/1000/day.

		1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
J01AA	Tetracyclines	0,19	0,17	0,15	0,16	0,16	0,16	0,15	0,15	0,15	0,16
J01CA	Penicillins with extended spectrum	0,10	0,10	0,10	0,11	0,11	0,12	0,12	0,13	0,14	0,15
J01CE	Beta-lactamase senstivie penicillins	0,22	0,19	0,18	0,16	0,15	0,14	0,14	0,13	0,13	0,13
J01CF	Beta-lactamase resistant penicillins	0,19	0,18	0,18	0,18	0,17	0,17	0,18	0,18	0,18	0,19
J01CR	Combinations of penicillins	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,02
J01DB-E	Cephalosporins	0,25	0,24	0,24	0,25	0,25	0,24	0,24	0,24	0,25	0,24
J01DH	Carbapenems	0,02	0,02	0,02	0,03	0,03	0,03	0,03	0,03	0,04	0,04
J01EA	Trimethoprim	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,04	0,04	0,05
J01EE	Trimethoprim and sulfonamides	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03
J01FA	Macrolides	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,02	0,02
J01FF	Lincosamides	0,02	0,02	0,03	0,03	0,03	0,03	0,03	0,03	0,04	0,04
J01GB	Aminoglycosides	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
J01MA	Fluoroquinolones	0,19	0,17	0,16	0,17	0,16	0,16	0,17	0,16	0,17	0,17
J01XA	Glycopeptides	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
J01XD	Imidazole derivates	0,03	0,03	0,03	0,04	0,04	0,04	0,04	0,04	0,04	0,04
J01XX	Other antibacterials	0,04	0,03	0,03	0,03	0,04	0,03	0,03	0,03	0,04	0,06
J01	All agents	1,4	1,3	1,3	1,3	1,3	1,3	1,3	1,3	1,3	1,4

Compliance to guidelines for cystitis and pneumonia needs to be improved within hospital care

In Sweden, by tradition, cephalosporins are used generously within hospital care. During the last ten years cephalosporins constitute 17-19% of the total antibiotic use. More than 80% of the cephalosporins are given as intravenous therapy and cefuroxime is the substance mainly used (Figure 3.1.16). Two point prevalence studies (further described in chapter 5), performed at Swedish hospitals in November 2003 and 2004, showed that the most frequent indication for cephalosporin treatment (DDD) was community acquired pulmonary infections.

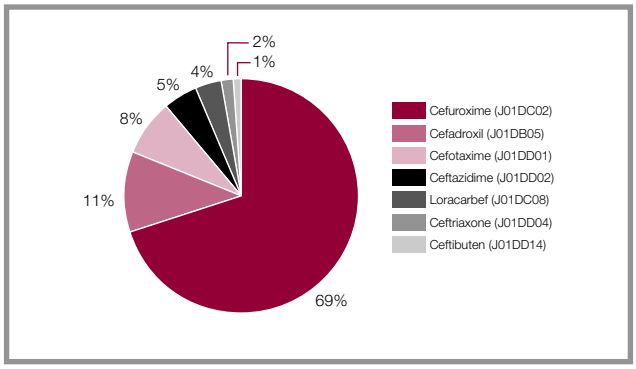

Figure 3.1.16. Cephalosporins, Hospital care, percent of DDD 2004

The pointprevalence studies further showed that women with uncomplicated urinary tract infections are frequently treated with fluoroquinolones. About 28% of women with community acquired cystitis were treated with fluoroquinolones.

A national working group has been formed within the STRAMA network for follow-up of the performed point-prevalence studies. Interventions will start during fall 2005 to improve compliance to recommendations concerning treatment of both pneumonia and cystitis.

Antibiotics in treatment of infections with MRSA, enterococci and multiresistant coagulase-negative staphylococci (vancomycin, teicoplanin and linezolid) have increased during the past three years (Figure 3.1.17). Still these drugs comprise a very small percentage of the total antibiotic use in hospital care. This increase is probably due to an increased frequency of patients infected with multiresistant coagualse-negative staphylococci in Swedish hospitals. However, the prevalence of patients infected with MRSA is still low in Sweden, compared to other European countries.

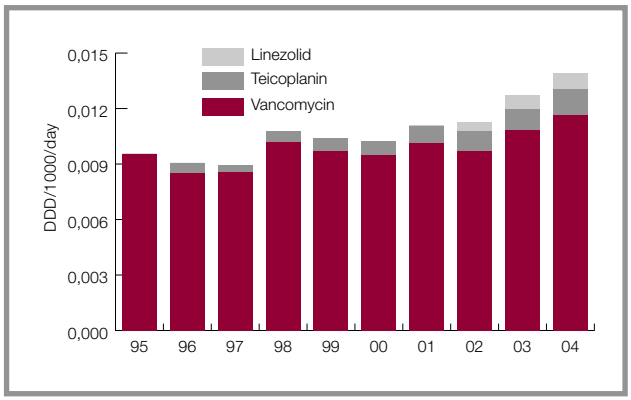

Figure 3.1.17. Vancomycin, teicoplanin and linezolid in hospital care 1995-2004, DDD/1000/day.

ESAC

Sweden is participating in the project European Surveillance of Antimicrobial Consumption, ESAC. The ESAC project does not separate methenamine from the antibiotics in group J01. Thus, in Figure 3.1.18 methenamine is included in the group "others". Norway, Sweden and Finland prescribed 2.0, 1.6 and 1.3 DDD/1000/day of methenamine respectively 2002 while all other countries prescribed less than 0.4 DDD/1000/day. The use of fluoroquinolones in Sweden is relatively high compared to other Nordic countries.

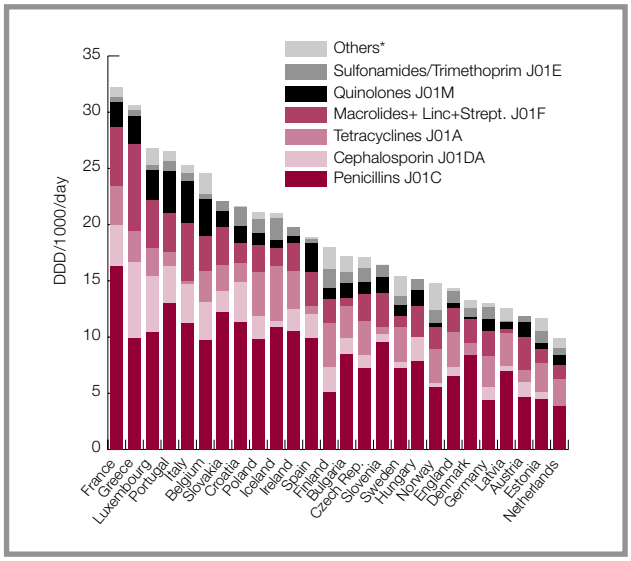

Figure 3.1.18. Antibiotic out-patient consumption 2002 in 26 European countries, ESAC-project. *Others = J01B + J01G + J01X + J01DF + J01DH.

Otto Cars, Gunilla Skoog

3.2. Use of antifungals

Out-patient care

As shown in Swedres 2003 the use of antifungals against fungal skin infections was increasing drastically after a commercial campaign concerning nail infections. The use has been the same during 2003 and 2004 (Figure. 3.2.1).

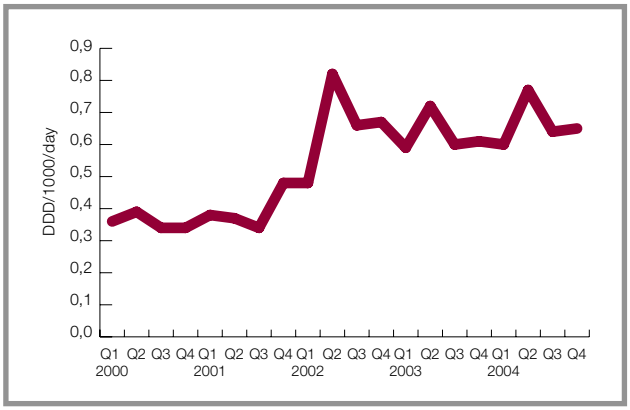

Figure 3.2.1. Antifungals for systemic use (D01B-fungal skin infections), out-patient care 2000-2004 quarter, DDD/1000/day.

Hospital care

The total use of antifungals for systemic use has not increased even though two new substances was introduced on the market 2002. A slight decrease is seen for amphotericin B and itraconazole while the new substances caspofungin and voriconazole increases (Figure 3.2.2).

Gunilla Skoog

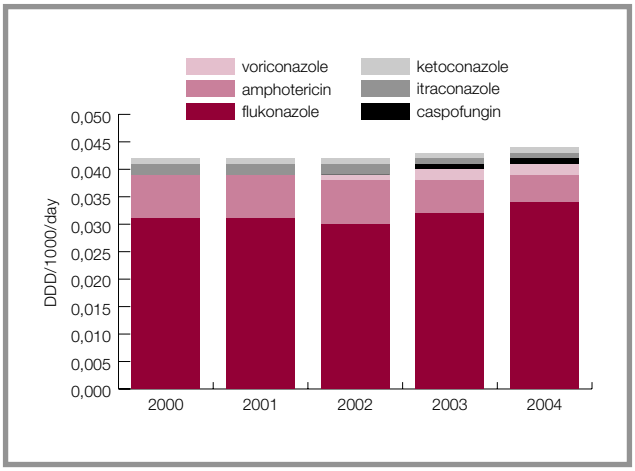

Figure 3.2.2. Antifungals for systemic use (J02), hospital care, 2000-2004, DDD/1000/day. Data in Swedres 2003 were unfortunately incorrect.

4. Antimicrobial resistance

Streptococcus pneumoniae

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 four years (Appendix 5), well-characterised data on many bacterial pathogens are now available.

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 last 2 years there has been a minor increase in the number of PRP cases reported through the Communicable Disease Act, but the annual incidence is still lower compared to the late 1990's (Figure 4.1). However, previous analysis (see Swedres 2002) indicates that the decrease in incidence seen during the period is closely related to a concurrent decrease in nasopharyngeal culturing propensity.

Data from year 2004 might also be affected by changes between notification systems, which could slightly overestimate the number of PRP cases.

The majority of PRP cases in Sweden are young children diagnosed by a nasopharyngeal culture. Only a few cases had a MIC of penicillin G above 2 mg/L. The age distribution where up to 70 % of the cases 6 years or younger and has not changed much during the last couple of years.

Case-finding intensity varies between counties, both due to regional differences in culturing propensity and differences in targeted screening programmes, which makes interregional comparison difficult. For a more detailed analysis of PRP trends during the last couple of years, please see Swedres 2002 and 2003.

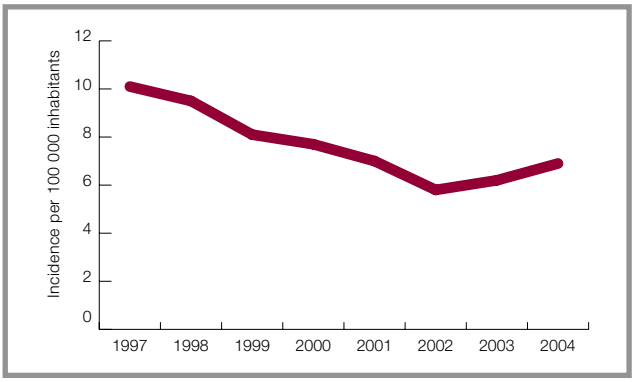

Figure 4.1. Annual PRP incidence 1997-2004.

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 the clinical microbiology laboratories, have been tested for susceptibility to penicillin (by means of oxacillin 1 µg screen disk), erythromycin, tetracycline, and the combination of sulfonamide and trimethoprim, using the disk diffusion method. The national overview of these studies is given in Figure 4.2. A trend of increasing resistance has been seen for all four groups of antibiotics. This trend was possibly broken in 2004.

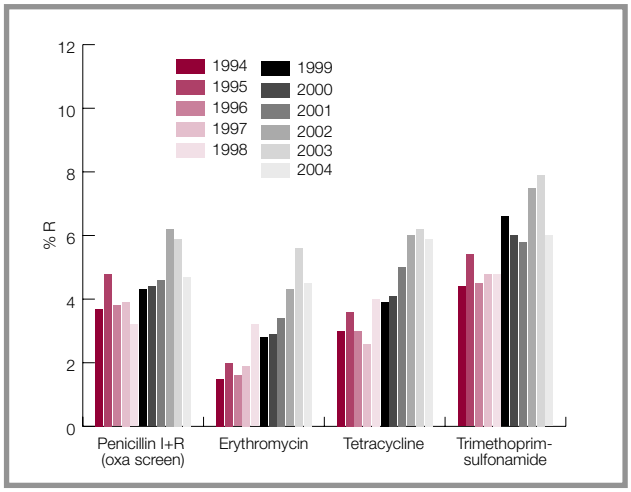

Figure 4.2. Overall national resistance rates of *S.pneumoniae* (resistant isolates as percentage of all pneumococcal isolates) for four different antibiotics 1994–2004 (data from the annual RSQC programme, approximately 3000 isolates per year).

Data from EARSS

Twentyone 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 4.3). Sweden is still among the low range countries.

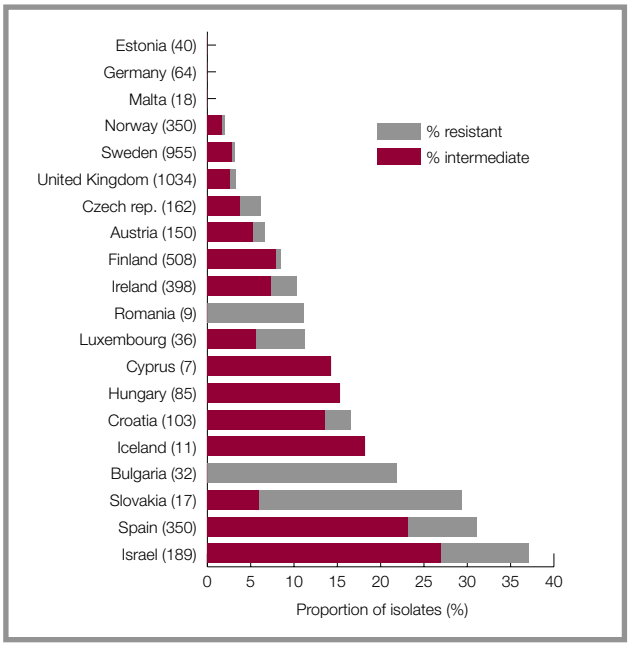

Figure 4.3. Frequencies of reduced susceptibility to penicillin among invasive isolates of *Streptococcus pneumoniae* in Europe 2004. Data from EARSS (www.earss.rivm.nl 2005-04-25).

The Swedish data on susceptibility to penicillin and erythromycin is given in Table 4.1. 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.

Table 4.1. Susceptibility to penicillin and erythromycin among Swedish invasive isolates of *Streptococcus pneumoniae* reported to EARSS.

	Penicillin*			
Year	S %	I %	R %	Total
1999	98.5	1.4	0.1	805
2000	98.0	2.0	0.0	803
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
	Erythromycin			
Year	S %	I %	R %	Total
1999	94.2	2.2	3.6	535
2000	96.7	0.5	2.8	643
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

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

Liselotte Högberg, Barbro Olsson Liljequist

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 in order to prevent spread of the organism. The decision to include both infection and colonization with MRSA in the Communicable Disease Act in the year 2000 was due to 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 2004 a total of 709 cases were notified to the Swedish Institute of Infectious Disease Control (Table 4.2.). This represents an increase of 30% compared to 2003 and is a continuation of a trend seen since the beginning of mandatory notifications in 2000. Most of the Swedish counties are experiencing an increasing incidence of MRSA cases. All age groups and both sexes were affected, with incidence rising with age.

Due to an ongoing outbreak in the county of Stockholm, the screening programs were dramatically intensified, resulting in an increase of patients sampled. A similar intensification has probably occured in other counties also and may account for part of the increase in incidence during 2004.

For the first time since 2000 there was a decreasing transmission of MRSA within Stockholm county. This decrease was most apparent in the health-care setting, with 75 new

Table 4.2. MRSA notified in 2000-2004 by county according to the Communicable Disease Act.

	2000		2001		2002		2003		2004	
County	Number	Incidence/ 100 000 inhab	Number	Incidence/ 100 000 inhab	Number	Incidence/ 100 000 inhab	Number	Incidence/ 100 000 inhab	Number	Incidence/ 100 000 inhab
Blekinge	7	4,6	1	0,6	3	1,9	2	1,3	3	2.00
Dalarna	0	0	4	1,4	1	0,3	2	0,7	3	1.1
Gotland	1	1,7	10	17,4	3	5,2	2	3,4	1	1.7
Gävleborg	2	0,7	1	0,3	12	4,3	5	1,8	5	1.8
Halland	10	3,6	25	9,0	13	4,6	13	4,6	9	3.2
Jämtland	0	0	0	0	2	1,5	5	3,8	1	0.8
Jönköping	7	2,1	5	1,5	5	1,5	24	7,3	14	4.3
Kalmar	3	1,2	2	0,8	5	2,1	6	2,5	16	6.8
Kronoberg	1	0,5	0	0	4	2,2	5	2,8	17	9.5
Norrbotten	3	1,1	5	1,9	6	2,3	9	3,5	7	2.8
Skåne	22	1,9	75	6,6	68	5,9	104	9,1	128	11.1
Stockholm	96	5,2	166	9,0	205	11,1	228	12,3	277	14.8
Södermanland	2	0,7	1	0,3	4	1,5	2	0,7	8	3.1
Uppsala	19	6,4	17	5,7	10	3,3	12	4,0	26	8.6
Värmland	9	3,2	7	2,5	5	1,8	11	4,0	18	6.6
Västerbotten	3	1,1	18	7,0	10	3,9	13	5,0	16	6.2
Västernorrland	14	5,6	12	4,8	7	2,8	10	4,0	5	2.1
Västmanland	3	1,1	8	3,1	7	2,7	11	4,2	12	4.6
Västra Götaland	110	7,3	54	3,6	48	3,1	63	4,1	118	7.8
Örebro	8	2,9	6	2,1	16	5,8	8	2,9	11	4.0
Östergötland	2	0,4	7	1,6	7	1,6	14	3,3	14	3.4
Total	**322**	**3,6**	**424**	**4,7**	**441**	**4,9**	**549**	**6,1**	**709**	**7.9**

cases in 2004 compared to 117 in 2003 (Figure 4.4). This decrease was partly balanced by an increase of community-acquired cases from 40 to 64 new cases, during the same time period. However, the increase in total number of MRSA cases between 2003 and 2004 was mostly due to the number of patients who acquired the disease abroad, an increase from 40 to 77 new cases.

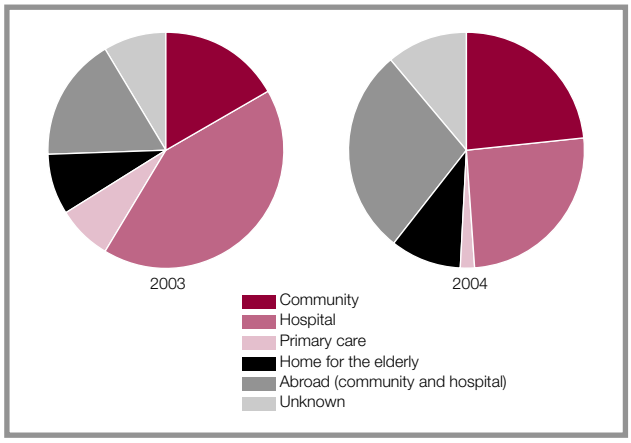

Figure 4.4. Probable location for acquiring MRSA, Stockholm county 2003 and 2004.

Typing of MRSA

A DNA-based method has been used for typing of most MRSA isolates since the year 2000 (pulsed field gel electrophoresis, PFGE). PFGE patterns were included in a database and compared with international reference strains (epidemic MRSA from European countries, the Harmony project) (Table 4.3). 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 sequence-based methods (MLST, see www.mlst.net) is also shown in Table 4.3.

Isolates with PFGE-patterns identical to or related to UK E15 were the most frequently seen each year since 2001, although their relative frequency decreased in 2004. They were with few exceptions found in the Stockholm area. The second most common group of isolates was the one 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. The third most common type of MRSA was the one with Berlin IV like PFGE patterns, increasingly found in all parts of Sweden. Worth noticing is that among the so called unrelated SE patterns there were a few which showed increasing numbers during the last three years. These were SE01-3, SE02-18, SE03-5, SE97-2 and SE98-1.

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, respectively,

Table 4.3. PFGE patterns of MRSA isolated in Sweden 2000-2004.

PFGE pattern	ST of reference patterns	No. of isolates with identical or related patterns (% of total) 2000	2001	2002	2003	2004
UK E15	22	22 (9.1)	76 (18.4)	107 (24.4)	119 (22.8)	104 (16.9)
DK E97-1	80	43 (17.8)	54 (13.1)	73 (16.7)	80 (15.4)	94 (15.3)
Berlin IV	45	23 (9.5)	51 (12.4)	14 (3.2)	63 (12.1)	72 (11.7)
Bel EC-3a	5	11 (4.5)	18 (4.4)	30 (6.8)	46 (8.8)	38 (6.2)
UK E16	36	33 (13.6)	48 (11.7)	41 (9.4)	30 (5.8)	49 (8.0)
UK E1 / Spa E1 / Gr-1	239, 241	31 (12.8)	29 (7.0)	35 (8.0)	18 (3.5)	20 (3.3)
Fra A	8	27 (11.2)	31 (7.5)	28 (6.4)	20 (3.8)	13 (2.1)
Fra B	8	3 (1.2)	18 (4.4)	16 (3.7)	27 (5.2)	47 (7.6)
UK E3	5	4 (1.7)	10 (2.4)	13 (3.0)	15 (2.9)	29 (4.7)
S German II	228	4 (1.7)	5 (1.2)	8 (1.8)	7 (1.3)	6 (1.0)
Unrelated SE-patterns		30 (12.4)	52 (12.6)	62 (14.2)	79 (15.2)	123 (20.0)
Unique	Not tested	11 (4.5)	20 (4.9)	11 (2.5)	17 (3.3)	29 (4.7)
Total		**242**	**412**	**438**	**521**	**615**

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 were included in the annual RSQC programme since 2001 (Appendix 5). Twenty-nine laboratories delivered data on consecutive isolates using the disk diffusion method for oxacillin (in 2004 cefoxitin replaced oxacillin), clindamycin, fusidic acid, aminoglycoside (gentamicin, netilmicin or tobramycin) and vancomycin. In 2004 erythromycin and ciprofloxacin were also tested. Resistance rates are presented in Figure 4.5.

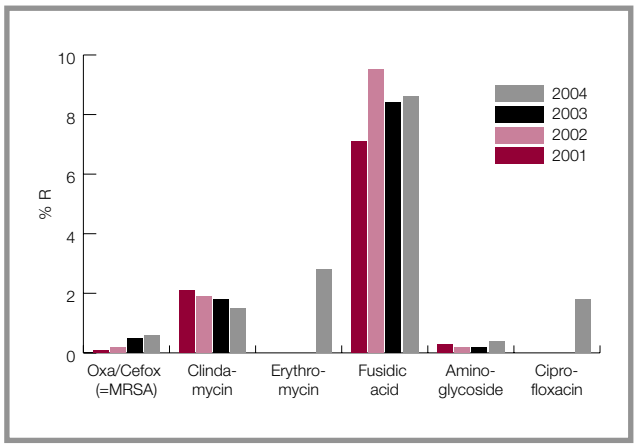

Figure 4.5. Resistance rates for *Staphylococcus aureus* 2001–2004 (data from the annual RSQC programme, approximately 3000 isolates per year).

The continuous increase of MRSA in wound infections, detected by the oxacillin and from 2004 the cefoxitin screening disks, is of concern and must be watched carefully. The high rates of fusidic acid resistance in wound infections from 2001-2003 continued also in 2004. One fusidic acid resistant clone (MIC of fusidic acid 4 m/L) was shown to cause impetigo in young children in 2002. The constant high resistance rate implies the continuing presence of this clone.

Data from EARSS

Twentyone of the Swedish laboratories (covering approximately 75 % of the population) are reporting susceptibility data on invasive isolates of *S. aureus* to EARSS (Appendix 5). On average 0.75 % of the invasive *S. aureus* isolates were MRSA (identified by the oxacillin screen disk test and confirmed by the detection of the *mecA* gene). Swedish data from the last five years indicate a low rate of MRSA among invasive isolates (Table 4.4.). Comparative data for Europe are given in Figure 4.6.

Table 4.4. *Staphylococcus aureus* susceptibility results (number of strains and percentage) using the oxacillin disk diffusion method according to SRGA in Sweden. Data reported from SMI to EARSS.

Year	S	I	R
1999	1307 (99 %)	0	13 (1.0 %)
2000	1469 (99.4 %)	0	9 (0.6 %)
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%)

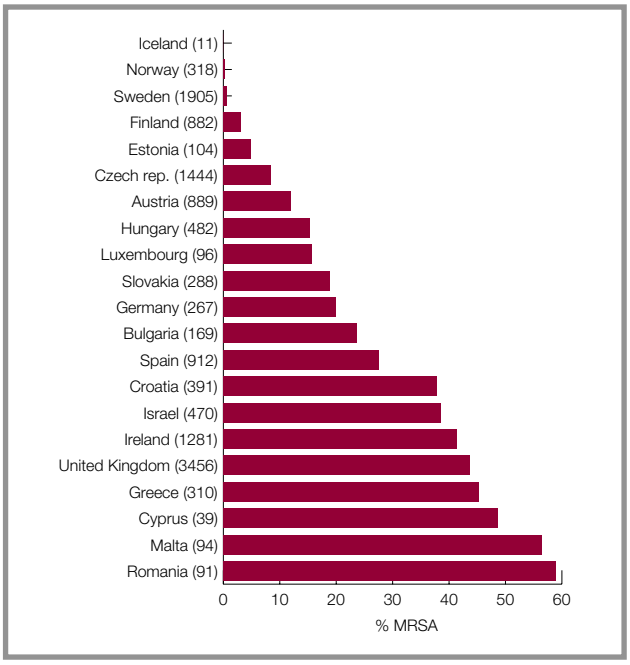

Figure 4.6. MRSA in Europe 2004. Data from EARSS (www.ears.rivm.nl 2005-04-25).

Pasi Penttinen, Barbro Olsson Liljequist, Åke Örtqvist

Enterococcus faecium and faecalis

Background

Enterococci, and more specifically vancomycin resistant enterococci (VRE), have become an important cause 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 2002 no more than 20 cases of VRE were reported per year. In 2003 this figure increased sharply to 51 cases. However, in 2004 the total number of VRE cases decreased to 23 (Figure 4.7). There were no cases in Stockholm County in 2004 (Figure 4.8), during 2000-2003 Stockholm County reported at least 8 cases per year. There was also a large decrease in the number of cases (15 to 3) reported by Örebro County following an outbreak that occurred there in 2003. These two factors largely account for the large decrease in the number of reported cases between 2003 and 2004. The median age of cases increased from 60 in 2002 to 67 in 2003 to 74 in 2004.

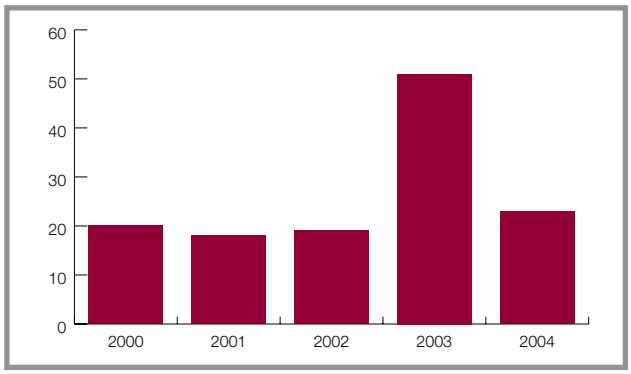

Figure 4.7. Annual number of VRE cases reported in Sweden.

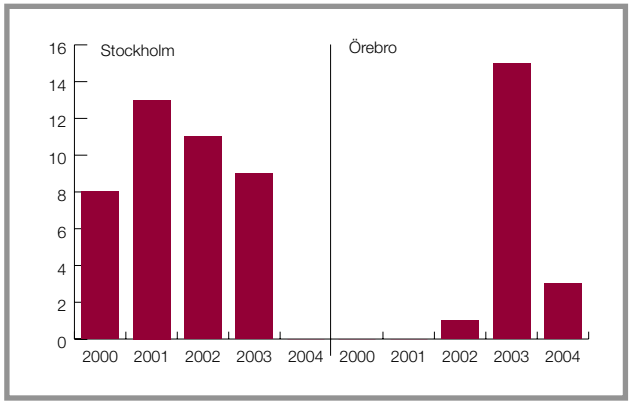

Figure 4.8. Reported cases of VRE in selected counties from 2000 to 2004 (other counties mostly did not show any noteworthy changes from 2003 to 2004 or did not report any VRE cases between 2000 and 2004).

The majority of VRE reported according to the CDA 2000-2004 were *Enterococcus faecium* carrying the *vanB* gene (n=92). Sixteen were *E. faecium* with *vanA*-gene, 5 *E. faecalis* with *vanA* and 1 was *E. faecalis* with *vanB*. According to PhP-typing of selected isolates, none of the *E. faecium* carrying the *vanA* gene showed any similarity with the isolates reported in SVARM 2003 (personal communication, A Iversen).

Annual Resistance Surveillance and Quality Control (RSQC) programme

Enterococcus faecalis has been included in the RSQC programme only three times. Focus has been on ampicillin, vancomycin and high level aminoglycoside resistance. In 2004 imipenem and linezolid were also tested, and data are shown in Figure 4.9. Up till now, no vancomycin nor linezolid resistant isolates were detected in these point prevalence studies. A dramatic increase in high level aminoglycoside resistance, correctly tested by using a gentamicin disk, was noted during the last decade.

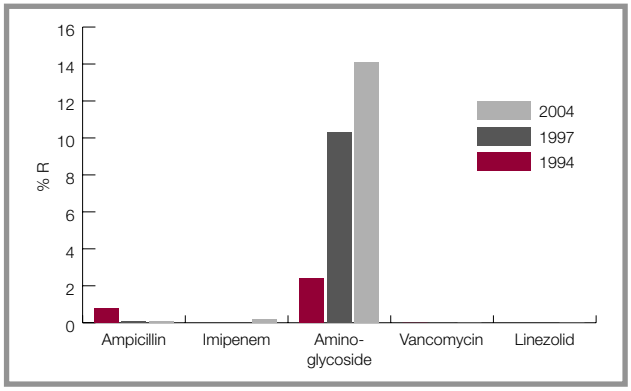

Figure 4.9. Resistance rates of *E. faecalis*, 1994, 1997, 2004, RSQC programme.

Data from EARSS

Since the year 2001, *Enterococcus faecalis* and *Enterococcus faecium* were included in the EARSS network (Appendix 5). The main focus has been on vancomycin resistance, but also on high-level resistance to aminoglycoside antibiotics. Twentyone 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 also found, representing 1.2 % (Tables 4.5 and 4.6). High-level aminoglycoside resistance was constantly more prevalent in *Enterococcus faecalis* (13-18 %) than in *Enterococcus faecium* (6-11 %) during this period.

Table 4.5. Susceptibility of invasive isolates of *Enterococcus faecalis* in Sweden 2001-2004.

	2001 Total (%R)	2002 Total (%R)	2003 Total (%R)	2004 Total (%R)
Ampicillin	479 (0)	453 (0)	612 (0)	590 (0.3)
Aminoglycosides	212 (12.7)	235 (17)	440 (17.5)	533 (15.4)
Vancomycin	395 (0)	430 (0)	593 (0)	592 (0)

Table 4.6. Susceptibility of invasive isolates of *Enterococcus faecium* in Sweden 2001-2004.

	2001 Total (%R)	2002 Total (%R)	2003 Total (%R)	2004 Total (%R)
Ampicillin	196 (71)	167 (72)	241 (76.3)	260 (78.1)
Aminoglycosides	99 (9.1)	96 (6.3)	170 (11.2)	227 (7.0)
Vancomycin	169 (0)	181 (0)	231 (2.2)	260 (1.2)

Pasi Penttinen, Barbro Olsson Liljequist

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 2004, a total of 290 cases were notified through both the previous voluntary and the mandatory notification systems.

Annual Resistance Surveillance and Quality Control (RSQC) programme

As part of the RSQC programme susceptibility data of *Streptococcus pyogenes* was collected every year since 1994, but in 2004 it was decided to omit this pathogen from the programme for one or two years. However, a collection of 50 isolates, gathered from 10 laboratories as part of a European study on the susceptibility of respiratory pathogens to macrolide antibiotics, was analysed in 2004. Tetracycline resistance but no macrolide resistance was found in this limited material, verifying the trends seen in the previous RSQC studies.

Data on Swedish invasive isolates were available from 2002-2004, collected during a surveillance study. 257 isolates were sampled and sent to Smittskyddsinstitutet during 2004. The frequencies of resistance were 3.7% for erythromycin, 2% for clindamycin, 23% for tetracycline and none for penicillin among these isolates. The most common *Emm*-/T-type combination among the tetracycline resistant isolates was emm81/T3.13.B3264

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Haemophilus influenzae

Notifications according to the Communicable Disease Act

All invasive *Haemophilus influenzae* infections became notifiable according to the Communicable disease act in 2004. Previously only invasive *Haemophilus influenzae* type B (HiB) infections were notifiable. During 2004, 38 cases of HiB were notified and during June- December 2004, 44 additional cases of *Haemophilus influenzae* were notified.

Annual Resistance Surveillance and Quality Control (RSQC) programme

There are no data in the RSQC programme on antibiotic resistance in *Haemophilus influenzae* for 2004 but new data will be collected in 2005.

Data on 100 isolates collected from 10 laboratories as part of a European study on the susceptibility of respiratory pathogens to macrolide antibiotics (see above for *S.pyogenes*) were analysed using broth microdilution for susceptibility to several antibiotics (Table 4.7). These figures were similar to those reported from the previous RSQC studies 1994-2001. MIC distributions can be found in ResNet.

Table 4.7. Resistance of respiratory isolates of *Haemophilus influenzae* to three antibiotic groups in Sweden 2003-2004.

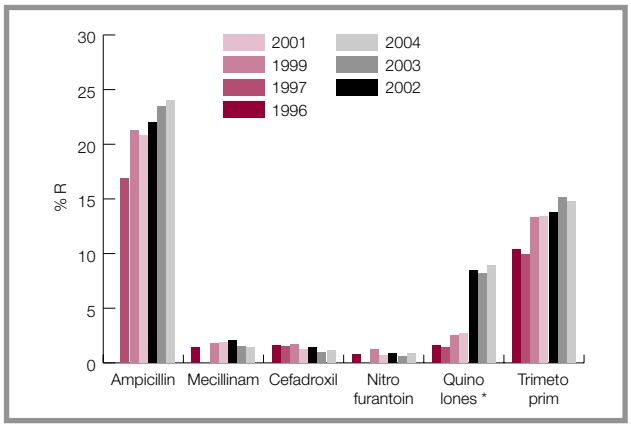
Antibiotic	2003-2004
Ampicillin (beta-lactamase production)	14%
Amoxicillin / clavulanate (BLNAR)	4%
Tetracycline	1%
Trimethoprim / sulfamethoxazole	9%

Pasi Penttinen, 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. The average resistance rates to ampicillin have shown a steady increase from 17 to 24 %. The same was true for trimethoprim where resistance rates increased from 10 to15 %. Fluoroquinolone resistance, detected by the screening disk nalidixic acid since 2002, has not shown any increase during the last three years, but has remained on an average of 8%.



Figur 4.10. Resistance rates (resistant isolates in percent of all *Escherichia coli* isolates) for six different antibiotics 1996-2004. *Between 1996-2001 fluoroquinolone resistance was detected with Norfloxacin, from 2002 with Nalidixic acid.

An investigation of a subset of *Escherichia coli* isolates from the 2004 RSQC programme was performed. From each of 25 laboratories all cefadroxil resistant isolates (n = 27), all nalidixic acid resistant isolates (n = 223) and 10 susceptible isolates (n = 257) were collected. MICs of cefotaxime, ceftazidime and ciprofloxacin were determined, and characterization of the cephalosporin resistance mechanisms was done. Of 27 cefadroxil resistant isolates (MIC > 32 mg/L, zone 6 mm), 3 displayed characteristics concordant with ESBL production, whereas the others showed slightly increased MICs of cefotaxime and ceftazidime which were not reduced in the presence of clavulanic acid. Of the 223 nalidixic acid resistant isolates (MIC > 32 mg/L, zone 6-10 mm), all had MICs of ciprofloxacin above the epidemiological cut off value 0,064 mg/L.

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 betalactam antibiotics, especially occurrence of strains producing beta-lactamases with so called extended spectrum (ESBL), resistance to aminoglycosides and to fluoroquinolones.

Twentyone Swedish laboratories have taken part in this surveillance and have delivered data on more than 2500 blood isolates in 2004. Results are presented in Table 4.8 together with data from the RSQC programme on urine isolates from 2001-2004. Ampicillin resistance, caused by production of plasmid-mediated betalactamase (TEM-type most common) was equally high in the two sets of isolates, yet these figures are low compared to most other countries in Europe. The level of resistance to third generation cephalosporins among blood isolates was only 0.5%, and in only half of those resistance was contributed to the presence of ESBL. ESBL of CTX-M type was 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 indeterminant/intermediate (I) isolates, the rates are almost the same in blood as in urine isolates. Data from other European countries 2004 are presented in Figure 4.11.

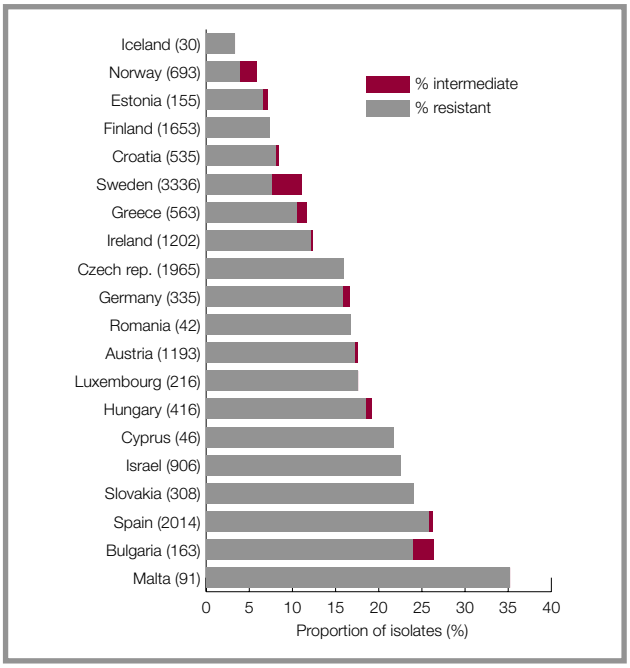


Figure 4.11. Resistance rates (% R and I) to fluoroquinolones in *Escherichia coli* in Europe 2004. Data from EARSS (www.earss.rivm.nl 2005-04-25)

Barbro Olsson Liljequist, Gunnar Kahlmeter

Klebsiella species

Rare cases of *Klebsiella pneumoniae* and *Klebsiella oxytoca* are found, which exhibit high-level resistance to third generation cephalosporins, often caused by ESBL. In *Klebsiella pneumoniae*, as in *Escherichia coli*, the ESBLs most frequently encountered are those of CTX-M-type. In *Klebsiella pneumoniae* they are present together with the species-specific chromosomal beta-lactamase SHV-1. In *Klebsiella oxytoca* no true ESBLs have been found, but a number of strains with hyperproduction of the chromosomal betalactamases typical of this species (OXY-1 or OXY-2) have appeared.

Barbro Olsson Liljequist

Table 4.8. *E. coli* from UTI and blood in Sweden 2001-2004.

	2001 Total (%R)		2002 Total (%R)		2003 Total (%R)		2004 Total (%R)	
	RSQC	EARSS	RSQC	EARSS	RSQC	EARSS	RSQC	EARSS
Ampicillin	3803 (20.8)	1513 (26.5)	5906 (22)	1753 (24.9)	4488 (23.5)	1953 (28.5)	3000 (24)	2019 (23.0)
Cefotaxime (3rd gen cef/ESBL)	Nt	2627 (0.5)	Nt	3062 (0.5)	Nt	3300 (0.4)	Nt	3290 (0.6/0.5)
Aminoglycosides *	Nt	1241 (1.0)	Nt	1585 (0.6)	Nt	2819 (1.0)	Nt	3313 (1.5)
Fluoroquinolones**	3814 (2.8 nor)	2273 (3.7 R/1.8 I cip)	4253 (8.5 nal)	2414 (5.1R/2.0I cip)	3971 (8.2 nal)	3120 (6.6R/1.7I cip)	3000 (8.9 nal)	3336 (7.6R/3.5I cip)

* gentamicin, tobramycin, ** nor = norfloxacin, cip = ciprofloxacin, nal = nalidixic acid. Nt = not tested.

Enterobacter species

There are no data in the RSQC programme on *Enterobacter* species for 2004.

Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pseudomonas aeruginosa was included the first year of the RSQC programme (1994) using the disk diffusion (DD) method, and also in 2003 and 2004. Those data are compared with one sentinel study from 1984, in which isolates were collected from 8 laboratories and tested at SMI (n = 200). MICs were determined by agar dilution method.

In 2003 laboratories were asked to collect and test 50 isolates of *Pseudomonas aeruginosa* from wound infections and 50 isolates (or as many as possible, not less than 30) from respiratory tract infections. In 2004 only isolates from wound infections were included. Results from all these collections are shown in Figure 4.12.

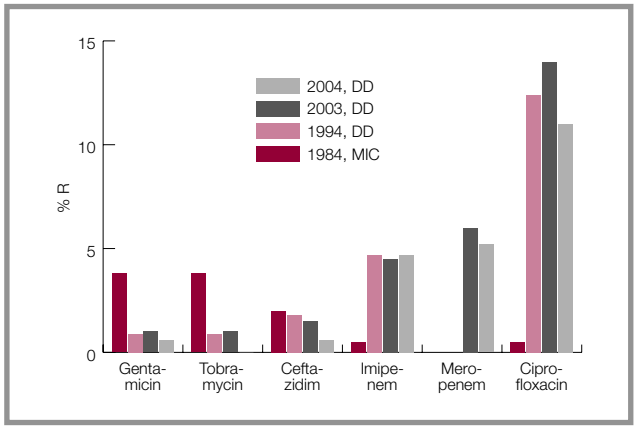


Figure 4.12. Resistance rates (resistant isolates in percent of all *Pseudomonas aeruginosa* isolates) for six different antibiotics 1984-2004.

Barbro Olsson Liljequist

Helicobacter pylori

Annual Resistance Surveillance and Quality Control (RSQC) programme

Helicobacter pylori derived from gastric biopsies has not until 2001 been included in the annual RSQC program but has been monitored locally at a few laboratories. In vitro resistance to metronidazole has been reported in 10-40 % of Scandinavian isolates (Table 4.9). Resistance to clarithromycin is less common (3 %) but is increasing and has locally at one laboratory reached over 10% for the first time. Resistance to tetracycline is less than 1 % and resistance to amoxicillin has only been described in a few strains and only outside Scandinavia. Antibiotic sensitivity patterns of isolates (n=100-600) from southwest of Sweden are presented. The population is about 300 000 and between 100-600 new *Helicobacter* strains are isolated yearly.

Mats Walder

Salmonella and Shigella spp.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Salmonella spp. and *Shigella* spp. derived from faecal cultures have not been included in the annual RSQC program 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 sensitivity patterns reflect their geographical origin. Too few strains are included in the Swedish survey to obtain a conclusive result. However fluoroquinolone resistance is high, between 20-25%, among *Salmonella* strains.

Mats Walder

Campylobacter spp

Annual Resistance Surveillance and Quality control (RSQC) programme

Campylobacter spp. derived from patients with diarrhoea has not until 2001 been included in the annual RSQC program but has been monitored locally at a few laboratories. About 50% of *Campylobacter* strains are imported cases. Since resistance to fluoroquinolones is a major concern worldwide it is interesting to notice that the small decline in quinolone resistance among *Campylobacter* isolates noticed a few years ago has now regained the former level of about 50% (Table 4.10). When screening for fluoroquinolone resistance with Nalidixic acid disks was introduced in Sweden in 2001 this was expected to increase resistance figures with 15-20%. However the increase has only been 2-3%.

Mats Walder

Table 4.9. *Helicobacter pylori*, University Hospital MAS, Malmö Sweden, 1994-2004,%R (- = not tested).

	1994 n=536	1995 n=588	1996 n=381	1997 n=331	1998 n=116	1999 n=149	2000 n=216	2001 n=188	2002 n=124	2003 n=112	2004 n=151
Clarithromycin	1.0	2.9	3.9	7.7	6.7	6.1	7.8	8.8	9.0	7.2	11.6
Metronidazole	29.0	32.1	35.2	39.8	34.3	33.1	30.5	40.2	44.1	42.6	41.0
Tetracycline	0.2	0.1	-	-	-	-	-	-	-	-	-
Amoxicillin	0	0	0	0	0	0	0	0	0	0	0

Table 4.10. *Campylobacter* spp University Hospital MAS, Malmö Sweden, 1991-2004,%R, based on 100 consecutive clinical isolates per year.

	1991	1992	1993	1995	1997	1998	1999	2000	2001	2002	2003	2004
Nalidixic acid									32	29	48	50
Ciprofloxacin	16	17	24	22	23	34	45	55	30	28	46	47
Tetracycline	27	30	28	27	30	33	35	45	28	30	22	29
Erythromycin	4	2	5	4	3	2	1	1	1	0.5	0	2

Neisseria gonorrhoeae

Notifications according to the Communicable Disease Act

Gonorrhoea is a notifiable disease, and 568 clinical cases of the disease were reported in 2004. Clinical isolates were analysed at the Swedish Reference Laboratory for Pathogenic Neisseria, Department of Clinical Microbiology, Örebro University Hospital.

In 2004, isolates from 149 patients were sent to the reference laboratory, representing 26% of the notified cases. Isolates from the counties containing the largest cities in Sweden were underrepresented in this material.

Susceptibility testing was performed according to standardized methodology using Etest for determination of MIC for ampicillin, cefixime, ceftriaxone, azithromycin, ciprofloxacin, and spectinomycin. Production of beta-lactamase was examined by using nitrocefin disks. Results for 2004 are compared with those from 1998, and 2000-2003 in Table 4.11.

Magnus Unemo, Hans Fredlund

Table 4.11. Antibiotic resistance rates (%) and ß-lactamase production of *Neisseria gonorrhoeae* in 1998, and 2000-2004 (data from the Swedish Reference Laboratory).

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

(- = not analysed)

* However, *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).

Neisseria meningitidis

Notifications according to the Communicable Disease Act

Invasive meningococcal disease is a notifiable disease. In 2004 59 clinical cases of the disease were reported. A total of 47 clinical isolates from blood or cerebrospinal fluid were analysed at the Swedish Reference Laboratory for pathogenic Neisseria, Department of Clinical Microbiology, Örebro University Hospital. Susceptibility testing was performed according to standardized methodology using Etest on Müller Hinton II agar medium with 5% defibrinated horse blood for determination of MIC for bensylpenicillin (pcG), fenoxymethylpenicillin (pcV), cefotaxime, ciprofloxacin, chloramphenicol and rifampicin. Production of beta-lactamase was examined by nitrocefin disks.

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 eleven isolates had MIC ≥0.5 mg/L. All the strains had cefotaxime - MIC ≤0.012 and ciprofloxacin - MIC ≤0.008. Chloramphenicol – MIC varied between 0.25 and 1.5 and rifampicin was not higher than 0.25 mg/L.

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

Per Olcén

Mycobacterium tuberculosis

During 2004 there was a 13% increase of the total number of new cases of TB, compared to 2003. Resistance against at least one of the five first line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide or streptomycin) was reported in 58 patients i.e. 15.8% of the 368 patients with culture confirmed *M. tuberculosis* or *M. africanum* (Figure 4.13).This corresponded to an increase with 33% compared to 2003 and this was the highest proportion of patients with resistant TB recorded since 1999. Resistant TB was reported in 7% of the Swedish born patients and 18% of those foreign borns. Among 21 patients with a previous history of TB after 1949, there were 5 patients with resistant TB (24%).

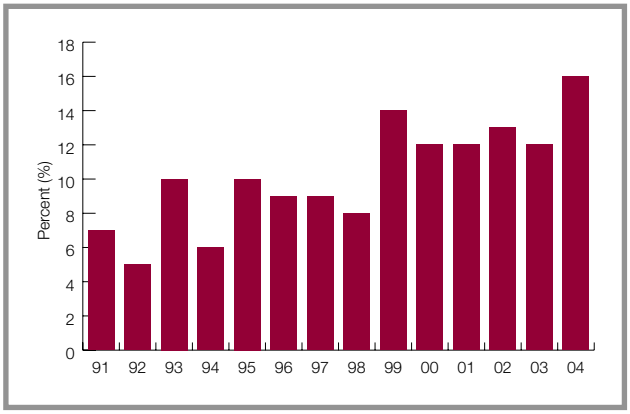


Figure 4.13. Proportion of patients with resistant TB (resistant to at least one of the first line drugs).

Resistance to isoniazid was most common, reported in 9.5 % of the patients, followed by streptomycin in 6.3%, rifampicin in 1.6% and pyrazinamid in 3.3% (Table 4.12). Single resistance to rifampicin was reported in one patient and MDR-TB in another five patients, all of them born abroad. The proportion of patients with resistant TB was especially high in Somalian born patients, 22 %, including 15% with isoniazid resistant strains.

Remark: Information is still incomplete regarding patients with a previous history of TB and also regarding national origin of all patients. Thus, the reported proportions of resistant TB in these subgroups might be corrected later on.

It should be noted that in 2004 some methodological changes took place that affects the epidemiological report of drug resistant tuberculosis. First, to harmonise with European standards it was decided to reduce the breakpoint concentration of isoniazid from 0.2 to 0.1 mg/L. Secondly, 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). Thirdly, routine testing of resistance to the drug streptomycin was discontinued, due to the lack of clinical relevance of resistance to this drug.

Finally, 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.

The first two changes is not expected to influence the results of susceptibility testing, external quality assurance continues to show over all good results. The lack of information on the resistance to streptomycin will affect the epidemiological statistics. The verification of drug resistance should give more reliable data. All these changes are ongoing and not fully implemented during 2004.

Sven Hoffner, Victoria Romanus

Table 4.12. Drug resistant tuberculois in Sweden. Resistance among initial isolates of *Mycobacterium tuberculosis* or *africanum* to at least one of the five drugs: isoniazid, rifampicin, ethambutol, pyrazinamid or streptomycin.

	2000	2001	2002	2003	2004
Culture confirmed *M. tuberculosis* or *M. africanum* (N=)	366	354	346	345	368
Any resistance Total (%)	12.8	12.4	13.6	11.9	15.8
Resistance to one drug only (%)	9.6	5.9	8.4	7.0	12.2
Resistance to two or more drugs (%)	3.3	6.5	5.2	4.9	3.5
Isoniazid	10.1	8.8	9.8	7.5	9.5
Rifampicin	1.4	1.7	1.2	2.9	1.6
Ethambutol	0.5	0.8	0.3	1.4	0.8
Pyrazinamid	3.0	1.7	1.2	2.0	3.3
Streptomycin	3.9	6.8	7.2	6.4	6.3
Isoniazid + rifampicin (MDR)	1.4	1.1	1.2	2.3	1.4

5. National and regional intervention projects

5.1 Urinary tract infections in women - a longitudinal study of antimicrobial resistance and effect of empirical therapy in Kronoberg County, Sweden.

Lower urinary tract infections in women 18-50 years are almost always treated empirically and urinary cultures are seldom performed. *E. coli* is the most common causative agent followed by *Staphylcoccus saprophyticus*. Due to antimicrobial resistance development there is a need to re-evaluate empirical therapy. The three most commonly used antimicrobials to treat UTI in Sweden are trimethoprim, mecillinam and fluoroquinolones, each having roughly 30% of the market. Antimicrobial resistance rates in *E. coli* are 15-20% for ampicillin, 3-5% for mecillinam with another 10-15% being low-level resistant and 3-5% for fluoroquinolones.

Our project was planned to shed light on the following questions:

- Are antimicrobial resistance rates lower in patients with few, uncomplicated UTI and fewer antimicrobial therapy courses than in patients perceived to have reiterated problems?
- If so, is the difference great enough to affect the empiric choice of therapy or the urine culture or antimicrobial susceptibility testing strategies?
- What is the importance of antimicrobial resistance in the outcome of empiric therapy?
- Is there a difference between trimethoprim, mecillinam and fluoroquinolones?

The study will not interfere with the diagnose and therapy of UTI in any other way than that the indications for culturing are widened to include all women 18-50 years with signs and symptoms of uncomplicated lower urinary tract infection in need of therapy. Since these women were not to be cultured under normal circumstances permission was obtained from the ethical committee to with-hold the result of the urinary culture until specifically asked for in which case the date and name of the physician was logged.

Since the project started 895 patients, all of which received therapy for an assumed UTI, have been enrolled. Of these 30% exhibited negative cultures. *E. coli* was grown from 80% and *S. saprophyticus* from 11% of the positive cultures.

Table 5.1. Resistance in *E. coli* from "the project" compared to all *E. coli* 2004.

E. coli resistance to	Project patients	All *E. coli* 2004
Ampicillin	19%	19%
Mecillinam	<1% R; 8% I	<1% R; 6% I
Trimethoprim	12%	11%
Nalidixic acid	4%	4%
Nitrofurantoin	1%	0%

Among the 895 patients:

- 83% had previously seen a physician due to urinary tract infection problems
- 54% had not received any antibiotics during the 12 months preceeding the current UTI
- 37% had received 1-3 antibiotic course over the past 12 months and 9% over the past month.
- 94% exhibited no complicating factors (diabetes, pregnancy, anomalies)
- 5% had symptoms which could indicate an upper UTI.

So far we have received 440 patient diaries of which 265 were from patients with UTI caused by *E. coli* and 114 from patients with negative urine cultures. The study will finish at the end of 2005.

Gunnar Kahlmeter

5.2 Is a drastic decrease in trimethoprim consumption followed by a related decrease in trimethoprim resistance?

The observation that resistance is associated with a biological cost has led to the widespread idea that by reducing the volume of antibiotic use the frequency of resistant bacteria in a population can also be reduced. However, the existing studies do not allow us to make any firm conclusions regarding any potential reversibility in community settings.

This project aims to determine in a controlled clinical intervention study if, how rapidly and to what extent the frequency of trimethoprim resistance in *E. coli* can be decreased by a sudden and drastic reduction in trimethoprim use. From October 2004 until the end of September 2006 all physicians in Kronoberg county will substitute trimethoprim and cotrimoxazole with other antibiotics (pivmecillinam, fluoroquinolones, cephalosporins, nitrofurantoin). The frequency of resistance in this particular population has been continuously monitored since 1990 and consecutive quantitative data are stored in a database which allows serial analysis of resistance rates for all antibiotics used for UTI treatment, including trimethoprim. To evaluate the potential change in the distribution of *E. coli* phenotypes and genotypes, caused by the intervention, all isolated gram negative strains from June 2004 to December 2006 will in addition to the routine analyse of resistance, be stored for further analysis.

This type of strategy has been extensively discussed but to the best of our knowledge there has yet not been a full scale prospective study performed in a community setting. Thus, the obtained results will have general important implications with regard to the feasibility of this type of approach. If successful, this type of intervention could be used on a larger scale to reduce the frequency of resistant bacteria. Up to this

date (March 2005) the reduction of trimethoprim/cotrimoxazole use is >80%.

Gunnar Kahlmeter, Martin Sundqvist

5.3 A qualitative study to describe views on resistance and treatment decisions for uncomplicated urinary tract infections.

In 2004 an intervention study started to evaluate the effect of minimised trimethoprim use on antibiotic resistance among *Escherichia coli* in the outpatient setting. During two years, physicians including general practitioners in the county of Kronoberg, avoid the use of trimethoprim, a first choice drug often prescribed in urinary tract infection. The main aim of this study, performed in conjunction with the intervention study, is to explore views on antibiotic resistance, as perceived by general practitioners (GPs) in the county of Kronoberg. Further it is to investigate perceptions on treatment decisions for uncomplicated urinary tract infections.

The study group consisted of 20 GPs in the county of Kronoberg. The GPs were selected by purposive sampling to receive a broad variation in age, sex and geographical location. Data were collected by face-to-face interviews using a pre-tested, semi-structured interview guide. The interviews were tape-recorded and typewritten verbatim. A phenomenographic approach was used to identify and describe a range of different views on antibiotic resistance. In addition, a content analysis was done to capture perceptions on treatment decisions for uncomplicated urinary tract infections.

Four different ways of experiencing resistance were identified:

a) Not problematic in the everyday practise and not worrying for the future situation.
b) Problematic in the everyday practise but not worrying for the future situation.
c) Not problematic in the everyday practise yet, but worrying for the future situation.
d) Problematic in the everyday practise and worrying for the future situation.

Moreover, the GPs that expressed greater worries considering resistance also seemed more willing to follow the recommendations regarding antibiotic prescribing. This offers an important insight valuable when issues on use of antibiotics are discussed and interventions are planned, since the comprehension of if and how resistance constitutes a problem, can be assumed to influence the GPs prescribing patterns.

Johanna Berg, Cecilia Stålsby Lundborg

5.4 Infections in families with young children

Respiratory tract infections are most common in young children. Those below three years contract on average five respiratory tract infections a year, but with rising age the frequency falls. Boys have higher morbidity than girls until the age of two, after which the proportions are reversed. Respiratory tract infections are the most common reason for antibiotic prescriptions despite that most of the infections are cured without antibiotic treatment. In Sweden the prescription of antibiotics varies markedly between different counties but the reasons for this is not known.

The aim of the study was to chart all the infection symptoms occurring during a month in families with small children and analysing the measures taken. One major objective was also to see what factors might influence the antibiotic prescription pattern. The study took place between October and April. All 18-month-old children and their families who came to the ordinary control at the health clinic were asked to participate. 954 (84%) families registered all infection symptoms during a month in a diary. They also noted whether they had been home from day-care, school or work, if they had claimed social insurance, if they had telephoned a doctor or nurse or if they had visited a doctor.

Of the 18-month-old children only 7% did not have any reported symptom during the month and 35% of the children had symptoms 15 days or more. With rising age the numbers of days with symptoms decreased. Symptoms from the respiratory tract were most common and a runny nose as a single symptom occurred in 28% of the symptom days. In mean each child hade 1.6 episodes with symptoms and the mean duration were 5.6 days.

A doctor was consulted in 8.5% of the infection episodes and in 4% of the symptom days. Antibiotics were used in 3.5% of the infectious episodes and in 2% of the symptom days.

In 27% of the symptom days the children needed to stay at home from day-care and in one third of these the social insurance were utilised.

Conclusion: In the small children there are many symptom days with mainly mild symptoms. Only a small proportion of the days lead to contact with health care and antibiotic consumption. About one fourth of days with symptoms lead to absence from day-care and the social insurance were claimed in just a minor proportion of the symptom days.

Katarina Hedin

5.5 The STRAMA Point Prevalence Study 2004 on hospital antibiotic use

STRAMA initiated in November 2003 a successful nationwide point prevalence study, PPS. The objective of the study was to introduce a nationwide survey system for frequent assessment of the use of antimicrobial agents in hospitals in relation to diagnose. The study was repeated during a two-week period in November 2004. Identical protocols were used in both studies. The performed studies in 2003 and 2004 present very similar results indicating the validity of the method.

Data were collected at the hospital ward level through personal visits. A case record form was used which included demographic data as well as the amounts and indications for antimicrobial agents against bacteria and fungi.

Three principal areas of the antimicrobial therapy in the hospital setting have been identified for further interventions. First, the duration of perioperative prophylaxis is too long. Secondly, antimicrobials with narrow spectrum can be used in a higher degree in treatment of community-acquired pneumonia in Sweden. Thirdly, the use of fluoroquinolones should be restricted in several indications, especially in community-acquired cystitis in women.

Demographic data of the two studies are presented in Table 5.2. The studied population approximates to 60% of all admitted patients in Swedish hospitals during one day.

Table 5.2. Demographic data, The STRAMA Point Prevalence Study 2003 and 2004.

PPS	2003	2004
Participating STRAMA-groups (out of 21)	19	18
No. of hospitals involved	54	49
University hospitals	9	7
County hospitals	20	19
Local hospitals	25	23
No. of patients admitted	13,536	11,348
No. of patients treated	4,178	3,622
Percent treated	30,9%	31,9%
Patients treated at:		
University hospitals	1,538	1,112
County hospitals	1,855	1,734
Local hospitals	785	776
Percent women treated	49,9%	49,9%
No. of children treated	266	192

Table 5.3. shows the therapy reasons for the antimicrobial therapy. Since one patient can have more than one therapy reason the total percentage is higher than the percentage of treated patients. Hospital acquired infection includes only those treated with antimicrobials.

Table 5.3. Therapy reasons for antimicrobial therapy in percent of all admitted patients.

	2003	2004
Community acquired infection	17,0	18,0
Hospital acquired infection	9,2	9,4
Perioperative prophylaxis	4,6	4,5
Medical prophylaxis	1,7	1,9

The observation already made in the 2003 PPS of too long duration of perioperative prophylaxis was observed also in 2004. Forty percent of therapies were longer than one day compared to 47% in 2003.

The most frequently used antibiotic class for treatment is cephalosporins. Table 5.4 shows the distribution of the used drugs in treatment and prophylaxis. Isoxazolyl-penicillin is the most frequently used group for prophylaxis. The total amount of antimicrobials used for adults was 43.1 DDD/100 admitted patients in 2004 study.

Table 5.4. Most commonly used antimicrobials for adults in percent of DDD in treatment and in prophylactic use.

	2003 Therapy	2003 Prophylaxis	2004 Therapy	2004 Prophylaxis
No. of DDD	4084	1000	3708	904
Cephalosporins	22	18	23	15
Isoxazolyl-penicillins	12	45	12	45
Fluoroquinolones	12	9	13	7
Broad-spectrum penicillins	10	4	10	4
Beta-lactamase sensitive pc	9	3	8	3
Imidazoles	5	7	3	7
Tetracyclines	5	3	5	4
Carbapenems	4	<1	5	<1

Analysis of different diagnoses showed over-use of broad-spectrum antimicrobials in community acquired infections. In pneumonia broad-spectrum antimicrobials like cephalosporins and tetracyclines were included in 52% of therapies and constituted 46% of the given DDDs. The corresponding results for penicillins were 27% of the therapies and 34% of the DDDs, Figure 5.1.

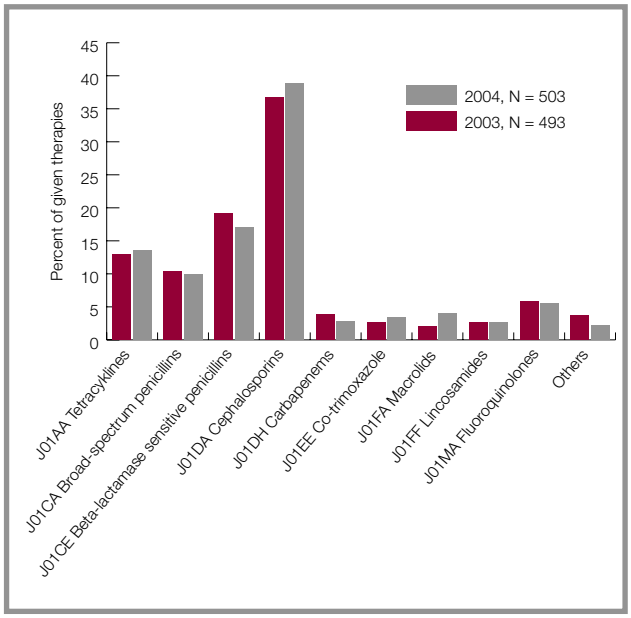


Figure 5.1. Distribution of antimicrobials in treatment of community acquired pneumonia, percent of the total amount of therapies, PPS 2003-2004.

For treatment of urinary tract infections in women fluoroquinolones were the second largest group of therapies, 33%, (Figure 5.2), but only 26% of the amount in DDD. Pivmecillinam was used in 36% of therapies but constituted 44% of the DDDs. The fluoroquinolone consumption can be expected to be too high.

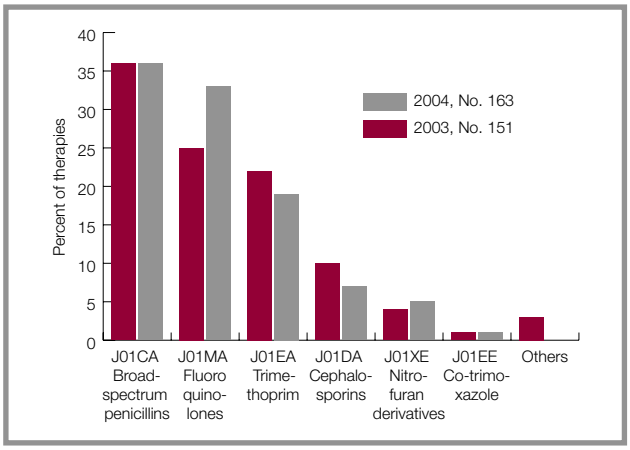


Figure 5.2. Distribution of antimicrobials in treatment of community acquired cystitis in women, percent of the total amount of therapies, PPS 2003-2004.

In assessment of the therapies 87% were considered as adequate empirical (60%) or adequate directed (27%) therapies. Thirteen percent of the treatments were assessed with incorrect dosage (3%), non-effective drug treatment (2%) or other deviations like use of too broad-spectrum or too long treatment (8%).

Mats Erntell

5.6 Evaluation of antibiotic treatment of Acute Otitis Media in children – a Report from the South Swedish Otitis Trial.

Acute otitis media is one of the most common bacterial infections in childhood. In Sweden, children presenting with acute otitis media constitute some 500,000 clinical consultations per year. Still, modern knowledge about the natural course of this common infection, as well as strong evidence for antibiotic treatment, is to a large extent lacking.

The objective was to study the clinical recovery from acute otitis media (AOM) in children, 2–16 years of age, managed with or without primary treatment with phenoxymethyl penicillin (PcV) i.e. the standard treatment according to national recommendations.

This investigation was a response to the request for further research, forwarded by the Swedish Consensus Statement on Treatment of Acute Otitis Media, arranged jointly by the Federation of Swedish County Councils, Swedish Medical Research Council, and the Swedish National Board of Health and Welfare, Stockholm, May 10-12, 2000.

Thirty-two general practices in the Counties of Kalmar, Jönköping and Östergötland in South-East Sweden took part in the study.

The investigation was designed as an open, prospective, clinical, randomised trial with two arms. Children aged between 2 and 16 years, presenting with one- or double-sided acute otitis media with a symptom duration of less than four days, were included. Otitis inclined children were not included. Exclusion criteria were perforation, children with chronic ear conditions or impaired hearing, allergy to PcV, concurrent disease with a need for antibiotic intervention, and children with 3 or more AOM episodes during past 6 months. Children with other chronic diseases or disorders were not included. The children were randomised to one of two different treatment strategies – one arm received a standard regimen of PcV for five days, the other arm was managed without primary antibiotic treatment.

In addition, children/parents who did not approve of randomisation were offered a possibility to still participate in the monitoring and follow-up, after making their own treatment choice (PcV or no antibiotics).

The parents were asked to register a health score and compliance on a daily basis for seven days. If the patient did not recover after three days of respite or the drum perforated, antibiotic treatment was initiated on day three according to the following: Children randomised to, or who actively choose PcV received Amoxicillin, while the groups treated without antibiotics received PcV.

A total of 261 patients carried out the trial; 179 were randomised to either PcV (n=92) or no primary antibiotic treatment (n=87), while 82 made their own treatment choice (59 PcV, 23 no antibiotics).

There was no significant difference in recovery time in either group with or without antibiotic treatment. The median recovery time was four days in all groups. The complications, reported per group, were:

- Randomisation PcV: one therapeutic failure, no perforation
- Randomisation no antibiotic: five therapeutic failures, four perforations
- Own choice Pc: one therapeutic failure, one perforation
- Own choice no antibiotic: no complications

Fever (temp 38C or more) was recorded in about one third of the patients. Patients who received PcV had a somewhat shorter mean duration of fever, 1.4 days vs. 1.9 days. However, this did not influence the median recovery time.

There were no significant differences in the number of otosalpingitis (middle ear effusion) or perforations at the final control after three months.

Our investigation supports the proposal from the Swedish Consensus Statement on Treatment of Acute Otitis Media, 2000, that it is equally safe to treat non-complicated acute otitis media without antibiotics, and that antibiotics provide little benefit in otherwise healthy children, aged 2-16 years. One prerequisite for this approach is a developed system for follow-up and adequate instructions to the patients and their parents in order to avoid serious complications.

Thomas Neumark

Appendix 1 – Abbreviations

AST, Antibiotic susceptibility testing

ATC, The Anatomical Therapeutic Chemical classification system

BLNAR, Beta-lactamase negative ampicillin resistant

CDA, Communicable Disease Act

DDD, Defined daily dose

DST, Drug susceptibility testing

EARSS, European Antimicrobial Resistance Surveillance System

ESAC, European Surveillance of Antimicrobial Consumption

ESBL, extended spectrum beta-lactamase

ICU, Intensive care unit

ISA, Isosensittest Agar

MDR, Multidrug resistance

MIC, Minimum 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 resistant pneumococci, MIC ≥ 0,5 mg/L

RSQC, Resistance Surveillance and Quality Control Programme

SMI, The Swedish Institute for Infectious Disease Control

SRGA, 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 31 December 2004.

	0-6	7-19	20-59	60-79	80-	All ages
Stockholm	158 052	294 535	1 051 764	284 445	84 104	1 872 900
Uppsala	23 354	51 749	166 608	47 342	13 511	302 564
Södermanland	18 720	44 931	131 710	50 955	14 754	261 070
Östergötland	29 542	70 216	218 004	75 140	23 088	415 990
Jönköping	24 846	58 634	166 336	60 085	19 390	329 291
Kronoberg	12 614	29 850	91 718	33 509	10 594	178 285
Kalmar	15 115	39 684	116 625	48 096	14 976	234 496
Gotland	3 653	10 160	29 650	10 985	3 213	57 661
Blekinge	10 399	23 955	75 921	31 078	8 982	150 335
Skåne	85 644	188 669	613 054	209 991	63 561	1 160 919
Halland	21 834	50 322	144 014	52 180	15 438	283 788
Västra Götaland	113 051	253 023	810 093	264 292	81 436	1 521 895
Värmland	18 047	44 963	138 342	55 548	16 647	273 547
Örebro	19 601	45 745	141 222	51 003	16 349	273 920
Västmanland	18 475	44 300	133 665	50 245	14 320	261 005
Dalarna	18 119	47 408	138 155	55 123	17 237	276 042
Gävleborg	18 200	45 489	139 993	56 195	16 722	276 599
Västernorrland	16 696	39 251	122 613	51 039	14 596	244 195
Jämtland	8 333	21 276	64 567	25 049	8 199	127 424
Västerbotten	17 652	43 520	135 907	46 947	12 849	256 875
Norrbotten	16 892	41 757	130 331	51 234	12 371	252 585
Total Country	**668 839**	**1 489 437**	**4 760 292**	**1 610 481**	**482 337**	**9 011 386**

Table App 2.2. Population of Sweden 1999-2004

Year	1999	2000	2001	2002	2003	2004
Population	8 861 426	8 882 792	8 909 128	8 940 788	8 975 670	9 008 883

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

	Number of analyses 2004							Number of positive cultures 2004			
Laboratory	Blood (pair of bottles)	Cerebro-spinal fluid	Nasopharynx	Throat	General culture	Screening for multi-resistant bacteriae	Faeces	*S. aureus*	*S. pneumoniae*	*S. pyogenes*	*E.coli*
Blekinge	3 359	49	889	1 921	4 449	1 632	3 350	1783	286	248	3 561
Borås	9 999	200	3 948	4 685	6 141	1 220	6 080	4065	810	799	7 193
Eskilstuna	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Falun	8 800	172	1 781	1 712	8 407	810	3 925	3546	345	538	6 169
Gotland	2 558	11	2 962	1 129	2 647	_	1 201	1287	462	158	2 101
Gävle	6 813	151	1 639	1 092	5 903	882	3 392	3114	313	282	5 370
Göteborg	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Halmstad	6 956	133	2 985	3 153	6 823	11 195	5 487	2811	651	439	6 397
Jönköping	9 720	856	2 540	4 060	10 609	1 875	6 014	4230	540	796	8 330
Kalmar	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Karlskrona	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Karlstad	11 424	171	808	2 043	10 494	4 120	3 936	4989	289	497	6 335
Kristianstad	7 124	116	5 006	5 126	9 818	4 223	6 576	4781	725	698	7 636
Linköping	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lund	17 268	1478	9 597	6 819	20 632	14 316	12 799	9 722	1 956	1486	16 362
Malmö	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stockholm - Capio Diagnostik	8 617	134	4 771	3 966	11 380	19 582	6 756	3 944	679	813	8 085
Stockholm - HS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stockholm - KS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stockholm - Medilab	-	-	9 529	4 927	5 379	6 830	7 519	3 121	660	644	7 720
Sundsvall	7 424	118	3 023	2 325	8 006	30 52	4 176	3 373	673	598	7 521
Uddevalla	11 527	206	1 623	3 007	7 109	2 597	5 220	3 577	376	494	9 281
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	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Västerås	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Växjo	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Västmanland	7 764	182	2 382	2 244	9 439	1 463	4 532	3 377	499	397	6 973
Örebro	11 203	214	6 534	1 818	11 149	1 868	4 409	5 301	994	513	6 600
Östersund	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	**130 556**	**4 191**	**60 017**	**50 027**	**138 385**	**75 665**	**85 372**	**63 021**	**10 258**	**9 400**	**115 634**

Appendix 3 – Surveillance of antibiotic consumption

Statistical sources and units of measurement

The ATC classification system and defined daily doses (DDD)
Since 1988, the Anatomical Therapeutic Chemical (ATC) classification system is used in Sweden for national drug statistics. To facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of the National Corporation of Swedish Pharmacies (Apoteket AB) are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway.

The sales of 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) 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. In 2003 a new system came into use, including data from 2000. Historical data from 1975 and onwards is still available from the old database. Due to technical reasons there might be a slight difference when comparing data between the two systems. Antibiotic use presented in this Swedres includes data from both sources.

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 DDDs.

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 (e.g. betalactam resistance in pneumococci, chromosomally mediated betalactam resistance in *Haemophilus influenzae*), and still in others by methods for enzyme detection (e.g. betalactamase detection in *Haemophilus influenzae* and *Neisseria gonorrhoeae*).

Phenotypic methods (disk diffusion or MIC) are from 2004 performed on one basic medium for AST, ISA (IsoSensitest Agar) from Oxoid Ltd, UK. For this medium and its corresponding antibiotic paper disks, interpretive criteria for SIR-categorization are provided by the SRGA-M. They are regularly updated and available through the website 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 surveys".

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. 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 (smittskyddsläkare) and to the Swedish Institute for Infectious Disease Control (SMI). Notifications, with the exception of STI, are done with full person identification. The clinical notification shall also include information on the likely source and route of infection, as well as other information of epidemiological importance.

Infections (or carriage) with four different antibiotic resistant pathogens are included in the list of notifiable diseases. 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, SmiNet. 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, VRE, 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 Epidemiological Report" 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 program (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.

Laboratory specific zone diameter distributions were compared with SRGA-M reference distributions. The median, the width and the shape of the distributions were used for methodological discussions with the laboratories. Provided the individual distributions fitted the reference distributions, the SRGA recommended breakpoints were used to calculate the resistance frequencies of clinical isolates from the 30 laboratories. In a few selected cases adjusted breakpoints based on the deviation of individual distributions were used.

ResNet for surveillance and quality control

From 2002 a web-based newly developed software (ResNet) receives data from the laboratories and, following approval of registered data by one of two web administrators, instantly displays it in the form of resistance frequencies on the geographical areas on maps of Sweden. Behind each resistance frequency the distribution of zone diameters or MICs

together with the relevant demographic data are directly accessible. The software will accept both MIC and zone distributions of well-characterized data sets. The graphs presenting the data are designed to include all necessary information in order for the graphs to be used on their own (in presentations etc). The software also displays 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/faecium*, and monitors variations in antimicrobial resistance over time and place.

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 once a year since 2000. 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 wellorganised network of clinical laboratories and high quality of routine susceptibility testing, is so far the largest contributor of national data to EARSS.

Sentinel surveillance

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

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

Appendix 6 – Recent publications

3.1 Use of antibiotics

André M, Mölstad S, Stålsby Lundborg C, Odenholt I and the Swedish Study Group on Antibiotic use. Management of urinary tract infections inprimary carer: 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

Andre M, Odenholt I, Schwan A, and the Swedish Study Group on Antibiotic Use. Upper respiratory tract infections in general practice: diagnosis, antibiotic prescribing, duration of symptoms and use of diagnostic tests. Scand J Infect Dis. 2002;34:880-6.

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. Scan J Infect Dis 2003; 35:836-42.

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. www.cdc.gov/eid. 2004;10:1082-7

Mölstad S, Stålsby Ludborg C, Karlsson AK, Cars O. Antibiotic prescription rates vary markedly between 13 European countries. Scand J Infect Dis 2002;34:366-71.

Stålsby Lundborg C, Olsson E, Mölstad S, and the Swedish Study Group on Antibiotic Use. Antibiotic prescribing in outpatients – a one-week diagnosis–prescribing study in five counties in Sweden. Scandinavian Journal of Infectious Diseases 2002;34:442.48.

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

3.2. Use of antifungals

Österlund A,. Läkarkåren tappar kontrollen när antimykotika säljs receptfritt. Läkartidningen 2002;99:39,3868-70 (in Swedish).

4. Antimicrobial resistance

Abelson Storby K, Osterlund A, Kahlmeter G. Antimicrobial resistance in *Escherichia coli* in urine samples from children and adults: a 12 year analysis. Acta Paediatr. 2004;93:487-91.

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

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Hallgren A, Saeedi B, Nilsson M, Monstein HJ, Isaksson B, Hanberger H, Nilsson LE. Genetic relatedness among Enterococcus faecalis with transposon-mediated high-level gentamicin resistance in Swedish intensive care units. J Antimicrob Chemother. 2003;52:162-7.

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;36:24-30.

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