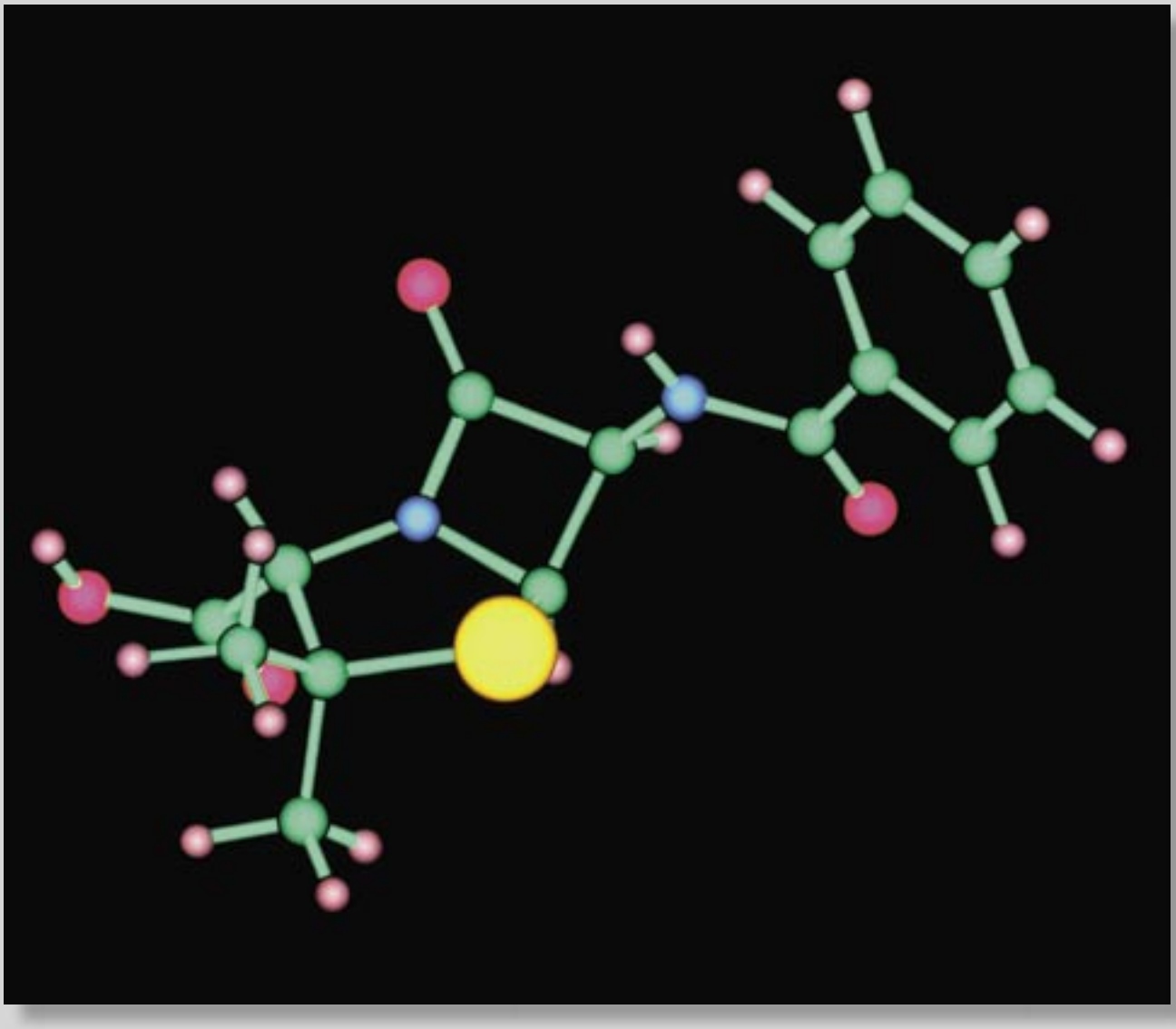
SWEDRES 2002

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

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Preface

The problem with antibiotic resistance in Sweden is still limited. However during the last year several reports have been presented revealing that the situation, in some countries, is alarming.

In November 2001 an EU-recommendation was adopted in which every member state is asked to put in place specific strategies on prudent use of antimicrobial agents. These strategies should comprise measures in relation to surveillance of antimicrobial resistance, surveillance of antimicrobial use, control and preventive measures, education and training, and research. Such a system has been in place in Sweden since 1995 through the Swedish Strategic Programme for the Rational Use of Antibiotics and Surveillance of Resistance (STRAMA) which is financially supported by the Swedish Government.

It is today generally accepted that all use of antimicrobials in different sectors contributes to the development of resistance. Therefore, in Sweden, human and veterinary medicine have collaborated over a number of years, not least within STRAMA. Based on this experience we are convinced that joint efforts between human and veterinary medicine are essential in order to counteract the threat that antimicrobial resistance poses to both human and animal health.

Overall, the figures in this report indicate that the Swedish strategy in human and veterinary medicine has been successful in containing resistance. The ultimate goal is to preserve the effectiveness of available antimicrobials for man and animals and the general concept is to use antimicrobials only when needed, on prescription only and that the choice of treatment is based on relevant information. In addition further efforts must be made to prevent infectious diseases both in human and in veterinary medicine.

In this document we have combined our annual reports: SWEDRES, Swedish Antibiotic Utilisation and Resistance in Human Medicine and SVARM, Swedish Veterinary Antimicrobial Resistance Monitoring. Our hope is that the report will serve as a basis for further policy recommendations and intervention strategies, and that it will increase our understanding of the dynamics of resistance.

1. Summary

Use of antimicrobials

In 2002, the total out-patient consumption of antibiotics was 13.9 defined daily doses/1000 inhabitants per day (DDD/1000/day). Still the most commonly prescribed antibiotic is betalactamase sensitive penicillin (penicillin V). This use is in accordance with Swedish guidelines for many community acquired infections where this antibiotic is recommended as first-line treatment. For most of the antibiotic groups only marginal differences in sales figures took place between 2001 and 2002. However, an increased use of beta-lactamase resistant penicillins has been noted for several years and continued in 2002. Regarding quinolones, a reduced use of norfloxacin was noted among women of all ages. This is believed to be the result of a national recommendation to restrict the use of this type of antibiotics for uncomplicated urinary tract infections. For the same period, however, an opposite trend was noted for men where an increase of both norfloxacin and ciprofloxacin was seen.

Since 1998 statistics on antibiotic prescriptions for inhabitants in each Swedish municipality are available. A wide variety in the number of prescriptions/1000 inhabitants is shown between the municipalities. In the age group 0-6 years there was in 2002 almost a four-fold difference between the community with the highest and the lowest figures and in the age group 80 years and older a three-fold difference was seen.

The total sales of antibiotics to hospitals were unchanged compared to 2001. Also for hospital consumption of antibiotics a major geographical difference was noted. In this year's report hospital use is expressed as DDD/1000/day as well as DDD/number of admissions. Both methods illustrate a major difference between counties with the highest and the lowest values, 66% and 48% difference respectively. The order among the counties is also affected by the denominator used.

Use of antifungals

During recent years, the emergence of resistance to antifungals has been of concern. An expert group has been established in order to improve surveillance and to implement strategies to minimize the risks for such development. Solid data reflecting the actual resistance

situation cannot yet be presented. Data on the consumption of antifungal agents are, however, available. Those figures show that the use of antifungals have increased during the last years. The sales of antifungals for systemic use in hospitals have increased almost eight-fold between 1985 and 2002. In out-patient care, over the counter (OTC) sale accounts for approximately 50% and 90% of the total sales for topical and gynaecological use, respectively.

Antimicrobial resistance

Sweden still has a comparatively low rate of infections caused by *S. pneumoniae* with reduced susceptibility to penicillin MIC ≥0.12 mg/L (PNSP). Since 1996, infections and carriage due to *S. pneumoniae* with penicillin MIC ≥0.5 mg/L (PRP) has been notifiable according to the Communicable Disease Act. A majority of the detected PRP isolates belonged to a limited number of international clones with MIC PcG-values below 2 mg/L. The highest incidence was found among children between 0- 6 years. In 2002, the proportion of PNSP and PRP out of all pneumococcal isolates was 6.2% and 1.6% respectively on the national level.

Methicillin resistant *S. aureus (*MRSA) is the one most rapidly spreading resistant pathogens within hospitals and is now a major nosocomial problem in many European countries. Infections and colonisation with MRSA has been notifiable according to the Swedish Communicable Disease Act since January 2000. In 2002 a total of 442 cases were reported and 69% were regarded as having acquired MRSA in Sweden. At least two thirds of the imported cases had acquired MRSA in health care settings abroad. Also among domestic cases the most common place of MRSA acquisition was reported to be health care facilities. Since 2000 a DNA-based typing method (pulsed field gel electrophoresis, PFGE) has been used for epidemiological typing of MRSA strains isolated in Sweden. 331 of the 405 isolates typed in 2002 belonged to previously recognized European clones.

Enterococci are the second most common cause of nosocomial Gram-positive infections. Most enterococcal infections are caused by *Enterococcus faecalis* although the percentage of *E. faecium* recovered from blood cultures is increasing which may be related to the lower antibiotic susceptibility of the latter. In particular, a significant increase of ampicillin resistance has occurred among *E. faecium* during the last decade. 71% of 196 invasive isolated of *E. faecium* reported to the EARSS network 2002 were resistant to ampicillin. Vancomycin-resistant *E. faecium* and *E. faecalis* (VRE) were made notifiable according to the Communicable Disease Act in the year 2000. In 2002, 20 cases were reported.

Streptococcus pyogenes is one of the most important respiratory tract pathogens. Resistance to tetracyclines is significant, 16% in 2002, whereas resistance to macrolides and clindamycin is low, below 2% and 1% respectively.

Escherichia coli, mainly derived from urinary tract infections, has been tested for commonly prescribed oral antibiotics for treatment of UTI. Resistance rates for ampicillin (22%) and trimethoprim(14%) were similar as in 2001. Ampicillin resistance was slightly higher among blood isolates, yet these figures are low compared to most other countries in Europe. Aminoglycoside resistance in *E. coli* is extremely rare in Sweden.Quinolone resistance has previously been tested using norfloxacin and has been below 5%. In 2002, it was proposed by SRGA-M to use nalidixic acid instead of norfloxacin to screen for resistance to fluoro-quinolones thereby including all isolates that deviated from the wild-type population of *E. coli* with respect to fluoroquinolone susceptibility. Using this method, fluoroquinolone resistance in *E. coli* was 8.5%. During 2002, 347 patients had *M. tuberculosis* confirmed by culture. Among these isolates resistance against at least one of the five drugs (isoniazid, rifampicin, ethambutol, pyrazinamide or streptomycin) was reported in 42 patients i.e. 12.1%. The situation is mainly the same as in 2000 and 2001.

National and regional intervention projects

The STRAMA diagnosis-antibiotic prescribing survey performed in five counties during one week of year 2000 was repeated in 2002 and included 5 377 patients with infectious complaint. 71% of the cases concerned different respiratory tract infections and for these diagnoses penicillin V was the mostly prescribed antibiotic. Between the two surveys a new recommendation concerning treatment of acute tonsillitis was issued by the Medical Products Agency.

The decrease in number of tonsillitis cases in the 2002 survey could be due to a change in consultation pattern due to these new recommendations. About six months before the first survey (2000) new guidelines concerning treatment of acute otitis media were distributed, recommending that for children above two years of age three days of expectancy for a spontaneous decline of symptoms could be used as an alternative to immediate antibiotic prescribing, These recommendations, however, seemed to have had little impact. The percentage of cases with acute otitis media was about the same in both studies; 8% in 2000 and 9% in 2002. In the diagnosis-antibiotic prescribing survey 13% of the cases concerned urinary tract infections. The use of quinolones had decreased significantly, while the use of nitrofurantoin was doubled in comparison with year 2000. The national study on antibiotic resistance and consumption in intensive care, ICU-STRAMA has continued during 2002.

Several other national and local intervention projects have been conducted during 2002 and is described in short in this report e.g. interactive learning, analysis and feedback of prescribing data, education of parents with children in day-care centres and quality aspect of antibiotic use in a University hospital. In addition a summary of the South Swedish pneumococcal intervention project is given.

Useful web addresses

Within the STRAMA project information on resistance, consumption and related subjects is presented continuously at the following useful websites:

- The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents, STRAMA: www.strama.org
- Swedish Institute for Infectious Disease Control: www.smittskyddsinstitutet.se
- Antimicrobial resistance-surveillance in Sweden, ResNet: http://www.srga.org/resnet_sok.htm
- ICU-STRAMA: http://e.lio.se/ivastrama/fr_eng.htm

2. Sammanfattning

År 2002 var den totala antibiotikaanvändningen inom öppenvården 13.9 definierade dygnsdoser/1000 invånare och dag (DDD/1000/dag). Det vanligast förskrivna medlet är penicillinaskänsligt penicillin (penicillin V). Denna användning är helt i linje med svenska rekommendationer där penicillin V rekommenderas som förstahandsbehandling vid många samhällsförvärvade infektioner. För de flesta antibiotikagrupper är det endast marginella skillnader i försäljningssiffror mellan 2001 och 2002. Dock har en ökad användning av penicillinasstabila penicilliner noterats under flera år och denna fortsatte även under 2002. Beträffande kinoloner har en minskad användning setts bland kvinnor i alla åldrar. Detta är troligen en effekt av de nationella rekommendationerna att minska användningen av denna typ av antibiotika vid okomplicerad urinvägsinfektion. Under samma period har dock en motsatt trend visat sig för män där en ökad användning av både norfloxacin och ciprofloxacin kan ses.

Sedan 1998 kan receptförsäljningen till invånarna i varje svensk kommun studeras. En stor variation i antal förskrivningar/1000 invånare kan ses mellan olika kommuner. I åldersgruppen 0-6 år var det under 2002 nästan en fyrfaldig skillnad mellan de kommuner som hade den högsta och den lägsta förskrivningen. I åldersgruppen 80 år och äldre var skillnaden trefaldig.

Den totala försäljningen av antibiotika till sjukhus var oförändrad jämfört med 2001. Även för användningen av antibiotika på olika sjukhus är det stor geografisk variation. I denna årsrapport är användningen vid sjukhus utryckt som DDD/1000/dag samt som DDD/vårdtillfälle. Båda metoderna visar en stor skillnad mellan de landsting som har den högsta förbrukningen och de med den lägsta. Skillnaden uppgick till 66% respektive 48%.

Användning av antimykotika

Under de senaste åren har utvecklingen av resistens mot antimykotika vållat viss oro. En expertgrupp har bildats med uppgiften att förbättra övervakningen samt implementera strategier för att minska risken för sådan utveckling. Pålitliga data som visar det aktuella resistensläget finns inte. Data över försäljningen av antimykotika finns däremot tillgängliga. Dessa uppgifter visar att användningen av antimykotika har ökat under de senaste åren. Försäljningen av antimykotika för systemiskt bruk inom slutenvården har ökat nästan åttafaldigt från 1995 till 2002. Inom öppenvården har den receptfria försäljningen stått för ca 50% respektive 90% av den totala försäljningen inom topikalt och gynekologiskt bruk.

Antimikrobiell resistens

Sverige har fortfarande jämförelsevis låg andel infektioner orsakade av *S. pneumoniae* med nedsatt känslighet mot penicillin MIC≥0.12 mg/L (PNSP). Sedan 1996 har infektioner orsakade av *S. pneumoniae* med penicillin MIC≥0.5 mg/L (PRP) rapporterats enligt Smittskyddslagen. En majoritet av PRP-isolaten härrör från ett begränsat antal internationella kloner med MIC PcG-värden under 2 mg/L. Den högsta incidensen ses bland barn mellan 0 och 6 år. År 2002 var andelen PNSP och PRP, bland alla pneumokockisolat 6.2% respektive 1.6% på nationell nivå.

Meticillinresistenta *S. aureus* (MRSA) är en av de patogener som har spridits snabbast inom sjukhusvården och är nu ett allvarligt nosokomialt problem i många europeiska länder. Infektion och kolonisation med MRSA har rapporterats enligt Smittskyddslagen sedan januari 2000. Under 2002 rapporterades totalt 442 fall och av dessa

bedömdes 69% ha smittats med MRSA i Sverige. Minst två tredjedelar av de importerade fallen hade smittats av MRSA genom kontakt med sjukvården. Även bland de inhemska fallen var den vanligaste smittvägen för MRSA någon form av vårdinrättning. Sedan 2000 har en DNA-baserad typningsmetod (pulsfält gel elektrofores, PFGE) använts för epidemiologisk typning av MRSA isolerade i Sverige. 331 av de 405 isolaten som typades under 2002 härrörde från tidigare kända europeiska kloner.

Enterokocker är den näst vanligaste orsaken till nosokomiala Gram-positiva infektioner. De flesta enterokockinfektioner orsakas fortfarande av *Enterococcus faecalis*. Dock ökar andelen av *E. faecium* isolerade från blododlingar, troligen beroende på minskad antibiotkakänslighet hos dessa. En signifikant ökning av ampicillinresistens bland *E.faecium* har noterats under de senaste åren. 71% av 196 invasiva isolat av *E.faecium* rapporterades som ampicillinresistenta till EARSS 2002. Vankomycinresistenta *E.faecium* och *E.faecalis* (VRE) gjordes anmälningspliktiga enligt Smittskyddslagen år 2000. År 2002 rapporterades 20 fall.

Streptococcus pyogenes är en av de viktigaste luftvägspatogenerna. Resistens mot tetracykliner är signifikant, 16% år 2002 medan resistens mot makrolider och klindamycin är låg, under 2% och 1% respektive. *Escherichia coli*, mestadels erhållna från urinvägsinfektioner, har testats mot de vanligast förskrivna läkemedlen för att behandla urinvägsinfektioner. Resistens mot ampicillin (22%) och trimetoprim (14%) låg på samma nivå som 2001. Ampicillinresistensen var något högre bland blodisolat, men nivån är fortfarande lägre än i många länder i Europa. Aminoglykosidresistens hos *Escherichia coli* är ovanlig i Sverige. Kinolonresistens har tidigare testats mot norfloxacin och har då legat under 5%. För år 2002 föreslog RAF-M att nalidixinsyra skulle användas i stället för norfloxacin för att testa för resistens mot fluorokinoloner. Därmed inkluderas alla isolat som avviker från normalpopulationen av *E. coli* i fråga om fluorokinolonresistens. Med denna metod var fluorokinolonresistensen hos *E. coli* 8.5%. Under 2002 fick 347 patienter *M. tuberculosis,* konfirmerad genom odling. Bland dessa isolat rapporterades resistens hos 12.1% mot åtminstone ett av fem läkemedel (isoniazid, rifampicin, etambutol, pyrazinamid och streptomycin). Läget är ungefär detsamma som under 2000 och 2001.

Nationella och regionala interventionsprojekt

STRAMA:s diagnos-receptundersökning som utfördes i fem landsting under en vecka 2000 upprepades 2002 och inkluderade då 5377 patienter som sökt på grund av en infektion. 71% av dessa fall rörde olika typer av luftvägsinfektioner och bland dessa var penicillin V det vanligast förskrivna läkemedlet. Mellan de båda interventionerna har nya rekommendationer beträffande behandling av akut tonsillit getts ut av Läkemedelsverket. Minskningen av antalet fall av tonsillit i undersökningen 2002 kan bero på ett förändrat vårdsökningsmönster på grund av dessa nya rekommendationer. Ungefär sex månader innan den första undersökningen (2000) kom nya rekommendationer beträffande behandling av akut otitis media.

Den nya rekommendationen föreslår tre dagars expektans för barn över 2 år för att invänta spontanläkning som ett alternativ till omedelbar förskrivning av antibiotika. Dessa rekommendationer verkar däremot inte ha slagit igenom. Andelen fall med akut otitis media var ungefär densamma i båda undersökningarna: 8% 2000 och 9% 2002. I diagnos-receptundersökningen utgjorde 13% av fallen urinvägsinfektioner. Användningen av kinoloner har minskat signifikant medan användningen av nitrofurantoin dubblerades, jämfört med 2000.

Den nationella studien av resistens och antibiotika-användning inom intensivvård, IVA-STRAMA har fortsatt under 2002. Ett flertal andra nationella och lokala interventionsprojekt har startat under 2002 och är kortfattat beskrivna i denna rapport, till exempel interaktivt lärande, analys och feedback av förskrivningsdata, utbildning av föräldrar med barn på daghem och kvalitetsaspekter av antibiotikaanvändningen på ett universitetssjukhus. Utöver detta finns även en sammanfattning av pneumokock-interventionsprojektet i Skåne.

3. Use of antimicrobials

3.1. Use of antibiotics

Out-patient care

General trends

In Sweden data on antibiotics, prescribed for outpatients, are available since 1974. A gradual increase was noted between 1980 and 1993 whereafter a decline has been observed. The reduction between 1993 and 2002 was 22%, or 3.82 defined daily doses/1000 inhabitants and day (DDD/1000/day) (17.7 and 13.9 respectively). The major part of this reduction took place during 1993 – 1997, since then the yearly figures have been relatively stable (Figure 3.1.1).

Despite a fairly constant level of antibiotic sales between 1997 and 2002 substantial changes can be shown when looking at different age groups. As shown in Figure 3.1.2. the reduction in antibiotic use has continued in children aged 0-6 years, while a continuous increase has occurred in persons above the age of 80.

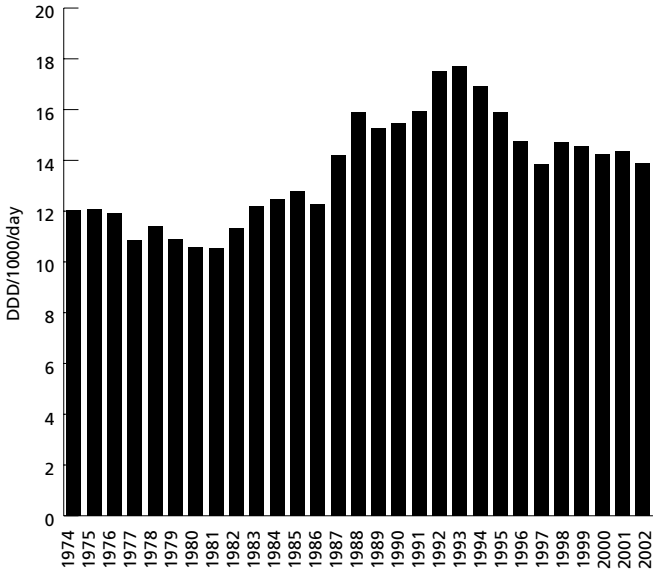


Figure 3.1.1. Antibiotics, prescribed for outpatients in Sweden (ATC group J01 excluding methenamine), DDD/1000/day, 1974-2002.

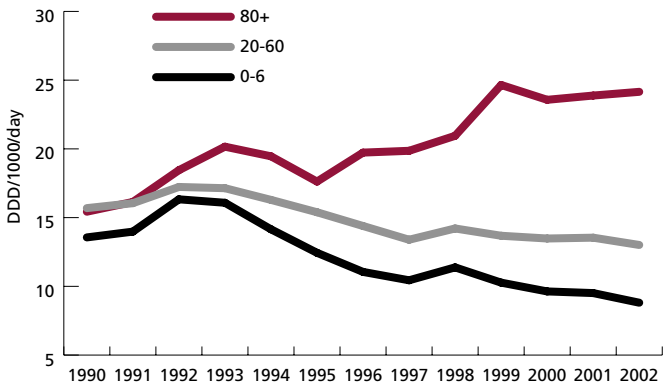


Figure 3.1.2. Antibiotics, different ages, 1990-2002, outpatients in Sweden (ATC J01 excl methenamine), DDD/1000/day.

The total use within the country, divided into different groups of antibiotics as well as in ages and sex, is presented in Table 3.1.1. The most commonly prescribed antibiotic, retrospectively as well as for year 2002, is beta-lactamase sensitive penicillin (Penicillin V). This is in accordance with Swedish guidelines in which this antibiotic is recommended as a primary choice for common respiratory tract infections. For most of the groups the figures for 2002 were unchanged compared to 2001. A marginal reduction was seen in the use of tetracyclines and macrolides for women. A marginal increase was seen for men in the use of penicillins with extended spectrum. The use of beta-lactamase resistant penicillins and quinolones is commented below.

Beta-lactamase resistant penicillins

The last years' increase in the use of beta-lactamase resistant penicillins (J01CF), expressed in DDD/1000/day, is also evident when the consumption is expressed as prescriptions/1000 inhabitants/year (Table 3.1.2). The large increase in use between 1974 and 1985 could be explained by the increasing number of penicillinase-producing *S. aureus* outside hospitals. Since then a continuing increase has been noted in all age groups. Between 2001 and 2002 the increase was most pronounced in the age-group below 19 years (between 28 to 45% prescriptions/1000 inhab) which may reflect the ongoing epidemic of impetigo caused by *S. aureus* resistant to fusidic acid. The high usage of beta-lactamase resistant penicillins in the elderly needs further analysis.

For the period 1993-2002, a diminishing use of quinolones was noted among women of all ages. This is believed to be the result of a national recommendation to restrict the use of this type of antibiotics for uncomplicated urinary tract infections. For the same period, however, an opposite trend was noted for men. Norfloxacin and ciprofloxacin account for the major part of the use. The use in different age groups during 1998 and 2002 is shown in Figure 3.1.3 and 3.1.4. For women, as well as for men, the use increased with age. The reduction in the overall use of quinolones among women consisted of a diminished use of norfloxacin in all age grops. The use of ciprofloxacin in women has been constant except for an increase that was noted in 2002 in ages over 80 (Figure 3.1.3) For men the use of both norfloxacin and ciprofloxacin increased between 1998 and 2002. This increase was most pronounced in the highest age groups (Figure 3.1.4).

Table 3.1.1. Antibiotic utilisation in out-patient care, different groups of antibiotics and different age-groups 1974, 1985, 1993, 2001 and 2002.

	Women, DDD/1000/day					Men, DDD/1000/day				
Age-group (years)	1974	1985	1993	2001	2002	1974	1985	1993	2001	2002
Tetracyclines (J01A)										
0-6	0	0	0	0	0	0	0	0	0	0
7-19	1.0	1.5	2.2	2.0	2.0	0.9	1.3	2.3	2.2	2.2
20-60	3.1	3.9	5.8	4.3	4.1	2.5	3.3	3.9	2.9	2.7
61-79	2.3	2.5	5.2	3.9	3.7	2.2	3.1	5.0	3.8	3.7
80-99	1.2	1.6	3.1	2.6	2.6	3.2	2.1	4.8	3.6	3.6
All ages	2.2	2.8	4.5	3.4	3.3	1.9	2.6	3.5	2.7	2.7
Penicillins with extended spectrum (J01CA)										
0-6	0.5	0.9	2.6	1.4	1.4	0.6	0.9	2.6	1.6	1.5
7-19	0.7	0.8	0.9	0.7	0.7	0.4	0.2	0.6	0.4	0.4
20-60	1.0	1.8	1.6	1.5	1.4	0.6	0.6	0.7	0.6	0.6
61-79	0.8	2.5	1.8	2.4	2.5	1.1	1.4	1.1	1.5	1.5
80-99	1.8	4.0	1.8	4.0	4.1	3.2	4.0	1.5	2.7	2.7
All ages	1.0	1.8	1.6	1.7	1.7	0.7	0.8	1.0	0.9	1.0
Beta-lactamase sensitive penicillins (J01CE)										
0-6	4.3	5.0	6.3	4.3	3.9	4.9	5.1	6.2	5.0	4.4
7-19	4.6	5.2	6.4	4.7	4.2	3.6	4.5	5.1	4.1	3.7
20-60	4.3	6.7	7.7	5.8	5.4	3.3	4.8	5.2	4.2	3.9
61-79	1.8	3.1	4.3	4.1	4.0	2.0	3.0	3.6	3.7	3.8
80-99	1.8	2.8	3.1	3.4	3.3	2.5	3.7	3.6	3.8	3.8
All ages	3.8	5.4	6.6	5.1	4.7	3.3	4.4	5.0	4.1	3.9
Beta-lactamase resistant penicillins (J01CF)										
0-6	0.0	0.2	0.2	0.2	0.3	0.0	0.1	0.2	0.3	0.4
7-19	0.2	0.2	0.4	0.5	0.7	0.1	0.3	0.4	0.6	0.8
20-60	0.2	0.5	0.8	0.8	0.8	0.1	0.7	0.9	0.9	1.0
61-79	0.1	0.7	1.8	1.7	1.8	0.3	1.2	2.1	2.3	2.4
80-99	0.8	1.7	3.6	4.4	4.6	0.5	1.2	3.5	4.7	5.1
All ages	0.2	0.5	1.0	1.1	1.2	0.1	0.6	1.0	1.2	1.3
Other beta-lactam antibacterials (J01D)										
0-6	0.0	1.1	0.6	0.6	0.6	0.0	1.0	0.6	0.6	0.6
7-19	0.0	0.3	0.4	0.4	0.4	0.0	0.2	0.4	0.3	0.3
20-60	0.1	0.4	0.7	0.5	0.4	0.1	0.2	0.4	0.3	0.3
61-79	0.1	0.5	0.8	0.5	0.5	0.2	0.5	0.7	0.6	0.5
80-99	0.2	0.3	0.7	0.9	0.8	-	0.7	1.0	1.0	1.0
All ages	0.1	0.5	0.7	0.5	0.5	0.1	0.4	0.5	0.4	0.4
Trimethoprim and derivatives (J01EA)										
0-6	-	0.1	0.1	0.2	0.2	-	0.0	0.1	0.1	0.1
7-19	-	0.3	0.3	0.4	0.4	-	0.0	0.0	0.0	0.0
20-60	-	0.7	0.6	0.7	0.7	-	0.1	0.1	0.1	0.1
61-79	-	1.4	1.4	1.5	1.5	0.0	0.5	0.5	0.5	0.5
80-99	-	1.7	2.5	3.3	3.3	-	1.8	1.4	1.7	1.8
All ages		0.8	0.8	1.0	1.0		0.2	0.2	0.2	0.2
Macrolides and Lincosamides (J01F)										
0-6	0.8	3.7	3.7	1.1	0.9	1.4	3.5	3.7	1.2	1.0
7-19	0.7	1.8	1.9	1.1	0.9	0.7	1.6	1.7	1.0	0.8
20-60	0.6	2.0	2.0	1.2	1.1	0.4	1.1	1.1	0.7	0.6
61-79	0.4	0.9	1.2	1.0	0.9	0.5	0.8	1.0	0.9	0.9
80-99	0.2	0.8	0.9	1.0	1.0	0.7	0.5	0.7	1.1	1.1
All ages	0.6	1.9	2.0	1.1	1.0	0.6	1.3	1.4	0.8	0.8
Quinolone antibacterials (J01M)										
0-6	-	-	0.0	0.0	0.0	-	-	0	0.0	0.0
7-19	-	-	0.2	0.2	0.2	-	-	0.1	0.1	0.1
20-60	-	-	1.1	0.9	0.8	-	-	0.8	0.9	0.9
61-79	-	-	2.3	1.8	1.7	-	-	2.5	2.7	2.7
80-99	-	-	3.2	3.1	2.9	-	-	3.6	4.9	4.9
All ages			1.2	1.0	1.0			1.0	1.1	1.1
All agents										
0-6	5.6	11.0	13.5	7.8	7.3	6.9	10.6	13.4	8.80	8.0
7-19	7.2	10.1	12.7	10.0	9.5	5.7	8.1	10.6	8.7	8.3
20-60	9.3	16.0	20.3	15.7	14.7	7.0	10.8	13.1	10.6	10.1
61-79	5.5	11.6	18.8	16.9	16.6	6.3	10.5	16.6	16.0	16.0
80-99	6.0	12.9	18.9	22.7	22.6	10.1	14.0	20.1	23.5	24.0
All ages	7.9	13.7	18.4	14.9	14.4	6.7	10.3	13.6	11.4	11.4

Table 3.1.2. Beta-lactamase resistant penicillins (J01CF), prescriptions/1000 inhabitants, different age-groups 1974, 1985, 1993, 2001 and 2002.

Beta-lactamase resistant penicillins (J01CF), prescriptions/1000 inhabitants/year										
	women					men				
	1974	1985	1993	2001	2002	1974	1985	1993	2001	2002
0-6	0.8	10.7	13.6	23.4	33.8	0.7	6.9	16.9	25.7	37.3
7-19	2.8	6.5	15.5	24.8	32.2	1.9	7.4	17.7	29.0	37.1
20-60	3.0	14.2	27.0	27.7	30.0	1.4	16.4	29.4	31.7	33.4
61-79	1.5	16.1	43.9	48.6	49.9	3.6	23.1	44.7	58.7	61.2
80-99	6.4	29.2	78.0	125.0	129.1	3.5	27.6	74.0	126.2	132.4
All ages	2.6	13.8	30.2	36.9	40.4	1.8	15.5	30.1	38.4	42.1

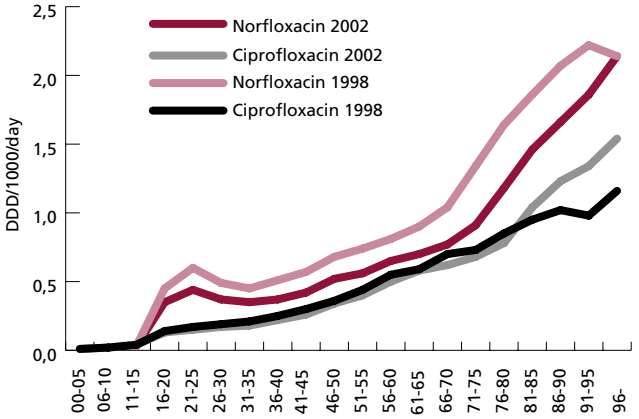


Figure 3.1.3. Norfloxacin and ciprofloxacin, women, all ages in Sweden, 1998 and 2002.

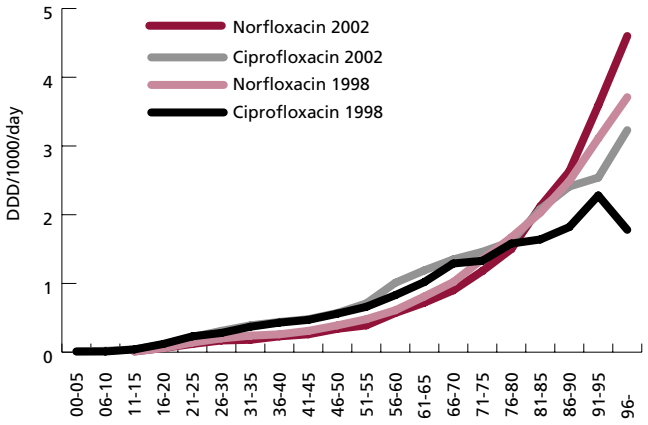


Figure 3.1.4. Norfloxacin and ciprofloxacin, men, all ages in Sweden, 1998 and 2002.

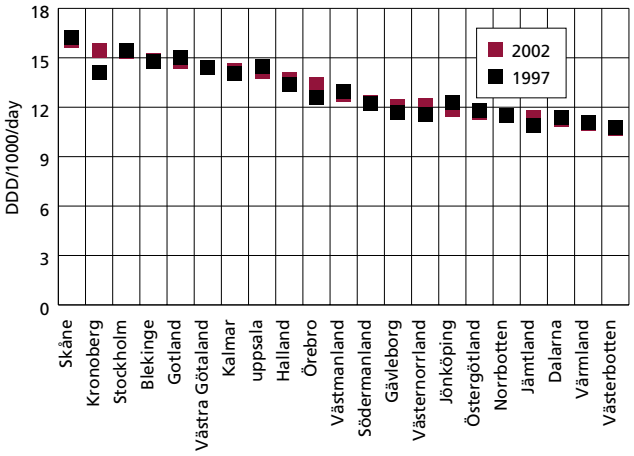


Figure 3.1.5. Antibiotics, prescribed for outpatients, Swedish counties (ATC group J01 excluding methenamine), DDD/1000/day, 1997 and 2002.

Geographical variations in consumption of antibiotics

The utilisation between the counties varied. In 2002 the difference between the county with the highest and the county with the lowest figures was 5.3 DDD/1000/day; 16.0 and 10.7 respectively (Figure 3.1.5). Data from 2001, presented in Swedres 2001, showed a similar relationship.

Since 1998 statistics on antibiotic prescriptions, at a municipal level are available. Looking at numbers of prescripitions/1000 inhabitants/year, in the age groups 0-6 years and 80 years and older, a wide variety between municipalities was seen. In the age-group 0-6 years almost a four-fold difference between the municipal with the highest and the lowest figures (1028 and 271 respectively) was noted in 2002 and in the age-group 80 years and older a three-fold difference was seen (1728 and 604 respectively) (Figure 3.1.6 and 3.1.7). Those with the lowest consumption are all rural municipalities with few inhabitants (usually < 1000 children). The difference between municipalities is reduced by half if only municipalities with similar population size and demographics are compared.

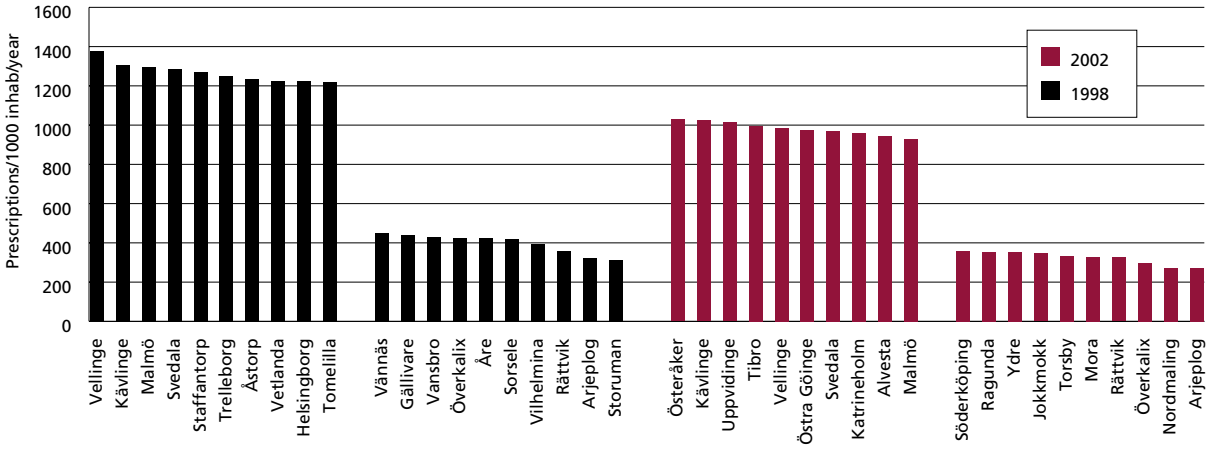


Figure 3.1.6. Antibiotics (ATC group J01 excluding methenamine), age group 0-6 years, ten municipalities in Sweden with the highest and lowest consumption, 1998 and 2002.

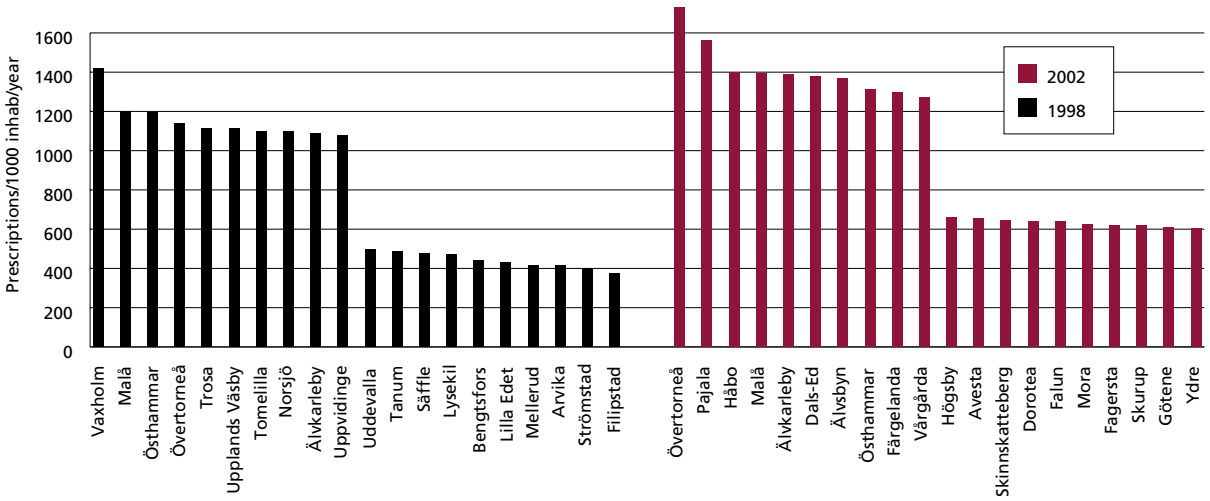


Figure 3.1.7. Antibiotics (ATC group J01 excluding methenamine), age group 80 years and older, ten municipalities in Sweden with the highest and lowest consumption, 1998 and 2002.

Hospital care

There has only been a marginal difference in the antibiotic consumption in hospital care since 1996. The total consumption for 2002 was 1.27 DDD/1000/day, i.e. unchanged compared to 2001 (Figure 3.1.8).

Hospital sale from The National Corporation of Swedish Pharmacies is available as DDD/1000/day. As this denominator could be misleading e.g due to variation in population demographics, we have chosen to present, as an alternative, the total number of defined daily doses/number of hospital admissions (DDD/NA) for each county during 1998 and 2000. Higher figures were generally noted when expressed as DDD/NA. The ranking of the counties was also affected (Figure 3.1.9). A major difference between the counties with the highest and the lowest values was seen using both methods. The difference was 66% when expressed as DDD/1000/day and 48% when DDD/NA was used.

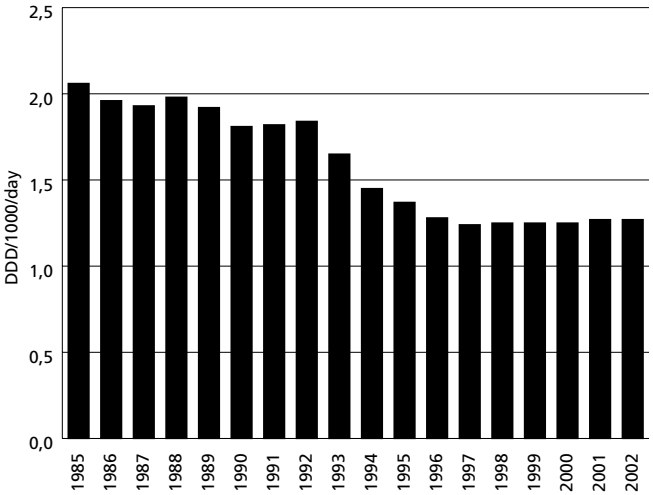


Figure 3.1.8. Antibiotic consumption (ATC group J01 excluding methenamine) in hospital care, Sweden, 1985-2002.

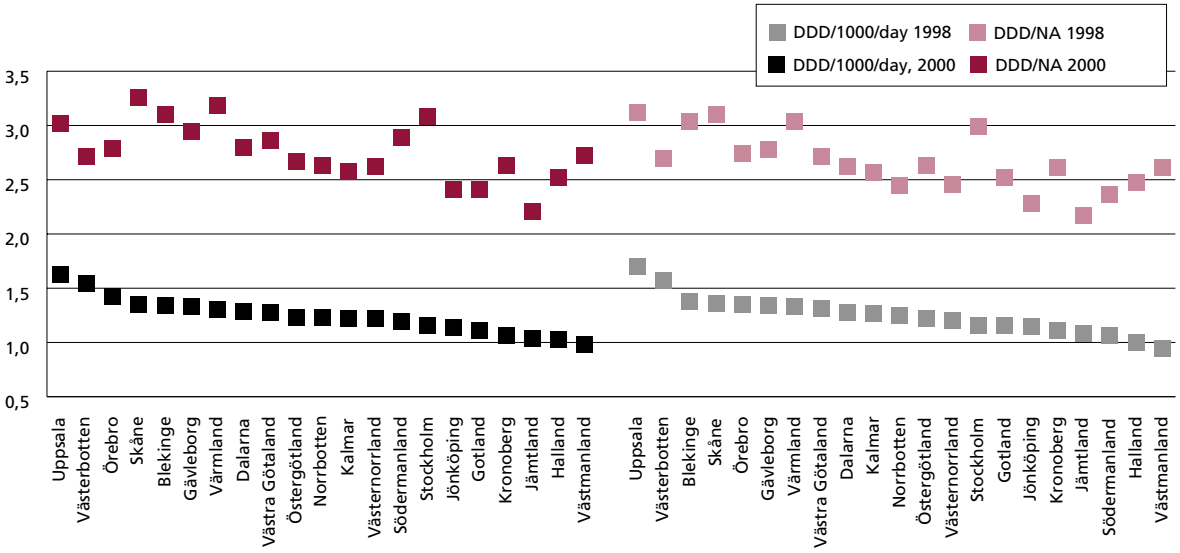


Figure 3.1.9. Antibiotic sales (ATC group J01 excluding methenamine), hospital care 1998 and 2002 in Sweden, expressed as DDD/1000/day and DDD/NA.

3.2. Use of Antifungals

Background

Although in the perspective of public health the resistance against antibiotics is still the most important problem, the emergence of resistance to antifungals is of concern. An expert group within the field of antifungals have been formed in Sweden (RAM) with the commission to follow fungul resistance and drug use. Solid data reflecting the actual situation regarding resistance are not yet available but data over the consumption are presented below. In the WHO ATC nomenclature both "antifungals" and "antimycotics" are used for these drugs but in this report we have chosen to use the name antifungals.

Out-patient care

Antifungals for topical use (D01A)

The sales of antifungals for topical use have been on a steady level for the last ten years, about 180 packages/1000 inhabitants and year. Over the counter (OTC) sale was made possible for some of these products in the middle of the 1980's. Data on such consumption are available from 1996 and since then, OTC accounted for approximately 50% of the total sale. Azoles and azoles combined with steroids dominate both the OTC and the prescription sales.

Antifungals for systemic use (D01B)

The prescription of antifungals for systemic use was quite stable in Sweden during the period 1974-1991. In 1992 a new substance, terbinafin, was approved and the number of prescriptions increased. Terbinafin replaced griseofulvin and the utilisation in 2002 was 0.67 DDD/1000/day. Griseofulvin was taken off the market in 2000.

Antifungals for gynaecological use (G01AF)

Imidazoles are used to treat gynaecological infections caused by yeast fungi such as Candida. These kinds of infections are increasing, especially recurrent infections. Solid data on OTC-sales are available from 1996 but have been estimated for 1993-1995 (Figure 3.2.1).

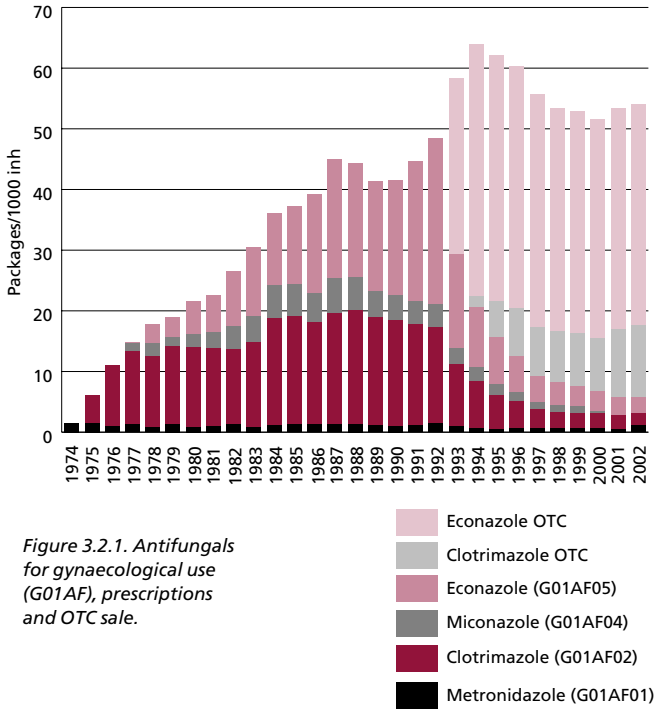


Figure 3.2.1. Antifungals for gynaecological use (G01AF), prescriptions and OTC sale.

Econazole and clotrimazole for local use became OTC products 1993 and 1994 respectively and the number of packages sold increased in accordance to this. The amount of packages sold as OTC dominated and represented about 90% of the total sale 2002. According to expert

recommendations from a workshop arranged by the Swedish Medical Products Agency in 2000, gynaecological infections caused by yeast fungi such as Candida should not be treated with OTC products for more than two occasions. In case of recurrences of symptoms the woman should be advised to see a doctor for accurate diagnosis. It seems likely that women with recurring infections use local imidazoles during long periods instead of seeking medical advice. During such long term treatment there is a risk for developing resistance against azoles.

Antifungals for systemic use (J02A)

Prescriptions of antifungals for systemic use have increased continuously during the last ten years. The compounds prescribed were itraconazole, fluconazole and ketoconazole. Fluconazole dominated which probably, to a large extent, depends on prophylactic use.

Hospital care

Antifungals for systemic use (J02A)

The sale of antifungals for systemic use has increased almost eight-fold between 1985 and 2002 from about 0.006/1000/day to 0.045/1000/day (Figure 3.2.2). This reflects the increasing frequency and continuously changing spectrum of invasive fungal infections. These infections mainly affect immunocompromised patients for whom neutropenia is the main risk factor. The use of systemic antifungals involves both treatment and prophylaxis. Fluconazole is the dominating compound used followed by amphotericin B. During 2002 two new compounds were introduced to the market, voriconazole and caspofungin.

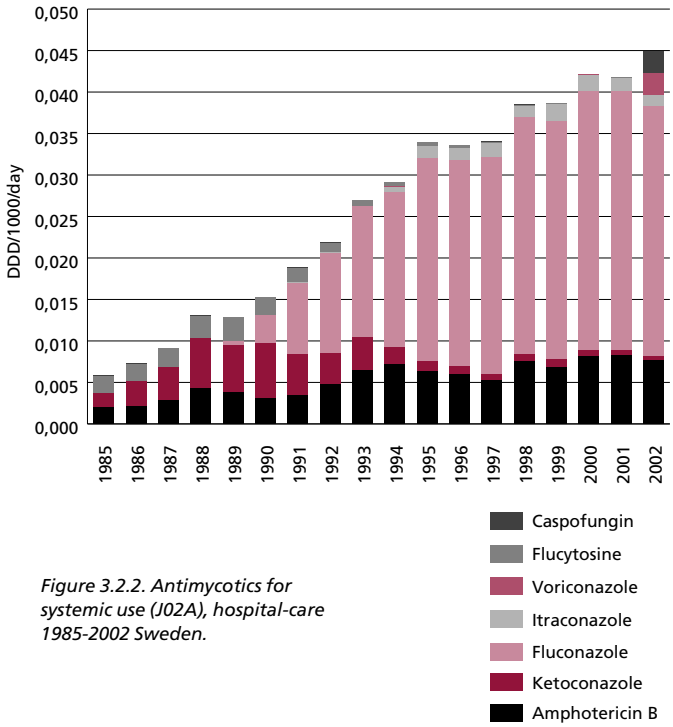


Figure 3.2.2. Antimycotics for systemic use (J02A), hospital-care 1985-2002 Sweden.

4. Antimicrobial resistance

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

Streptococcus pneumoniae

Background

The pneumococcus (*Streptococcus pneumoniae*) is the main bacterial cause of respiratory tract infections, such as pneumonia and acute otitis media, and thus a major global cause of morbidity and mortality. Pneumococcal infections mainly affect the small children and the elderly. Due to an immature immune response to the bacteria, the spread of pneumococci is mainly seen among small children, especially in crowded settings, such as day-care centres.

During the 1980s, resistance to penicillin, the classical drug of choice for treatment of pneumococcal infections, emerged and spread rapidly within and between countries in Europe. Many countries experienced resistance rates between 40-60%, resulting in fewer treatment alternatives and greatly increased costs for the care of patients with pneumococcal infections. Resistance to penicillin is often appearing together with resistance to other groups of antibiotics such as macrolides, tetracyclines and trimethoprim-sulfonamides. Sweden still has a comparatively low rate of infections caused by *S. pneumoniae* with reduced susceptibility to penicillin, MIC ≥0.12 mg/L (henceforth designated PNSP). Since 1996, infections 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 (Appendix 5).

Notifications according to the Communicable Disease Act Surveillance

Sweden still has a low incidence of PRP compared to many other parts of Europe. A majority of the detected PRP isolates belonged to a limited number of international clones with MIC PcG-values below 2 mg/L. Only a few isolates presented higher MIC-values, and these generally originate from persons who had acquired their infections abroad. These strains did not spread further in the community.

The highest incidence was found among children between 0-6 years. Males were dominating slightly in all age groups, except among the 19-65 year olds where women were in majority. Most cases were reported between late autumn and early spring, with exception for the oldest age group (>65 years) where the number of notifications showed no clear seasonal pattern.

All but a few cases were detected by nasopharyngeal culture. Case-finding intensity varied between counties, both due to contact tracing routines and culturing propensity (Swedres 2001). This made it hard to compare incidence between counties. County figures below are expressed as PRP proportion, i.e. the proportion of PRP out of all pneumococci to adjust for the differences in culturing propensity (Figure 4.1).

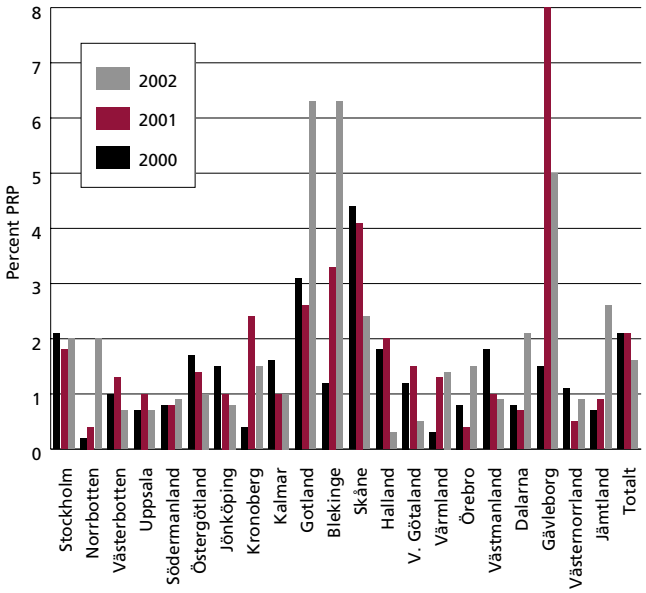


Figure 4.1. PRP proportion (percent PRP out of all isolated pneumococci) per county and year

Long-term national trends

During the last six years, the national incidence of PRP has decreased by 43%. This reduction has almost entirely taken place in the youngest age group, while the incidence in the other age groups has remained unchanged (Figure 4.2).

The strong negative trend for the national incidence between 1997 and 2002 could possibly be explained by two factors:

1) A declining trend is seen in the reported incidence of all pneumococci (regardless of resistance), together with a fall in the number of performed nasopharyngeal cultures, indicating that case-finding activity has decreased. In contrast to the declining national trend for PRP incidence, the proportion of PRP out of all pneumococcal isolates has remained unchanged during the same period until 2002, when it decreased slightly (Figure 4.3).

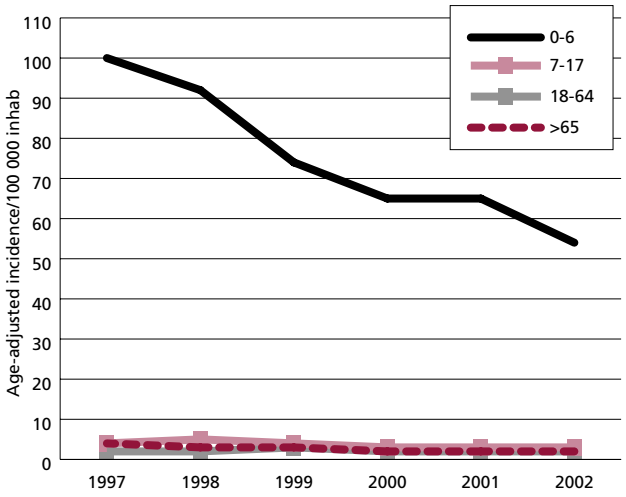


Figure 4.2. Age-adjusted PRP incidence during 1997-2002.

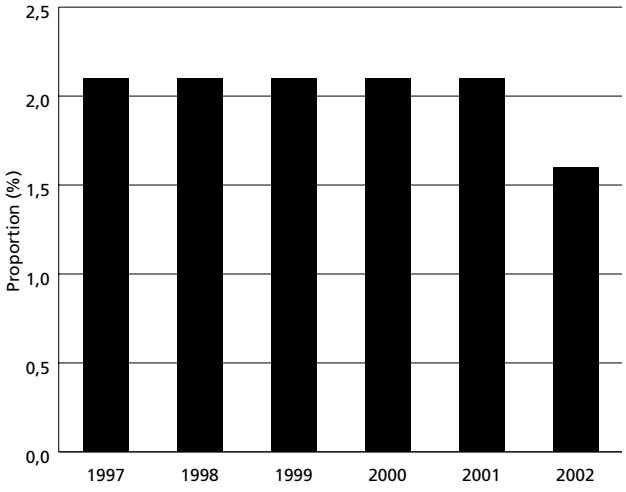


Figure 4.3. Proportion (%) of PRP out of all pneumococcal isolates.

2) A large decrease in local incidence by more than two thirds has been reported from Skåne county. Skåne has a large population, and the high incidence in this region has influenced the national figures strongly, especially in the beginning of the period. In 1997, Skåne county accounted for 40% of the national incidence, but this proportion has been reduced to 10% in 2002. When analysing national incidence data for the same period with Skåne county excluded, a less dramatic trend is seen (Figure 4.4).

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pneumococci have been one of the targets for the annual Resistance Surveillance and Quality Control (RSQC) programme since 1994. In these studies, approximately 3000 consecutive clinical nasopharyngeal isolates of *S. pneumoniae*, i.e. 100 isolates from each of all clinical microbiology laboratories, have been quantitatively tested for susceptibility to penicillin (by means of oxacillin

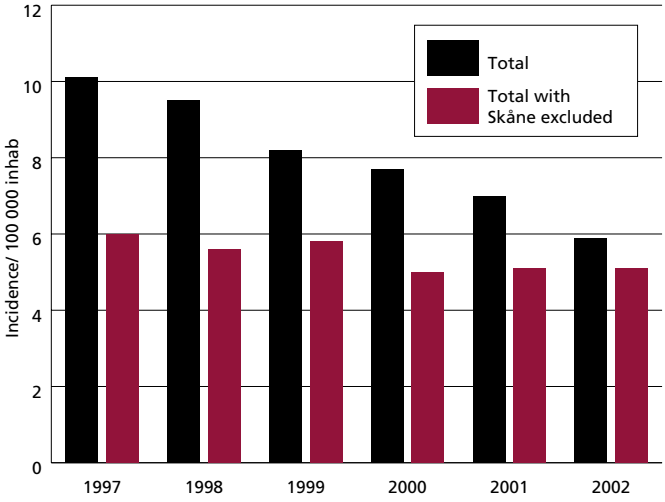


Figure 4.4. National PRP incidence with and without Skåne county included.

1 µg screen disk test), erythromycin, tetracycline, and combinations of sulfonamides and trimethoprim, using the disk diffusion method. The national overview of these studies is given in Figure 4.5.

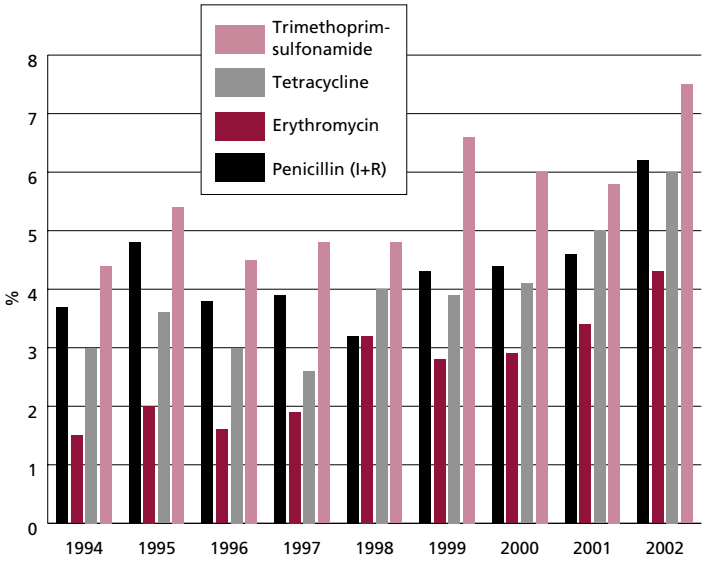


Figure 4.5. Overall national resistance rates (resistant isolates in percent of all pneumococcal isolates) for four different antibiotics 1994–2002 (data from the annual RSQC programme, approximately 3000 isolates per year).

Data from the EARSS network

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) (Appendix 5). The Swedish data on susceptibility to penicillin and erythromycin is given in Table 4.1. Overall resistance levels 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 comparable.

Table 4.1. Invasive isolates of Streptococcus pneumoniae reported to EARSS.

Year	Antibiotic	S%	I%	R%	Total
1999	Penicillin *	98.5	1.4	0.1	805
	Erythromycin	94.2	2.2	3.6	535
2000	Penicillin *	98.0	2.0	0.0	803
	Erythromycin	96.7	0.5	2.8	643
2001	Penicillin *	97.2	2.3	0.5	788
	Erythromycin	95.4	0.2	4.4	653
2002	Penicillin *	97.5	2.4	0.1	783
	Erythromycin	94.7	0.1	5.2	700

* S<0.12 mg/L; I ≥ 0.12-1.0 mg/L; R ≥ 2.0 mg/L

Staphylococcus aureus

Background

Staphylococcus aureus is a common pathogen which colonises nasal cavities of about 30% of the healthy humans without causing symptoms of infection. Among antibiotic resistant pathogens, causing nosocomial infections, methicillin resistant *S. aureus* is the one most rapidly spreading within hospitals and is now a major problem in many hospitals in Europe.

Methicillin-resistant *S. aureus* (MRSA), although representing different clonal types, have the mecA gene in common.

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 colonisation with MRSA in the Communicable Disease Act in the year 2000 was due to an increasing national alertness, responding to the situation seen in many other European countries, where MRSA now represents an increasing proportion of staphylococcal infections in hospital settings, totally exceeding 50%. By disseminating information and taking measures to contain the spread of MRSA, it is hoped that a similar situation can be prevented in Sweden.

Notifications of MRSA according to the Communicable Disease Act

Infection and colonisation with MRSA has been notifiable according to the Communicable Disease Act since January 2000.

The most notable change in MRSA incidence during this

Table 4.2. MRSA notified in 2002 by county according to the Communicable Disease Act.

County	2000		2001		2002	
	Number	Incidence/ 100 000 inhab	Number	Incidence/ 100 000 inhab	Number	Incidence/ 100 000 inhab
Stockholm	97	5.3	166	9.0	205	11.1
Uppsala	19	6.4	17	5.7	10	3.3
Södermanland	2	0.7	1	0.3	4	1.5
Östergötland	2	0.4	7	1.6	7	1.6
Jönköping	7	2.1	5	1.5	5	1.5
Kronoberg	1	0.5	0	0	4	2.2
Kalmar	3	1.2	2	0.8	5	2.1
Gotland	1	1.7	10	17.4	3	5.2
Blekinge	7	4.6	1	0.6	3	1.9
Skåne	22	1.9	76	6.7	68	5.9
Halland	10	3.6	25	9.0	13	4.6
Västra Götaland	110	7.3	54	3.6	48	3.1
Värmland	9	3.2	7	2.5	6	2.1
Örebro	8	2.9	6	2.1	16	5.8
Västmanland	3	1.1	8	3.1	7	2.7
Dalarna	0	0	4	1.4	1	0.3
Gävleborg	2	0.7	1	0.3	12	4.3
Västernorrland	14	5.6	12	4.8	7	2.8
Jämtland	0	0	0	0	2	1.5
Västerbotten	3	1.1	18	7.0	10	3.9
Norrbotten	3	1.1	5	1.9	6	2.3
Total	323		425		442	

period is the increasing incidence in the Stockholm region reflecting an ongoing MRSA epidemic. The Stockholm region, with a fifth of the total Swedish population, gave rise to nearly half of the reported MRSA cases in Sweden in 2002 (Table 4.2.). If the Stockholm figures were excluded, the total incidence for the rest of the country would be rather stable during the years 2000-2002.

During 2002 a total of 442 cases were reported. The MRSA incidence was highest among the elderly, although the absolute figures were more evenly distributed (Figure 4.6).

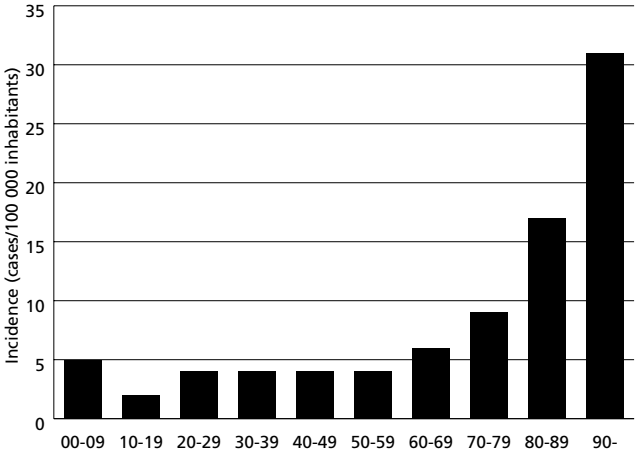


Figure 4.6. Age adjusted incidence of MRSA (n=442).

Slightly less than half of the reported cases were considered to be infected with MRSA (Figure 4.7).

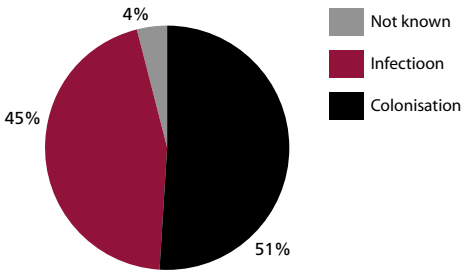
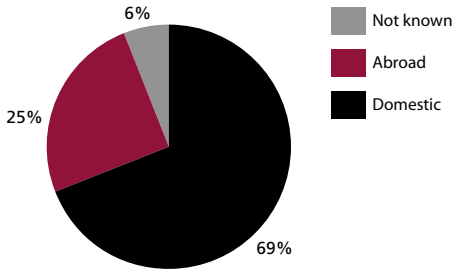


Figure 4.7. Percentage colonized and infected MRSA cases 2002 (n=442).

Of the total number of reported cases in 2002, 69% were regarded as having acquired MRSA in Sweden. At least two thirds of the imported cases had acquired MRSA in health care settings abroad (Figure 4.8).



Figur 4.8. Reported origin of MRSA 2002 (n=442).

Among the domestic cases the most common place of MRSA acquisition was reported to be health care facilities (Figure 4.9).

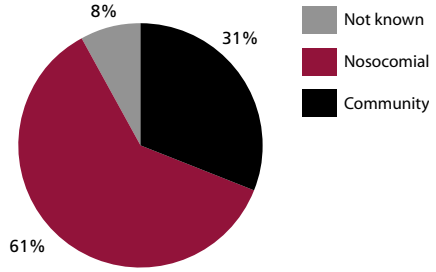


Figure 4.9. Reported place of acquisition for domestic MRSA-cases (n=305).

Most cases of health care related acquisition were reported to have taken place in hospital settings (Figure 4.10). Many of the MRSA-cases in the older age-group has frequent contacts with both in-patient and out-patient health care services as well as nursing homes. This made it difficult to determine where the patient initially acquired MRSA. The multiple contacts with health care services for many of these patients posed a great challenge in information exchange between health care providers.

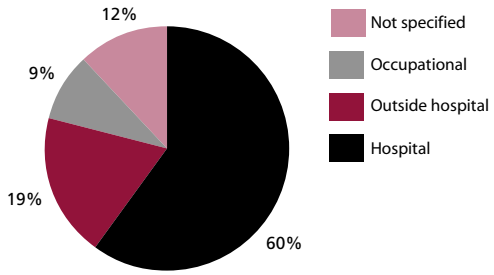


Figure 4.10. Reported way of domestic health care related acquisition (n=186).

Typing of MRSA

A DNA-based typing method (pulsed field gel electrophoresis, PFGE) was used for epidemiological typing of MRSA isolated in Sweden. PFGE patterns were included in a database and compared with international reference strains (epidemic MRSA from European countries, the

Harmony project). Most Swedish MRSA isolates since year 2000 have been analysed by this method. This has enabled us to get a national overview and to relate MRSA isolated in Sweden to European epidemic strains (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 local names (e.g. SE97-3). These patterns could be either related or unrelated to a reference strain.

Table 4.3. PFGE patterns of MRSA isolated in Sweden 2002 (n=405).

PFGE pattern	No. of isolates(no. with related SE-patterns)	Total
UK E15	91 (15)	106
DK E97-1	58 (18)	76
UK E1	1 (30)	31
UK E16	5 (25)	30
Fra A	19 (4)	23
Bel EC-3a	0 (20)	20
Fra B	1 (12)	13
UK E3	0 (12)	12
Berlin IV	0 (12)	12
S German II	0 (5)	5
Spa E1	3 (0)	3
Unrelated SE-patterns	74	74

Annual Resistance Surveillance and Quality Control (RSQC) programme

Staphylococcus aureus from wound infections were included in the annual RSQC programme in 2001 and 2002 (Appendix 5). Twenty-nine laboratories delivered data on consecutive isolates using the disk diffusion method for oxacillin, clindamycin, fusidic acid, aminoglycoside (gentamicin, netilmicin or tobramycin) and vancomycin. Resistance rates, compared to corresponding data for invasive isolates (as reported to EARSS), are presented in Table 4.4.

Table 4.4. Resistance rates for Staphylococcus aureus in 2001 and 2002 (RSQC-data compared to EARSS-data)

Year		*RSQC wound isolates*		*EARSS (Sweden), invasive isolates*	
	Antibiotic	Total (n)	R (%)	Total (n)	R (%)
2001	Oxacillin	3466	0.1	1632	0.9
	Clindamycin	3458	2.1	1588	1.2
	Fusidic acid	3209	7.1	586	2.5
	Aminoglycoside	2817	0.4	1575	0.3
	Vancomycin	2910	0	1395	0
2002	Oxacillin	4291	0.2	1842	0.7
	Clindamycin	3778	1.9	1826	1.8
	Fusidic acid	3812	9.5	797	2.9
	Aminoglycoside	2755	0.2	1711	0.5
	Vancomycin	2841	0	1653	0

The observation from year 2001 of rising levels of fusidic acid resistance was verified also in 2002. One fusidic acid resistant clone (MIC of fusidic acid 4 m/L) has caused impetigo in young children and now comprised almost 10% of the isolates.

Data from the EARSS network

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 0.7% 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 four years indicates a low and constant rate of MRSA among invasive isolates (Table 4.5). Comparative data for Europe are given in Figure 4.11.

Table 4.5. 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*	*Total*
1999	1307 (99%)	0	13 (1.0%)	1320
2000	1469 (99.4%)	0	9 (0.6%)	1478
2001	1618 (99.1%)	0	14 (0.9%)	1632
2002	1830 (99.4%)	0	12 (0.6%)	1842

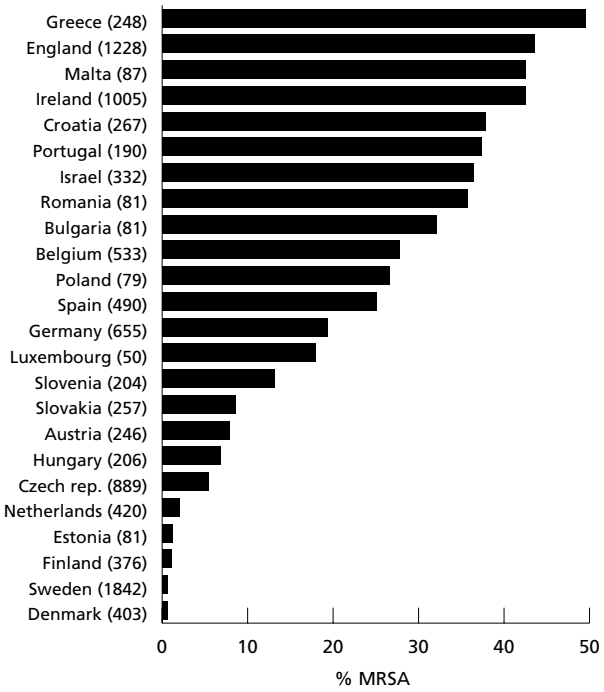


Figure 4.11. MRSA in Europe 2002. Data from EARSS (www.ears.rivm.nl 2003-04-06).

Enterococcus faecium and faecalis

Background

Enterococci are the second most common cause of nosocomial Gram-positive infections and the third most common cause of nosocomial bacteremia. Most enterococcal infections are still caused by *Enterococcus faecalis* although the percentage of *E. faecium* recovered from blood cultures is increasing which may be related to the lower antibiotic susceptibility of the latter. In particular, a significant increase of ampicillin, carbapenem and quinolone resistance has occurred among *E. faecium* during the last decade. Therapy is difficult because of the intrinsic resistance of *E. faecium* against many classes of antibiotics like aminoglycosides (low-level resistance) and cephalosporins. Resistance to tetracyclines, macrolides, and chloramphenicol is also frequent. Vancomycin-resistant *E. faecium* and *E. faecalis* (VRE) were first isolated in 1986 and the prevalence of VRE in hospitals is increasing, particularly in the United States and more recently also in some countries in Europe.

Vancomycin resistance is mediated by the vanA or vanB gene complexes carried on transposons, thereby enabling dissemination between enterococcal strains and species. The gene complexes can appear in both *E. faecalis* and *E. faecium*, however vanA-containing *E. faecium* are by far most frequently encountered. The presence of either of these genes leads to resistance to vancomycin, whereas resistance to teicoplanin, another glycopeptide antibiotic, is achieved only by the vanA gene.

Enterococci, and specifically VRE, have become important causes of nosocomial outbreaks in many parts of the world, usually involving high-risk populations such as immunosuppressed and intensive care patients. Like MRSA, VRE were made notifiable pathogens according to the Communicable Disease Act in the year 2000. Surveillance of this pathogen was previously done through the voluntary laboratory reporting system.

Notifications of VRE according to the Communicable Disease Act

Like MRSA, VRE were made notifiable according to the Communicable Disease Act in the year 2000. The number of reported VRE cases remains on a low and stable level. Since 2000, the number of annually reported cases has varied between 18 and 20 cases. In 2002, 20 cases were reported. In the three years of mandatory reporting, Stockholm has contributed to more than half of the reported cases (32/58), and is the only county with domestically acquired cases in each of the three years (Figure 4.12). The clustering of cases in Västerbotten County in year 2000 reflected a local hospital outbreak with an increased case-finding and contact tracing.

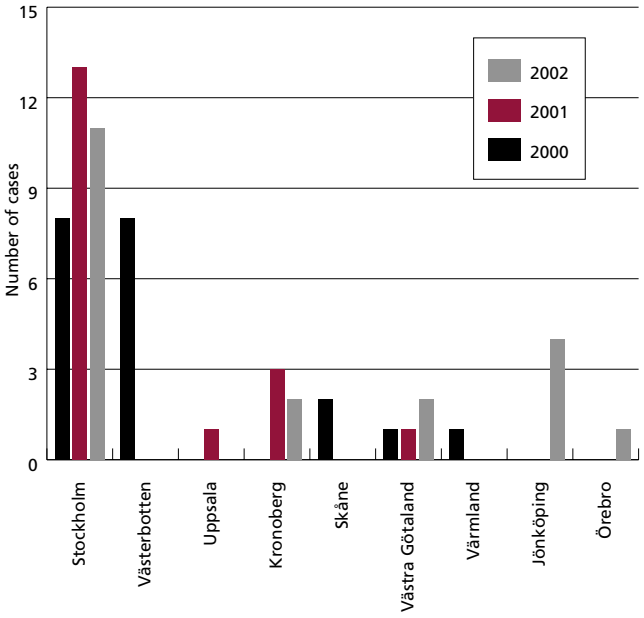


Figure 4.12. Reported VRE cases by county 2000–2002 (counties not in the graph did not report any case).

Carriage/infection with VRE is increasingly common with older age, except for the oldest age group (Figure 4.13).

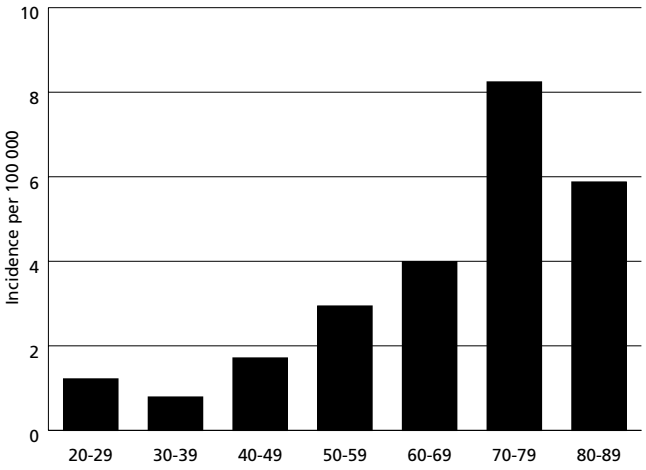


Figure 4.13. Reported VRE cases 2000–2002; age adjusted incidence.

Data from the EARSS network

Since the year 2001, *Enterococcus faecalis* and *Enterococcus faecium* were included in the EARSS network (Appendix 5). The main focus was on vancomycin resistance, but also on high level resistance to aminoglycoside antibiotics. This latter property may be of major clinical concern since it makes combination therapy using penicillin and aminoglycoside of no use. From Sweden 21 laboratories (covering approximately 75% of the population) contributed with quality assured routine disk diffusion data (Table 4.6).

Table 4.6. Susceptibility of invasive isolates of Enterococcus faecalis and Enterococcus faecium to three antibiotic groups in Sweden 2001 and 2002. Data from EARSS.

Year		Enterococcus faecalis, invasive isolates		Enterococcus faecium, invasive isolates	
	Antibiotic	R (%)	Total (n)	R (%)	Total (n)
2001	Ampicillin	0	479	71	196
	Amino glycosides*	13	212	9	102
	Vancomycin	0	396	0	172
2002	Ampicillin	0	453	72	167
	Amino glycosides*	15	368	5,6	88
	Vancomycin	0	368	0	148

* gentamicin or tobramycin

Streptococcus pyogenes

Annual Resistance Surveillance and Quality Control (RSQC) programme

Being one of the most important respiratory tract pathogens, *Streptococcus pyogenes* (group A streptococci, beta-haemolytic streptococci group A) has been one of the regular pathogens of the national surveillance program since 1994. The antibiotics chosen for surveillance are those which are considered as treatment options and for which resistance mechanisms have been described. Penicillin is still the drug of choice, and remarkably enough resistance development to penicillin or other betalactams has never been described in clinical isolates. Resistance to macrolides (represented by erythromycin), clindamycin and tetracyclines occur more or less frequently.

Resistance to erythromycin and clindamycin are in some cases mechanistically related (altered target, so called MLS-resistance) but in others unrelated (efflux mechanism) and affecting only erythromycin.

Summarized data for the years 1994-2002 are presented in Figure 4.14.

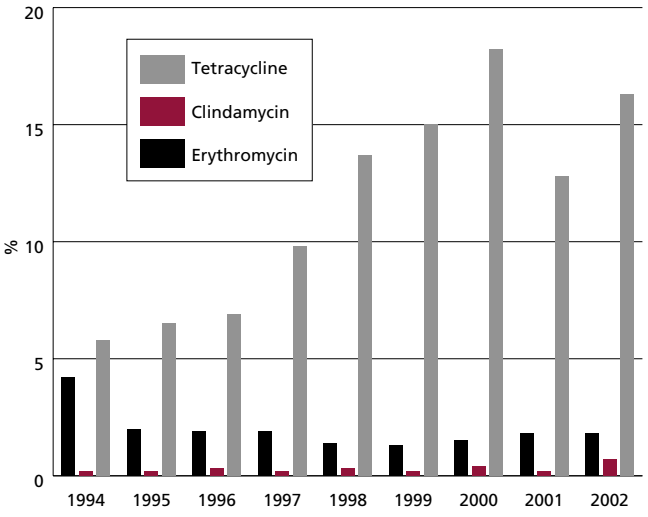


Figure 4.14. Streptococcus pyogenes in Sweden.

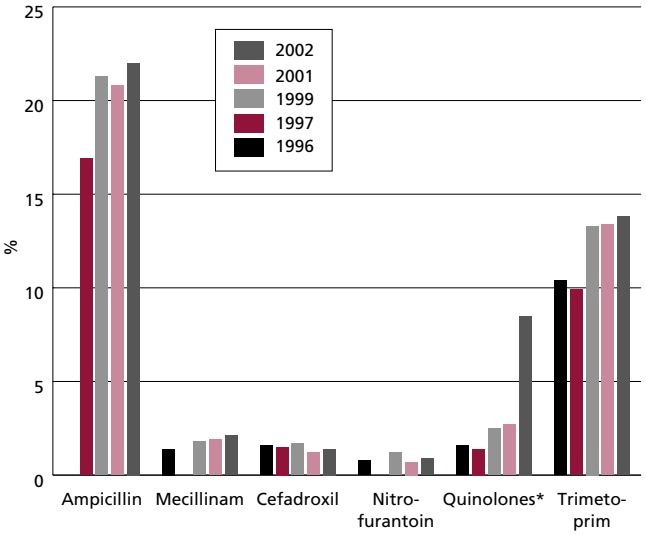
Haemophilus influenzae

There are no data on *Haemophilus influenzae* for 2002.

Escherichia coli

Annual Resistance Surveillance and Quality Control (RSQC) programme

Escherichia coli, mainly derived from urinary tract infections, has been included in the 100-strains studies several times since 1996. Resistance to commonly prescribed oral antibiotics for treatment of UTI were tested each year. Resistance to ampicillin varied between 17 and 23% with slightly higher figures since 1999. The same was true for trimethoprim resistance where resistance rates varied between 8 and 15%. Quinolone resistance (represented by norfloxacin) was below 5% but slightly increasing year by year, requiring special attention. In 2002, it was proposed by SRGA-M to use nalidixic acid instead of norfloxacin to screen for resistance to fluoroquinolones. It was anticipated that the screening result R would include all isolates that deviated from the wild-type population of *E. coli* with respect to fluoroquinolone susceptibility. This was shown to be true when analysing data from 6 laboratories who delivered data for both nalidixic acid and norfloxacin, and when adjusted breakpoints close to the wildtype populations were applied for norfloxacin.



Figur 4.15. Resistance rates (resistant isolates in percent of all Escherichia coli isolates) for six different antibiotics 1996-2002.
** Between 1996-2001quinoloneresistance was tested with Norfloxacin, from 2002 tested with Nalidixic acid.*

Data from the EARSS network

Escherichia coli derived from invasive infections (blood isolates) have been part of the European Antimicrobial

Resistance Surveillance System (EARSS) since the year 2001. Focus for the surveillance activities has been on resistance to betalactam antibiotics, especially occurrence of strains producing betalactamases with so called extended spectrum (ESBL), resistance to aminoglycosides and to fluoroquinolones.

Twentyone Swedish laboratories have taken part also in this surveillance and delivered data on more than 1500 blood isolates. A summary of the results is presented in Table 4.7 and compared with the 100-strains study on UTI isolates from 2001. Results were comparable between the two different data sets. Ampicillin resistance, caused by production of plasmid-mediated betalactamase (TEM-type most common) was slightly higher among blood isolates, yet these figures are low compared to most other countries in Europe. Aminoglycoside resistance in *Escherichia coli* is extremely rare in Sweden. Resistance to fluoroquinolones is still low but needs special attention to avoid a situation as in the south of Europe (Figure 4.16. Data from EARSS).

Table.4.7. E. coli from UTI and blood in Sweden 2001.

2001	RSQC, urine isolates		EARSS (Sweden), Invasive isolates	
Antibiotic	R (%)	Total (n)	R (%)	Total (n)
Ampicillin	20.3	3803	26.5	1512
Cefotaxime (3rd gen cef.)	Nt	Nt	0.5	2500
Aminoglycosides*	Nt	Nt	0.5	2759
Fluoroquinolone**	2.8 (nor)	3814	3.7 (cip)	2273

* gentamicin, netilmicin, tobramycin, ** norfloxacin, ciprofloxacin

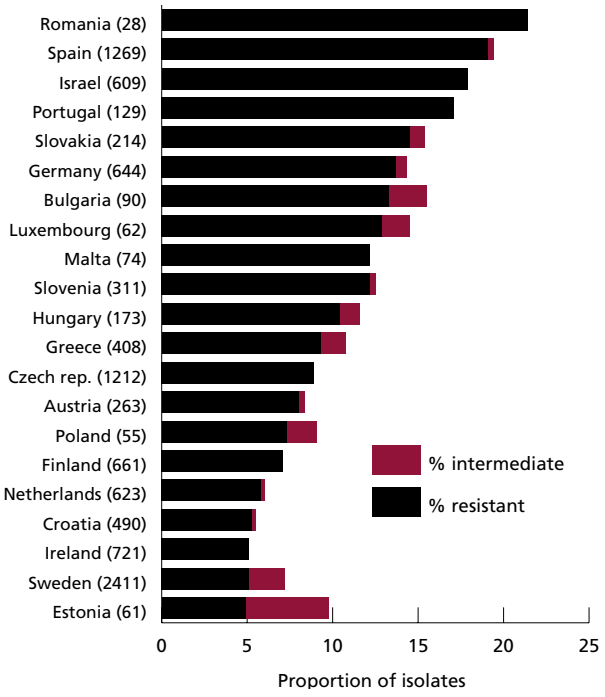


Figure 4.16. Resistance rates (% R and I) to fluoroquinolones in Escherichia coli in Europe 2002 (Data from EARSS).

Klebsiella pneumoniae

There are no data on *Klebsiella pneumoniae* for 2002.

Enterobacter species

There are no data on *Enterobacter* species for 2002.

Helicobacter pylori

Sentinel surveillance

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. Resistance to clarithromycin is less common (3%) but is increasing and has reached 7-9% locally. 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 isolats (n=100-600) from South-West of Sweden are presented in Table 4.8. (population app. 300 000).

Table 4.8. Helicobacter pylori, University Hospital MAS, Sweden 1994-2002,%R (- = not tested)

Year	Total number	Clarithro mycin	Metroni dazole	Tetra cycline	Amoxi cillin
1994	536	1.0	29.0	0.2	0
1995	588	2.9	32.1	0.1	0
1996	381	3.9	35.2	-	0
1997	331	7.7	39.8	-	0
1998	116	6.7	34.3	-	0
1999	149	6.1	33.1	-	0
2000	216	7.8	30.5	-	0
2001	188	8.8	40.2	-	0
2002	124	9	44.1	-	0

Salmonella and Shigella spp.

Sentinel surveillance

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.

Other gastrointestinal pathogens

Sentinel surveillance

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 quinolones is a major concern worldwide it is interesting to notice a small decline in quinolone resistance among *Campylobacter* isolates (Table 4.9). This is despite the fact that many laboratories perform resistance screening with nalidixic acid since 2001, which was expected to increase resistance figures with 25-30%.

Table 4.9. Campylobacter jejuni/coli, University Hospital MAS, Sweden 1991-2002, %R (n=100)

	Percentage of resistant strains (R%)			
Year	Nalidixic acid	Ciprofloxacin	Tetracycline	Erythromycin
1991	-	16	27	4
1992	-	17	30	2
1993	-	24	28	5
1995	-	22	27	4
1997	-	23	30	3
1998	-	34	33	2
1999	-	45	35	1
2000	-	55	45	1
2001	32	30	28	1
2002	29	28	30	0.5

Pseudomonas aeruginosa

There are no data on *Pseudomonas aeruginosa* for 2002.

Stenotrophomonas maltophilia

There are no data on *Stenotrophomonas maltophilia* for 2002.

Neisseria gonorrhoeae

Notifications according to the Communicable Disease Act

Gonorrhoea is a notifiable disease and in 2002, 505 clinical cases of the disease were reported. Clinical isolates were analysed at the Swedish Reference Laboratory for pathogenic Neisseria, Department of Clinical Microbiology, Örebro University Hospital.

In 2002, isolates from 120 patients were sent to the reference laboratory, representing 24% of the notified cases. Isolates from large city areas were underrepresented in this material. Susceptibility testing was performed according to standardized methodology using E-test for determination of MIC of bensylpenicillin (penicillin G), ampicillin, cefuroxime, cefixime, ceftriaxone, azithromycin, tetracycline, ciprofloxacin and spectinomycin. Production of beta-lactamase was detected using nitrocefin discs. Results for 2002 are compared with those from 1998, 2000 and 2001 in Table 4.10.

Table 4.10. Resistance rates (%) of Neisseria gonorrhoeae for nine antibiotics in 1998-2002 (data from the reference laboratory in Örebro).

	1998 (n=348)	2000 (n=131)	2001 (n=141)	2002 (n=120)
Penicillin G	32	42	38	48
Ampicillin	24	37	37	39
Cefuroxime	0	2	0	4
Cefixime	-	-	-	0
Ceftriaxone	0	-	-	0
Azithromycin	0	-	-	0
Tetracycline	32	52	56	54
Ciprofloxacin	10	28	43	48
Spectinomycin	0	0	0	0

(- = not analysed)

Neisseria meningitidis

Notifications according to the Communicable Disease Act

Invasive meningococcal disease is a notifiable disease. In 2002 47 clinical cases of the disease were reported. A total of 36 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 E-test for determination of MIC of bensylpenicillin, fenoxymethylpenicillin, cefotaxime, chloramphenicol, ciprofloxacin and rifampicin. Production of beta-lactamase was detected using nitrocefin discs.

None of the isolates produced beta-lactamase. Five isolates (14%) had reduced susceptibility to penicillin (MIC > 0.1 mg/L), but all were susceptible to cefotaxime. No resistance was seen to any of the other tested antibiotics.

Mycobacterium tuberculosis

During 2002 resistance against at least one of the five drugs (isoniazid, rifampicin, ethambutol, pyrazinamide or streptomycin) was reported in 42 patients i.e. 12.1% of the 347 patients with *M. tuberculosis* confirmed by culture. The situation is mainly the same as in 2000 and 2001. (Figure 4.17. and Table 4.11).

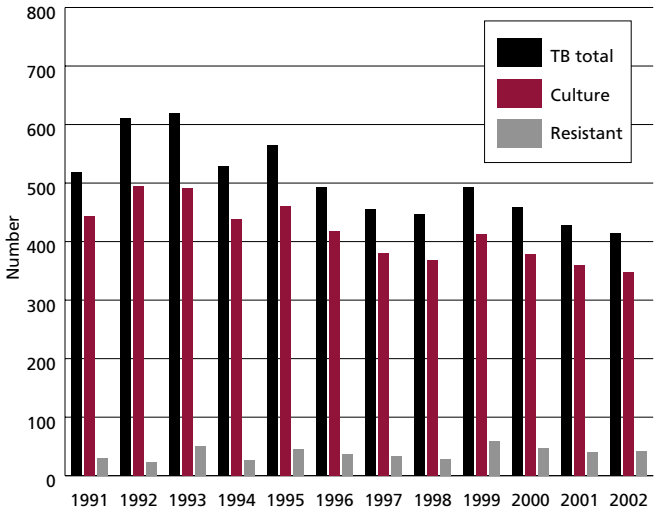


Figure 4.17. Tuberculosis in Sweden 1991-2002. Number of cases confirmed by culture and number of whom with reported drug resistance.

Table 4.11. Drug resistant tuberculosis 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.

Year of diagnois	1991-1997	1998	1999	2000	2001	2002
Total number	3 065	364	412	366	359	347
Any resistance total (%)	7.9	7.7	14.4	12.9	11.3	12.1
Resistance to one drug only (%)	5.5	5.8	10.0	9.6	5.3	7.5
Resistance to two or more drugs (%)	2.3	1.9	4.4	3.3	5.3	4.9
Isoniazid (%)	5.2	5.8	10.2	10.1	7.5	9.2
Rifampicin (%)	1.1	1.4	2.2	1.4	1.7	1.4
Ethambutol (%)	0.4	0.5	0.7	0.5	0.6	0.3
Pyrazinamid (%)	1.2	1.6	3.2	3.0	1.4	0.9
Streptomycin (%)	3.5	2.7	5.3	3.9	6.4	6.3
Isoniazid + rifampicin (MDR) (%)	0.9	1.4	1.7	1.4	1.1	1.2

Resistant TB was reported in 4.1% of Swedish born patients (4/98) and 15.3% of foreign born patients (38/249). Resistance to isoniazid was most common, observed in 9% of the patients (4,1% of Swedish borns and 11,2% of foreign borns), followed by Streptomycin in 6.3%.(1% of Swedish borns and 8,4% of foreign borns). Combined resistance against the two main drugs, isoniazid and rifampicin, defined as multidrug resistance (MDR) was reported in 4 patients (1,2%). Single resistance to rifampicin was reported in one patient (Figure 4.18).

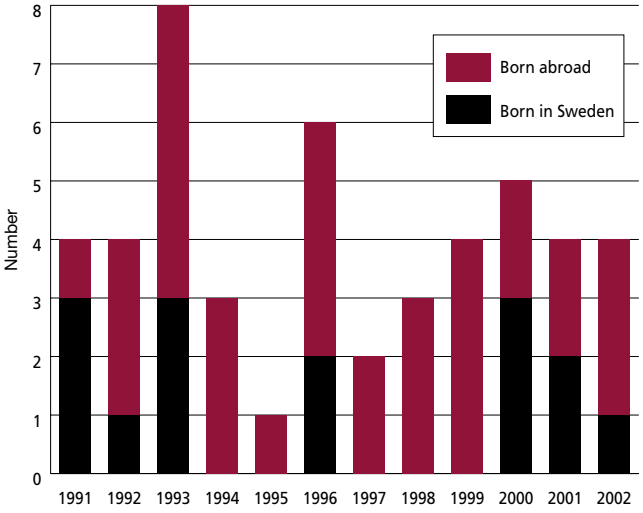


Figure 4.18. Annual number of cases with MDR-TB related to national origin.

Twelve patients diagnosed in 2002 with isoniazid resistant TB belonged to a cluster with identical fingerprints of RFLP (restriction fragment length polymorphism) comprising about 70 patients reported during 1996-2002. The majority of patients in this cluster are residing in Stockholm and most of them are of African origin. They developed TB after several years in Sweden and there are several factors indicating that infection in many cases has taken place in Sweden.

5. National and regional intervention projects

STRAMA

Because of the multi-faceted nature of the resistance problem and the need for a cross-sectional national forum, the STRAMA network was formed in 1994 (www.strama.org). All authorities and organisations concerned are represented in the network. The Swedish Institute for Infectious Disease Control has the principal responsibility for surveillance of resistance and is thereby a main collaborator on a national level. During the period 2000-2002 the network has been supported financially by the Swedish Government with 3 million SEK annually. In addition to the continuous regular activities to optimise antibiotic use and minimise resistance several specific projects have been performed within the STRAMA network. Some of these projects and related studies are presented below.

The STRAMA diagnosis-antibiotic prescribing survey 2002

In November 2000 a diagnosis-antibiotic prescribing survey was performed in five Swedish counties (Kronoberg, Östergötland, Dalarna, Uppsala and Jämtland) covering approximately 1.3 million inhabitants (14% of the total Swedish population). In November 2002 the survey was repeated in the same counties. During one week the physicians in about 140 primary care centers completed a one-page form for each patient with a complaint concerning an infection. The form contained information regarding age and sex of the patient, time of the day (office or out-of office hours), reported length of symptoms, if fever was present the last 24 hours, smoking habits, if diagnostics were used, diagnosis and if treatment with antibiotics was prescribed (drug and treatment length). It was also possible to indicate that the prescription was to be collected later if symptoms did not decay spontaneously.

In 2002, altogether 5377 forms were included in the preliminary analysis. Of these 71% concerned respiratory tract infections, 13% urinary tract infections, 10% skin and soft tissues infections and 6% other types of infections. The distribution between the main diagnostic groups was almost identical with the previous survey in 2000.

Gender and age distribution was also similar in 2000 and 2002, with about 60% of forms concerning women and 25% of the forms concerning children up to seven years of age.

In Figure 5.1. the number of cases per diagnosis, the proportion of these receiving an antibiotic and the proportion where any diagnostic tool was used, is shown.

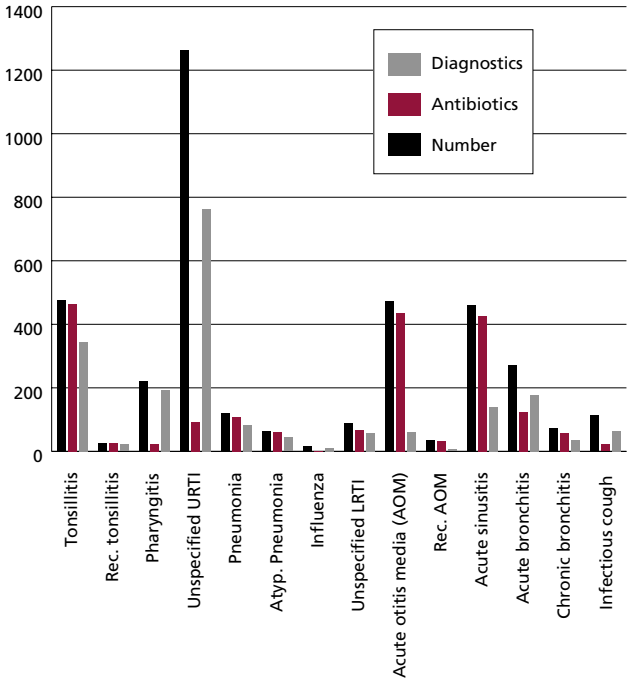


Figure 5.1. Use of antibiotics and diagnostics in respiratory tract infections. The number of cases per diagnosis, the number of these receiving an antibiotic and the number of cases where any diagnostics were used.

In Figure 5.2 the pattern of antibiotic use for a few selected respiratory tract infections are shown. Penicillin V is the dominating antibiotic. In tonsillitis it was used in 82% of cases. The number of recorded tonsillitis cases were fewer in 2002 (n=501) compared to 2000 (n=820) corresponding to 9% and 11% of the total number of cases respectively. In the period between the two surveys new national expert recommendations concerning treatment of acute tonsillitis were issued. Although small, this decrease in number of cases could be due to a change in consultation pattern, due to the new recommendations.

About six months before the 2000 survey new recommendations concerning treatment of acute otitis media were distributed. These guidelines recommended that in children above two years of age as an alternative to immediate antibiotic prescribing, three days of expectancy for a spontaneous decline of symptoms could be used. These recommendations seemed to have had little impact in the 2000 survey. A preliminary analysis of the 2002 data also shows limited impact. The percentage of cases with acute otitis media were about the same in both studies 9% in 2002 compared to 8% in 2000.Thus, so far the expectation that the new recommendations would possibly decrease the number of patients actually visiting a health center for acute otitis media (due to telephone advice that treatment with

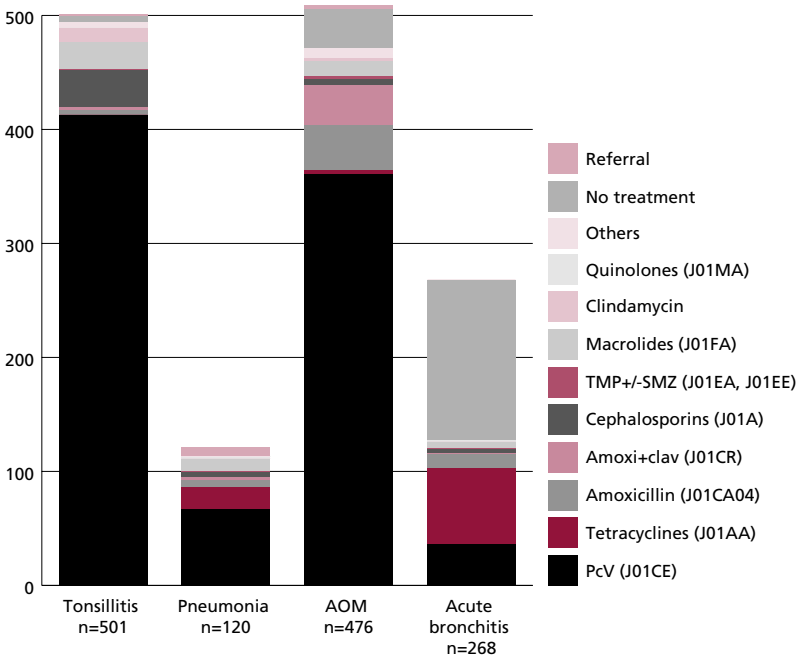


Figure 5.2. The pattern of antibiotics for some of the respiratory tract infections in the 2002 STRAMA Diagnosis-antibiotic prescribing study.

antibiotics would not be necessary) seem not to have been fulfilled.

Since 1990 the treatment recommendations for uncomplicated cystitis in women in Sweden have been to vary between alternative first-line drugs (trimetoprim, pivmecillinam, nitrofurantoin and a few selected cefalosporins). Quinolones have not been recommended as first-line drugs in cystitis. Trimetoprim was the dominating agent in the 2000 survey, followed by pivmecillinam and quinolones and a very limited use of nitrofurantoin. In the 2002 survey the quinolone use had decreased significantly, while the use of nitrofurantoin had doubled, although still at a low level (Figure 5.3).

In conclusion the similarity in patterns of diagnosis and use of antibiotics between the two surveys 2000 and 2002 strengthen the assumption that the collected material reflects the actual pattern of diagnosis and antibiotic use in primary care in the included counties. The included counties were chosen so as to reflect regions with higher and lower use of antibiotics. There are however no reasons to assume that the pattern would be extremely different in other parts of Sweden. These studies confirm that new treatment recommendations are difficult to implement (e.g. treatment strategies for otitis media) but that long term continuous efforts as in the case of not using quinolones for uncomplicated cystitis in women could change prescribing patterns. This is in line with previous research finding that changes including substitution of one therapy for another are easier to establish than a recommendation not to treat.

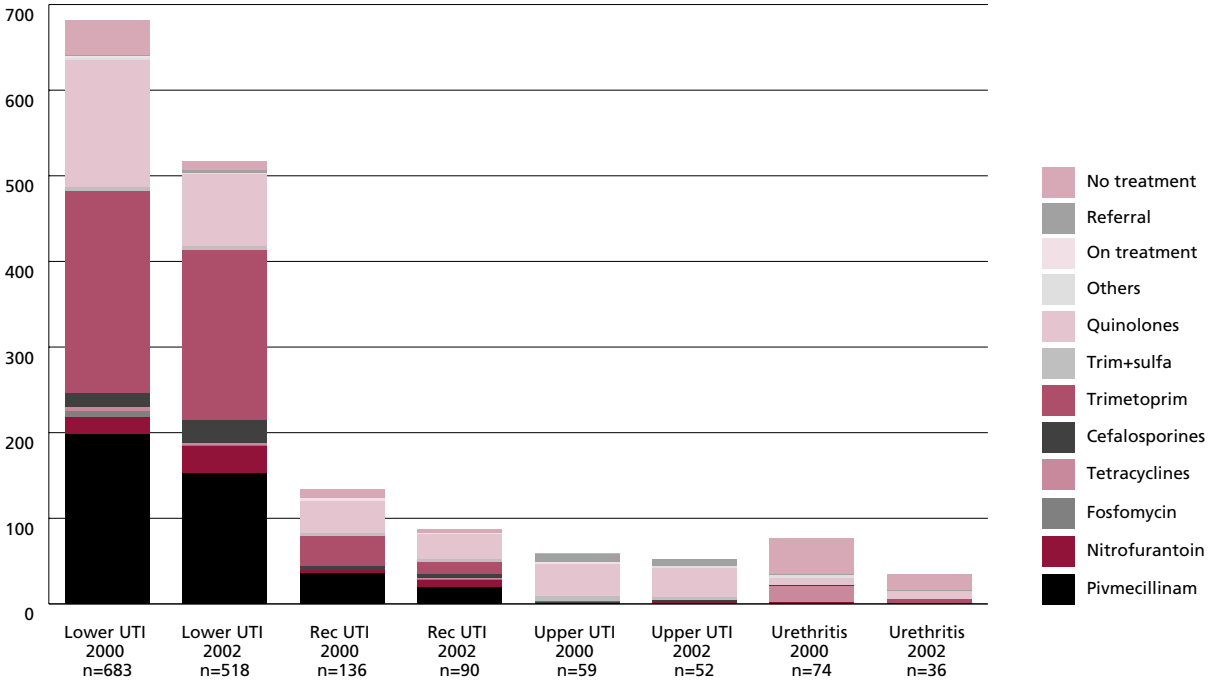


Figure 5.3. The pattern of antibiotics for urinary tract infections in the 2000 and 2002 STRAMA Diagnosis-antibiotic prescribing study.

ICU-STRAMA

ICU-STRAMA was established in 2000 within the framework of STRAMA. The aim of ICU-STRAMA is to develop a programme for the coordinated collection of information about antibiotic policy within Intensive Care Units. The purpose is also to use these data ("data for action") to e.g. optimise infection control, and to prevent the emergence of antibiotic resistant strains within the ICU. The project has a local perspective and has become a resource for local initiatives aimed at promoting more appropriate use of antibiotics and improved infection control. The incentive for participating has been the possibility of receiving statistical analyses of antibiotic consumption, antibiotic resistance and quality of infection control for each individual ICU. Data about each participating ICU has been made available on the home page. As the database has been created as part of a research project, the identity of the individual ICUs is not made public.

A web-based tool has been developed and all participating ICUs can view their own data in relation to other ICUs on Internet within 24 hours from submitted. Statistical analysis will also be published.

Examples of regional STRAMA activities

Interactive learning

Practical clinical problems concerning optimal use of antibiotics were discussed in meetings attended by some 250 physicians in the county of Halland. After presentation of a patient's history the discussions focused on appropriate diagnosis and effective treatment of different infectious diseases. Among topics covered were sore throat, middle ear infections, Lyme borreliosis, urinary tract infections and diarrhoea from Clostridium difficile. Specialists were available for comments at any moment. An electronic device for interactive learning ("mentometer") was used. This technique is a powerful tool for getting a quick and anonymous response from an audience. The sessions were completed by a few questions concerning evaluation. In conclusion this type of educational activities were much appreciated by the attendant physicians.

Analysing and feed-back of prescribing data

Surveillance of prescribing data can sometimes be used for targeted intervention. As an example the prescribing pattern of topical mupirocid ointment was analysed in the county of Halland. It turned out that only a few physicians were responsible for the majority of prescriptions on this ointment. Some of these prescribers attended the above mentioned local educational STRAMA-activity, where the proper use of this antibiotic was discussed. The desired use in MRSA-carriers only was pointed out, without mentioning why or by whom it has been recently prescribed. Within one month the use of mupirocin in the county was significantly reduced, probably as a consequence of the information at this single occasion.

Education of parents with children in day-care centres

75% of all absence from day-care centres and 10-20% of all visits in primary care centres are caused by respiratory tract infections, where >50% are due to uncomplicated common colds. Consumption of antibiotics among children aged 0-6 years varies widely between the communities in the area that was studied. In Vellinge, a community with 30.000 inhabitants, 1.600 children between 1-5 years attend 30 day-care centres and 200 children are taken care of by "day-mothers" in their private homes. There are 2 primary care centres with altogether 9 general practitioners. Education of parents and staff was offered at evening courses by the local general practitioners and the project leader, an ENT-specialist.

The number of medical visits and antibiotic consumption in children 0-6 years was registered before and after the intervention took place and compared to similar groups in Malmö community. The number of doctor's visits and antibiotic consumption at Vellinge decreased by 14% and 15% respectively in the first period of the study compared to the same period previous year. At the same time the number of doctor's visits at Malmö increased by 2%. During the second period of the study medical visits again increased by 2% at Vellinge but there was a further decrease in antibiotic consumption with 11%. Comparable figures for Malmö were a decrease in the number of medical visits by 14% and an unaltered antibiotic consumption. The quota between number of medical visits and number of prescriptions shows fewer prescriptions/visit for children in Vellinge during this period than the year before and fewer than in Malmö. Despite the fact that Vellinge still has a high number of prescriptions for children 0-6 years compared to other communities in the area, there was a decrease during the study period compared to the same period the year before.

Despite the limited intervention, approximately 50% of the parents took part in it, a definite decrease in antibiotic prescriptions was found. By engaging local doctors in parental education at day-care centres you cannot only increase the parents' ability to evaluate the symptoms of the child but also make the doctors aware of their prescription habits.

Quality aspects on antibiotic usage in a Swedish university hospital

In a point prevalence study 46 wards at Huddinge University Hospital were visited once during the period April -June, year 2000. Patients with antibiotic treatment were identified and the medical records were reviewed according to a protocol. Diagnoses as documented in the medical records were registered for treated patients, oral information was recorded for patients on prophylaxis.

Altogether 236/723 (33%) of the patients were on antibiotics; four had both treatment and prophylaxis, 177 treatment only and 54 prophylaxis only. For one patient it was impossible to determine whether it was treatment or prophylaxis. At least one indication for antibiotic treatment was documented in the medical record for 158/181 (87%) of the treated patients. In another 7 patients (3,9%) oral information was available from the responsible nurse. Non-specific conditions such as "high CRP", fever of unknown origin, post-operative difficulties etc were the indications for treatment of 11% of the patients.

Antibiotic therapy was initiated within two days of admission in 113 and after more than two days in 68. The rate of cultures before treatment were 68% and 72%, respectively.

Thirty patients were on surgical prophylaxis, among whom 13 (43%) still were on prophylaxis at least one day post-operatively. Medical prophylaxis were given to 25 patients with defined immune-deficiency (19 of whom were transplanted).

A distinct documented indication for antibiotic treatment was missing in 24% of all treated patients. Documentation of tentative, or verified diagnosis, is a prerequisite for the discussion of adequacy of empiric treatment. Routines can be improved, maybe with the help from computerised medical records.

Even if rates of cultures before treatment around 70% can be considered acceptable, the rate can still be improved particularly among patients admitted > 2 days before treatment, where risk for infection with nosocomial, and thus more resistant, strains is increased.

The proportion of patients on prolonged surgical prophylaxis seemed, as in other studies, unacceptably high. Review of clinical routines according to guidelines recently published by the Swedish Medical Products Agency, is necessary.

The proportion receiving medical prophylaxis was surprisingly high. Since many of these patients receive quinolones or trimethoprim-sulfametoxazole, careful attention should be paid to the development of resistance among Gramnegatives in these units.

South Swedish Pneumococcal Intervention Project, SSPIP

Sweden has for many years reported low frequencies of PNSP, but in the southernmost county, Skåne, the rates increased during the late 1980s, to about 8-10% in 1992, while the rest of the country still reported unchanged low frequencies. Put in the perspective of international experiences where a rapid increase of PNSP occurred when the frequency reached this level, the situation in Skåne County lead to the initiation of an intervention project (South Swedish Pneumococcal Intervention Project) in 1995, aiming at limiting the spread especially in preschool children. In the project, traditional communicable disease control measures are combined with actions aiming at reducing the use of antibiotics. This county has for long had the highest utilisation of antibiotics in Sweden, especially of macrolides and broad spectrum antibiotics.

In short, all individuals with a culture yielding penicillin-resistant pneumococci with MIC ≥ 0.5mg/L for penicillin (PRP) regardless of resistance to any other antibiotics in Skåne County have since 1995 been reported to the regional Centre of Communicable Disease Control (CCDC). Whenever an individual with a clinical infection due to PRP (index case) is identified, nasopharyngeal cultures are obtained from family members and other close contacts to identify asymptomatic PRP carriers (contact cases). All carriers are followed weekly with nasopharyngeal cultures at the local primary health care center until two consecutive cultures yielding no growth of PRP have been obtained. If the index case is a child attending any form of group day care, nasopharyngeal cultures are obtained from the other children and staff members at that day care group. Pre-school children are denied out of home day care until they are PRP negative.

During the period July 1995 - June 2001 2 269 PRP carriers (1 865 individuals) have been registered at the CCDC in Skåne County. Of the 2 269 PRP cases, 40% were index cases and 60% contact cases. 1 704 of the PRP cases were children aged 1-6 years (75%). Seventy-one per cent of these children attended day care centers, 6% attended family day care and 23% were cared for at home.

During the project the frequency of PRP (index cases) and PNSP (from clinical nasopharyngeal cultures) has been evaluated. Cultures taken at contact tracing were excluded. Since the start of the project the average frequency of index cases with PRP (= the number of index cases with PRP divided by the number of pneumococci found in clinical nasopharyngeal cultures) has been rather stable, 2-3% each season. Also the average frequency of cultures positive for PNSP have been stable, around 7% although unevenly distributed in the county. In the southwestern part of the county where the epidemic seems to have started

the frequency of PNSP has remained high during the entire project period, while the frequencies have remained low in the northern and the eastern part of the county.

In parallel, the use of antibiotics in out-patient care in Skåne County has decreased during the six seasons, especially in children aged 0-6 years. The use of macrolides among children aged 0-6 years was halved. Even though the decreased utilisation of antibiotics was seen in all municipalities, the municipalities with the highest utilisation in 1995-1996 still had the highest utilisation in 2000-2001. Those municipalities were all situated in the southwestern part of the county.

Whether the decreased spread of PNSP in Skåne County is a result of the actions of the SSPIP or of the decreased utilisation of antibiotics in the county or both is difficult to tell since these actions were started simultaneously. In other countries actions against unnecessary utilisation of antibiotics has been the only measure to combat the spread of PNSP, in most cases with little success, probably in part caused by the fact that the actions have been initiated in a much later phase of spread of PNSP with much higher frequencies of PNSP.

Appendix 1 – Abbreviations

AST	Antibiotic susceptibility testing
ATC	The Anatomical Therapeutic Chemical classification system
DDD	Defined daily dose
DST	Drug susceptibility testing
EARSS	European Antimicrobial Resistance Surveillance System
ICU	Intensive care unit
MDR	Multidrug resistance
MIC	Minimal Inhibitory concentration
MRSA	Methicillin resistant Staphylococcus aureus
PFGE	Pulsed field gel electrophoresis
PNSP	Penicillin non-susceptible pneumococci, MIC ≥ 0,12 mg/L
PRP	Penicillin non-susceptible pneumococci, MIC ≥ 0,5 mg/L
RSQC	Resistance Surveillance and Quality Control Programme
SRGA-M	The Swedish Reference Group of Antibiotics- subcommittee on Methodology
SSPIP	South Swedish Pneumococcal Intervention Project
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 2002.

	Age (years)				
County	0-6	7-17	18-64	> 65	Total
Blekinge	10 061	20 769	89 605	29 440	149 875
Dalarna	17 994	41 616	162 778	54 248	276 636
Gotland	3 778	8 939	34 379	10 285	57 381
Gävleborg	17 944	39 738	164 733	54 597	277 012
Halland	21 236	43 248	165 197	48 870	278 551
Jämtlands	8 154	18 723	75 643	25 427	127 947
Jönköping	24 437	50 987	192 780	59 767	327 971
Kalmar	15 068	34 833	137 469	47 257	234 627
Kronoberg	12 320	25 823	105 765	33 070	176 978
Norrbotten	16 926	36 698	153 241	46 767	253 632
Skåne	83 290	162 297	698 736	200 767	1 145 090
Stockholm	150 514	252 703	1 187 642	259 608	1 850 467
Södermanland	18 283	39 009	154 472	47 242	259 006
Uppsala	22 484	44 806	188 748	42 617	298 655
Värmland	18 117	39 043	161 634	54 625	273 419
Västerbotten	17 553	37 910	155 267	44 500	255 230
Västernorrland	16 050	34 077	144 820	49 372	244 319
Västmanland	17 955	38 541	155 706	46 710	258 912
Västra Götaland	110 902	219 252	921 619	256 457	1 508 230
Örebro	19 613	39 474	164 693	49 632	273 412
Östergötland	29 275	60 470	251 156	72 537	413 438
All counties	651 954	1 288 956	5 466 083	1 533 795	8 940 788

Table App 2.2. Population of Sweden 1997-2002 (December 2002)

	1997	1998	1999	2000	2001	2002
Population (x1000)	8846	8851	8861	8882	8908	8940

Table App 2.3. Denominator data from the microbiological laboratories.

	Catchment area and population		Number of analyses						Number of pos. Cultures					
Laboratory	Catchment area	Catchment population (x1000)	Blood (pair of bottles)	Cerebro-spinal fluid (CSF)	Nasopharynx	Ceneral culture	Screen MRB	Faeces SSYC	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*E coli*	*Enterococcus sp*	*Enterococcus faecalis*	*Enterococcus faecium*
Borås	SW Götaland	273	9432	165	5108	6574	735	6886	4290	1009	7354		1984	213
Eskilstuna	Södermanland	257	5839	126	6049	8311	1023	4615	3293	929	6506		2152	95
Falun	Dalarna	278	7726	158	2097	7274	520	4103	3277	428	6222		1379	163
Gävle	Gävleborg	277	6611	176	2435	6327	678	3532	3156	459	5901		1528	175
Göteborg	V Götaland	700	24191	1162	3952	19053	7384	15371	24910	5605	102003		1648	673
Halmstad	Halland	275	5680	96	3408	8095	11210	5876	2723	566	5785		1151	254
HS, Stockholm	Stockholm	900	20220	900	19030	27582	4967	13584	10178	3267	17859		3658	649
Jönköping	Jönköping county	340	7974	142	2192	10561	588	5630	3521	512	601		509	160
Kalmar	Kalmar county	235	5664	240	4882	6969	2620	5962	3594	990	7686		2047	229
Karlskrona	Blekinge	152	3275	77	1045	4793	1353	2666	2054	30	3799		1070	164
Karlstad	Värmland	274	10757	134	779	10308	3640	4455	4796	293	6587		1950	390
Kristianstad	NE Skåne	203	6428	105	5336	11035	1340	8188	5031	958	7640		2217	264
KS, Stockholm	Stockholm	900	21709	2214	29662	36100	10000	13989	11850	3739	19195		276	600
Linköping	Östergötland	412	12467	456	5040	17871	21357	7943						
Lund	Skåne	520	15000	1200	10700	20500	11000	13900	7841	2477	16847		4942	277
Malmö	Skåne	510	12502	250	4629	13836	7174	13460	6587	1367	13003		4114	384
Medilab	Stockholm		0	0	7839	3160		4771	1803	747	4219	1054		
St Göran	Stockholm+ national		3530	136	5887	9421	1272	7467	3155	895	15260		2221	388
Skövde	Skaraborg	260	8823	124	2628	5696	689	4793	3362	584	8887		20	5
Sunderby (Luleå)	*Norrbotten*	*260*	*5380*		*3351*	*6297*		*4261*						
Sundsvall	Västernorrland	245	7323	115	3706	9769	2877	4824	3657	697	7779	2371		
Uddevalla	V Götaland	280	10636	171	1906	7901	761	5716	4044	387	10084		2992	266
Umeå	Västerbotten	255	6920	580	1710	8717	2000	4850	2968	301	6613		173	157
Uppsala	Uppland	300	11510	763	4314	14379	2326	6558	3945	821			43	34
Umeå	Västerbotten	255	6920	580	1710	8717	2000	4850	2968	301	6613		173	157
Visby	Gotland	58	2458	39	4085	2958	200	1283	1400	632	2156		510	80
Västerås	Västmanland	265	6916	197	3552	7823	659	5871	3282	664	7183		2128	123
Växjö	Kronoberg	190	3604	80	1772	4989	1231	3715	2378	360	4894		698	97
Örebro	Örebro county	274	11839	249	8483	11940	2057	4474	5707	1182	6911		2988	247
Östersund	Jämtland	128	4185	277	2241	5557	893	2002	2674	459	4959		1414	120

Italics indicate that data is not available for year 2002. Data from 2000 is presented instead.
In retrospective analysis using laboratory data, missing data is replaced by data from the nearest available year.

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. The system is recommended by the WHO.

To facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of Apoteket AB are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway. Due to a reclassification in the ATC classification system, methenamine is since 2000 included in the ATC group J01. For historical comparisons we have excluded methenamin from the presentations in this report.

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.

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

Table Appendix 3.1. ATC-codes and drug names in Sweden 2002.

J01AA	Doxycycline, lymecycline, oxytetracycline, tetracycline,
J01BA	Chloramphenicol
J01CA	Ampicillin, pivampicillin, amoxicillin, bacampicillin, pivmecillinam, mecillinam, piperacillin
J01CE	Bensylpenicillin, phenoximethylpenicillin
J01CF	Dicloxacillin, cloxacillin, flucloxacillin
J01CR	Amoxicillin and enzyme inhibitor, piperacillin and enzyme inhibitor
J01DA	Cefalexin, cefoxitin, cefuroxime, cefadroxil, cefotaxime, ceftazidime, ceftriaxone, cefixime, cefepime, cefpodoxime, loracarbef, ceftibuten
J01DF	Aztreonam
J01DH	Meropenem, imipenem
J01EA	Trimethoprim
J01EE	Sulfamethoxazole and trimethoprim, sulfadiazine and trimethoprim
J01FA	Erythromycin, roxithromycin, clarithromycin, azithromycin
J01FF	Clindamycin
J01GB	Tobramycin, gentamicin, amikacin, netilmicin
J01MA	Ofloxacin, ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin
J01XA	Vancomycin, teicoplanin
J01XC	Fusidic acid
J01XD	Metronidazole, tinidazole
J01XE	Nitrofurantoin
J01XX	Fosfomycin, methenamine

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 suseptibility 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 (MRSA, VRE) and in other instances by MIC-determination using broth- or agar-dilution or with Etest (betalactam resistance in pneumococci, chromosomally mediated betalactam resistance in *Haemophilus influenzae*), and still in others by methods for enzyme detection (betalactamase detection in *Haemophilus influenzae*, Neisseria gonorrhoeae and others).

Phenotypic methods (disk diffusion or MIC) are always performed on one of two basic media for AST, PDM Antibiotic Sensitivity Medium from Biodisk, Sweden, and ISA (IsoSensitest Agar) from Oxoid Ltd, UK. For these two media and their corresponing antibiotic paper disks, interpretive criteria for SIR-categorization are provided by the SRGA-M. They are regularly updated and available through the web-site www.srga.org.

Internal and external quality assurance and quality control of susceptibility testing is performed by each laboratory. Internal quality control includes using international QC strains regularly (every day, once a week) and analysing data in relation to national guidelines. Validation of susceptibility testing can also be done by histogram analysis of consecutive clinical isolates (see www.srga.org) .

External quality control is often done by participation in UK-NEQAS and/or other international programs, whereas quality assurance is one of the features of the Swedish "100-strains or RSQC 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 (SFS 1988: 1472). With the exception of certain sexually transmitted infection (STI), both the clinician caring for a patient with a notifiable disease (clinical notification) and the laboratory diagnosing the pathogen causing the disease (laboratory notification) are obliged to notify. This double notification significantly enhances the sensitivity of the surveillance system.

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

Infections (or carriage) with four different antibiotic resistant pathogens are included in the list of notifiable diseases. Penicillin-resistant *Streptococcus pneumoniae* with Penicillin G MIC ≥ 0.5 mg/L (PNSP) 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 latter three pathogens have previously been notified through the "Voluntary Laboratory Notification" from 1996.

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 and PNSP 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 (every two weeks for MRSA) on the SMI Internet homepage (http://www.smittskyddsinstitutet.se) and yearly in "Communicable Diseases in Sweden – the Yearly Report of the Department of Epidemiology" and in this report. Data on drug-resistant TB is also annually published in "the Swedish Tuberculosis Index".

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

Voluntary laboratory reporting

A system for individual, anonymised case reporting of certain very rare (or not yet identified) pathogen-resistance combinations is under construction. Examples of pathogens suggested for this system are given in Table I. 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 Quality Control programme (RSQC surveys) further developed into ResNet 2002

In 1994 a model for the concomitant surveillance of antimicrobial resistance and quality assurance of antimicrobial susceptibility testing was devised. In Sweden there are 30 microbiological laboratories, each covering a county (or part of county) of Sweden. The demographics of the laboratories, their geographic areas and their corresponding populations are well characterized. The antimicrobial susceptibility testing methods of the laboratories are standardized through the combined work of the SRGA-M (Swedish Reference Group of Antibiotics – subcommittee on Methodology) and the 30 laboratories (see also Appendix 5).

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.

Development of ResNet

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

From 2002 a web-based newly developed software (ResNet) will receive the data from the laboratories and, following approval or registered data by one of two web administrators, instantly displayed it in the form of resistance frequencies on the geographical areas on maps of Sweden. Behind each resistance frequency the distribution of zone diameters or MICs together with the relevant demographic data are directly accessible. The software will accept both MIC and zone distributions of well-characterized data sets, and the graphs presenting the data are designed to include all necessary information in order to be used on their own (in presentations etc). Recently the software has been updated to display also the quantitative data of invasive isolates which form the Swedish part of the EARSS network (see below).

EARSS

EARSS, funded by DG SANCO of the European Commission, is an international network of national surveillance systems, collecting comparable and validated antimicrobial susceptibility data for public health action. EARSS performs on-going surveillance of antimicrobial susceptibility of invasive infections of *Staphylococcus aureus, Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis/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 2001 27 countries provide susceptibility data regularly. Information about EARSS, as well as a database yielding information about the susceptibility results for each country, year and pathogen, is available through a web-site (www.earss.rivm.nl).

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

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

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

Sentinel surveillance

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

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

Appendix 6 – Recent publications

3.1 Use of antibiotics

Cars O, Mölstad S, Melander A. Variation in antibiotic use in the European Union. The Lancet 2001;357:1851-53.

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.

Österlund A, Edén T, Olsson-Liljequist B, Haeggman S, Kahlmeter G, and the Swedish study group on Fusidic acid-resistant *Staphyloccous aureus*. Clonal spread among Swedish children of a *Staphylococcus aureus* strain resistant to fusidic acid. Scand J Infect Dis 2002;34: 729-34.

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Appendix 5

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Contributors

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