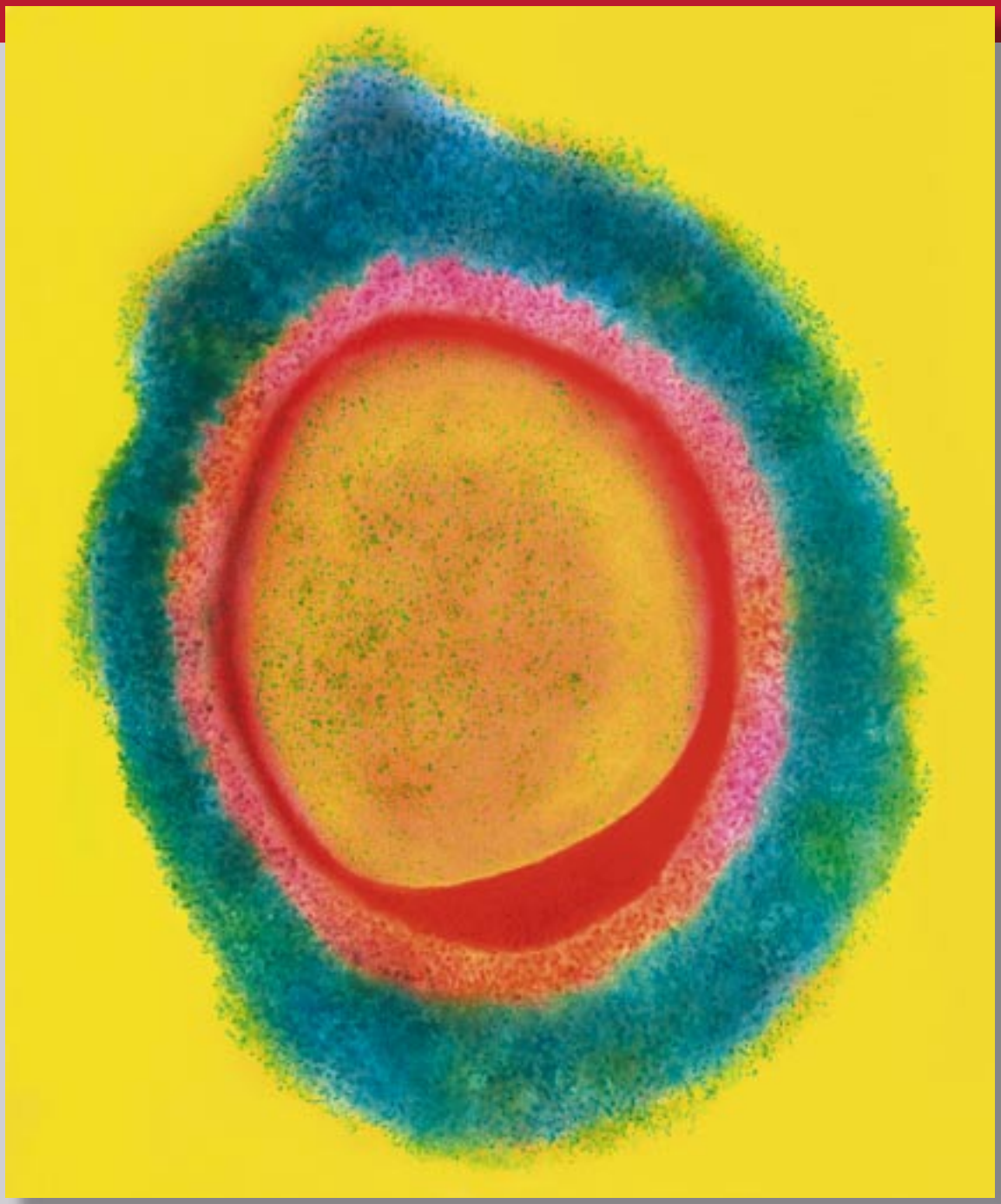
SWEDRES 2001

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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Cover photo: Resistant Staphylococcus bacterium. Photo: KARI LOUNATMAA / SCIENCE PHOTO LIBRARY

1. Preface

Antimicrobial resistance is an increasing threat to human health. Although, the prevalence of resistant bacteria in Sweden is low in comparison to many other countries, international trends are alarming and bacteria and their resistance genes do not respect geographical borders.

The increasing prevalence of penicillin non-susceptible pneumococci in Southern Sweden in the early 1990s became a warning signal and initiated national coordination of efforts to prevent further spread. As monitoring antibiotic utilisation and surveillance of resistance are essential tools in this work, a national system has successively been built for surveillance of resistance and a national network, STRAMA, is monitoring the antibiotic utilisation pattern and coordinates efforts to optimise antibiotic usage.

This first yearly report presents the structure of those systems as well as historical and current data that has been collected and examples of interventions that have been performed.

Stockholm October 2002

2. Summary

Use of antimicrobials

In Sweden, as compared to many other countries, detailed and extensive information on drug utilisation is available. Since 1975, the National Corporation of Swedish Pharmacies regularly produces sales statistics on medicines. Data are given both as the number of prescriptions and as defined daily doses (DDDs) per 1000 inhabitants per day. In this report, representative examples on the utilisation pattern of antibiotics are presented. Approximately 90% of all antibiotics are prescribed for out-patients. Between 1986 and 1992, the antibiotic use in out-patients increased from 12.8 DDD/1000/day to 17.5 DDD/1000/day (42%) without obvious medical reasons. The initiation of the STRAMA network and other initiatives, most probably led to an increased awareness among health care workers and the general public of the need to reduce inappropriate antibiotic prescribing to minimise resistance. Between 1994 and 1997, a decline of the antibiotic use in out-patients was seen and the level of use has then stabilised although on a higher level than seen in 1986 and earlier. The total out-patient antibiotic use in 2001 was 14.38 DDD/1000/day.

There is a strong tradition in Sweden to use therapy directed towards the most probable etiological agent(s) of the infection. This is illustrated by the fact that the most commonly used antibiotic in Sweden is beta-lactamase sensitive penicillins (almost exclusively penicillin V). This group accounted for 33% of total DDDs, followed by tetracyclines (23%) in 2001. The relation between various antibiotic groups has been relatively stable over the years, although a marked reduction is seen for macrolides. This decrease occurred in all age groups, but was most prominent in children aged 0–6 years where the reduction of macrolide use between 1993 and 2001 was approximately 60%. The overall reduction of antibiotic usage in this age group during the same time period was approximately 40%. Also the utilisation of penicillins with extended spectrum has been reduced, except in patients above 60 years of age. In elderly people, aged 80–99 years, an increase in total antibiotic use was noted between 1997 and 2001, which mostly concerned penicillins with extended spectrum, penicillinase-resistant penicillins and fluoroquinolones (in men).

Data on antibiotic sales to hospitals are available from 1985. That year, the total utilisation was 2.1 DDD/1000/day followed by a decrease to 1.3 DDD/1000/day in 2001. Part of this reduction is caused by a major change in health care structure in 1992, when more than 30,000 beds were transferred to the municipalities where antibiotic use is registered as out-patients prescriptions. In 1985, penicillins with extended spectrum constituted the largest group with 0.44 DDD/1000/day. In 2001, cephalosporins (0.24 DDD/1000/day) was instead the largest antibiotic group used in hospitals.

Antimicrobial Resistance

In Sweden, routine susceptibility testing of clinical isolates is performed using well-standardised methods. The Swedish clinical microbiology laboratories, in collaboration with the Swedish Reference Group for Antibiotics and its subcommittee on methodology (SRGA-M) have successfully standardised the disk diffusion method. Each laboratory

performs internal and external quality assurance and control. A national programme for surveillance of antibiotic resistance has been designated and rests currently on:

1. The statutory notifications regulated in the Communicable Disease Act;
2. Voluntary reporting of some specified unusual or newly identified resistances;
3. The long tradition of combined resistance surveillance and quality control carried out by the Swedish microbiology laboratories, the RSQC programme;
4. The Swedish commitment to report resistance in certain bacteria isolated from invasive disease to the European Antimicrobial Resistance Surveillance System (EARSS);
5. Sentinel surveillance of resistance in certain pathogens by single dedicated laboratories;

Streptococcus pneumoniae with reduced susceptibility to penicillin has been well below 5% for many years with the exception of the Skåne Region in southern Sweden, where the rate increased in the early 1990s to about 8–15%. Since 1996, infection and carriage due to *S. pneumoniae* with reduced susceptibility to penicillin has been notifiable according to the Communicable Disease Act. In recent years, the dominant epidemic clone in Sweden has been of serotype 9V. Most of the cases have been children, but small peaks have further been noticeable in the age group 30–39 years and ≥ 70 years. Infection and colonisation with methicillin-resistant *Staphylococcus aureus* (MRSA) is included in the Communicable Disease Act from year 2000. The prevalence of MRSA in Sweden is still low compared to many other European countries. In the year 2001, 0.8% of invasive isolates of *S. aureus* was MRSA. During that year 2001, a total of 429 cases of MRSA were reported of which 69% were considered to have acquired MRSA within Sweden. Vancomycin-resistant *Enterocoocus faecium* and *Enterococcus faecalis* were made notifiable according to the Communicable Disease Act in the year 2000, and the number or reported cases remains very low. For *Streptococcus pyogenes*, summarized data on the national level for the years 1994–2001 shows a doubling of the tetracycline resistance rates (6–12%) and declining erythromycin resistance rates (below 3% in 2001). Beta-lactamase production in *Haemophilus influenzae* is approximately 10%, and has remained constant during the years 1994–2001. *Escherichia coli*, mainly derived from urinary tract infections, have been tested since 1996. Resistance to ampicillin has varied between 17 and 23%, and resistance to trimethoprim between 8 and 15%. Among *Enterobacter species*, resistance to cefuroxime and cefotaxime was 35 and 23%, respectively in 1997. For *Pseudomonas aeruginosa*, an increase in the number of isolates resistant to fluoroquinoloes have been noted. Drug resistance in tuberculosis varied between 5 and 10% during the 1990s and increased to 14% in 1999. Multidrug resistant tuberculosis has only been reported in 1% of the patients.

Interventions to minimise resistance

In order to prevent further development of resistance, several interventions have been initiated in Sweden. A national network, STRAMA, was formed in 1994. This network consists of a national co-ordinating committee and 25 regional groups. Within this network, authorities, professional organisations and specialists from different medical fields have been involved in many national or local projects to describe, analyse and influence prescribing practices. Recent examples of such activities are a diagnosis-antibiotic prescribing survey performed in five counties describing antibiotic prescribing in more that 7000 out-patients with infections and educational outreach sessions by pharmacists in collaboration with general practitioners using educational material of fictitious cases. To optimise antibiotic usage in intensive care units (ICU) a special nation-wide project, ICU-STRAMA, was initiated for the coordinated collection of information about antibiotic use, resistance and infection control measures. A policy program for detection and prevention of dissemination of multiresistant bacteria in Swedish health care institutions has been published. Interventions have also been directed against the spread of specific pathogens. For example, an Expert Committee to identify intervention strategies to limit the spread of pneumococci with reduced susceptibility to penicillin was formed in 1994 by the National Board of Health and Welfare. Large-scale attempts to implement these recommendations started in March 1995. In the Västra Götaland Region, where an increase in the incidence of MRSA was observed in 1999-2000, an action plan for MRSA in municipality health care and primary care has been published.

3. Use of antimicrobials

In Sweden as compared to many other countries detailed and extensive statistics on drug utilisation are available. Data are given both as number of prescriptions and as defined daily doses (DDDs) per 1000 inhabitants per day. Specific information on data collection methods is given in Appendix 3. In this report representative examples on the utilisation patterns of antibiotics are presented.

Out-patient care

Recent statistics show that more than 90% of antibiotics are prescribed for outpatients, of which approximately 50% emanate from primary care [Apoteket AB, 1990-2000]. During the period 1974 to 1986 the antibiotics utilisation was relatively constant. Between 1986 and 1993 there was an increase of antibiotic consumption from about 12 to 18 DDD per 1000 inhabitants per day (DDD/1000/day), an increase by almost 50% (Figure 3.1). Since then, there has been a decrease by almost 20% [Mölstad S et al, 1999]. The figure for 2001, on a national level, were 14.4 DDD/1000/day. For certain antibiotics and age groups the reduction was even more prominent (see below).

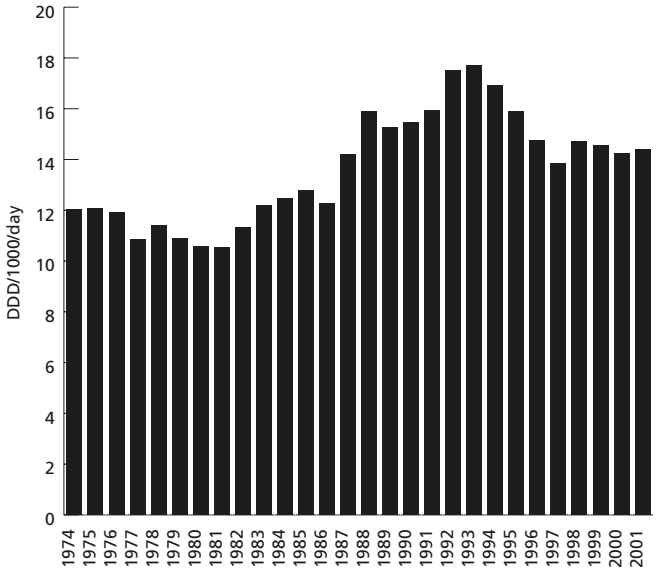


Figure 3.1. Antibiotic utilisation in Sweden (ATC group J01 excluding methenamine), DDD/1000/day, out-patient care, 1974 – 2001.

In Sweden, there is a strong tradition to use therapy directed to the most probable etiological agent(s) of the infection. This is illustrated by the fact that the most commonly used antibiotic is beta-lactamase sensitive penicillins (ATC group J01CE, almost exclusively penicillin V). This group accounted for 33% of total DDDs, followed by tetracyclines (23%) year 2001 (Figure 3.2). The relation

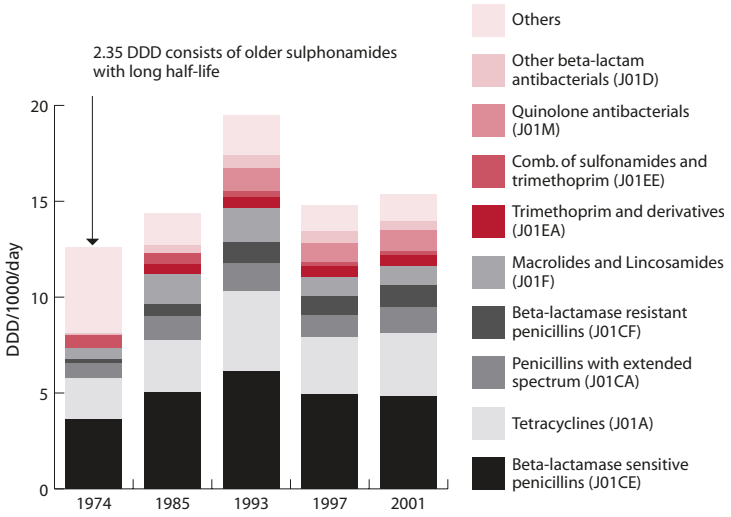


Figure 3.2. Utilisation of different antibiotic groups in out-patient care 1974-2001, different substances. It should be noted that in the group Others for 1974, 2.3 DDDs consisted of older sulphonamides with long half-life that were taken off the market 1985.

between various antibiotic groups has been relatively stable over the years, although a marked reduction is seen for macrolides. Combinations of sulfonamides and trimethoprim have almost disappeared from the Swedish market compared to other countries [Cars O et al, 2001] [Mölstad S et al, 2002].

At a county level there is a wide variation between the counties with the highest and the lowest sales (16.5 and 11.0 DDD/1000/day, respectively) for year 2001 (Figure 3.3). It should be noted that the sales between 1993 and 2001 have been reduced for all counties, also in those with a level below the national average.

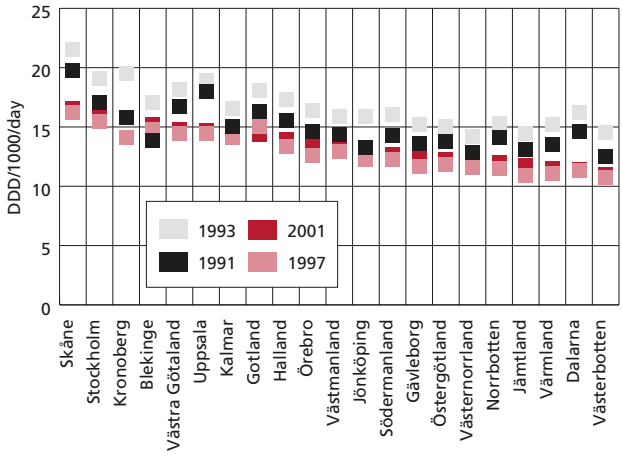


Figure 3.3. Antibiotic utilisation in out-patient care in Swedish counties (J01 excluding methenamine) 1991, 1993, 1997 and 2001, DDD/1000/day.

The distribution between antibiotic groups was quite similar in all counties, except for beta-lactamase sensitive penicillins (J01CE), where the differences between the counties with the lowest and highest sales were more than 100% in 2001 (Table 3.1).

Table 3.1. County with the highest and lowest sales, out-patient care 1993 and 2001 (DDD/1000/day).

	County with the highest sales of antibiotics		County with the lowest sales of antibiotics	
	1993	2001	1993	2001
Beta-lactamase sensitive penicillins (J01CE)	7.7	5.9	5.3	2.9
Tetracyclines (J01A)	5.4	3.8	3.0	2.7
Quinolone antibacterials (J01M)	1.3	1.3	1.0	1.1
Penicillins with extended spectrum (J01CA)	1.7	1.6	0.9	0.9
Beta-lactamase resistant penicillins (J01CF)	1.1	1.1	1.1	0.8
Trimethoprim and derivates (J01EA)	0.6	0.7	0.6	0.7
Macrolides and lincosamides (J01F)	2.5	1.2	1.5	0.8
Comb of sulfonamides and trimethoprim (J01EE)	0.3	0.1	0.3	0.1
Others	1.0	1.0	0.7	0.9
Total	21.6	16.5	14.2	11.0

In out-patient care it is also possible to examine the prescribing pattern regarding age and sex (Table 3.2). The total figures for 1993 and 2001 in the youngest age group 0–6 years, show that there has been an overall reduction by more than 40%. For the age group above 80 years there has instead been an increase by about 20%. The utilisation in women is higher in all age groups except 0–6 and above 80. The gender difference is mostly pronounced in the age group 20–60 years, where women use about 50% more than men

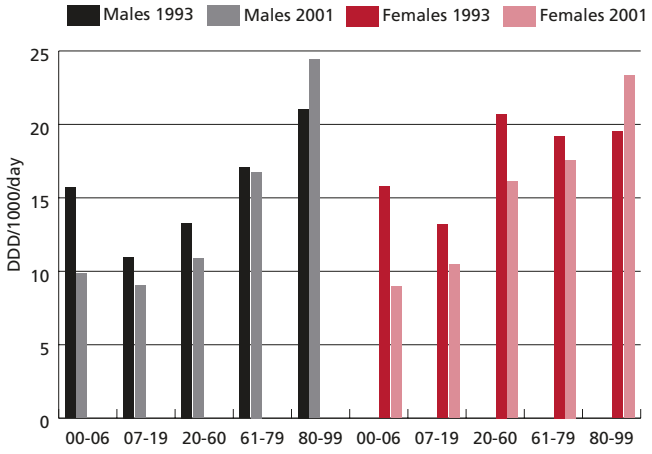


Figure 3.4. Antibiotic utilisation in out-patient care in Sweden (ATC group J01 excluding methenamine), males and females different ages.

(Figure 3.4). The highest consumption is found in the age-groups 0–6 years and 80 years and older. As the prescribed daily doses for children are lower then the DDDs it is important to study this group also by looking at numbers of prescriptions/1000 inhabitants as presented in Table 3.3.

Table 3.3. Different groups of antibiotics, age-group 0 – 6 years, prescriptions/1000 inhabitants/year

	1993	1997	2001
Beta-lactamase sensitive penicillins (J01CE)	531.6	443.9	416.8
Penicillins with extended spectrum (J01CA)	171.0	96.1	100.8
Macrolides and Lincosamides (J01F)	188.1	58.5	55.2
Other beta-lactam antibacterials (J01D)	42.9	62.7	54.1
Quinolone antibacterials (J01M)	0.3	0.4	0.8
Others	224.7	149.7	137.8
Total	1158.6	811.3	765.5

For the age group 0–6 years the most prominent reduction between 1993 and 2001 concerned penicillins with extended spectrum and macrolides (Figure 3.5). The regional differences from 1995 for the age groups 0–6 years for total antibiotic use (J01), beta-lactamase sensitive penicillins (J01CE) and macrolides (J01FA) are illustrated in map charts (Figure 3.6)

In the age-group 80 years and older two thirds are women. Between 1993 and 2001 there was an increase in antibiotic use by about 20% (Figure 3.7), which mostly concerned penicillin with extended spectrum and beta-lactamase resistant penicillins. Men consumed relatively more quinolones and tetracyclines, women relatively more penicillins with extended spectrum and trimethoprim (Table 3.2).

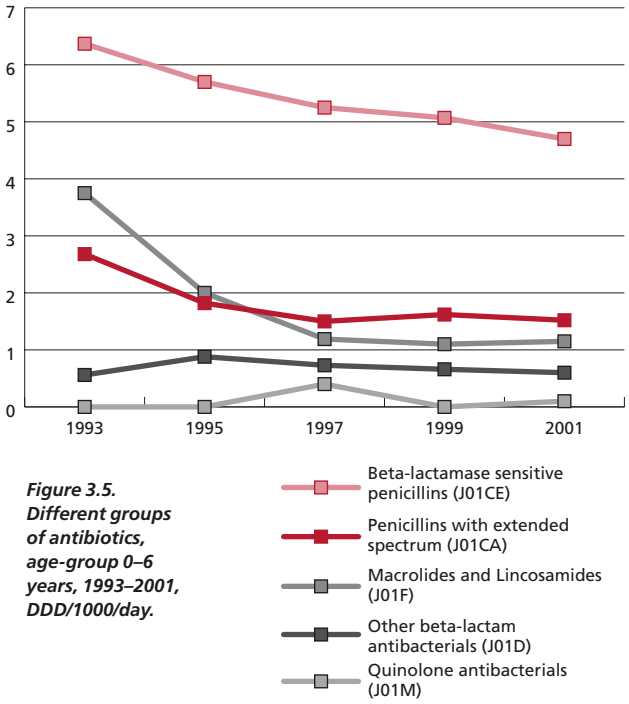
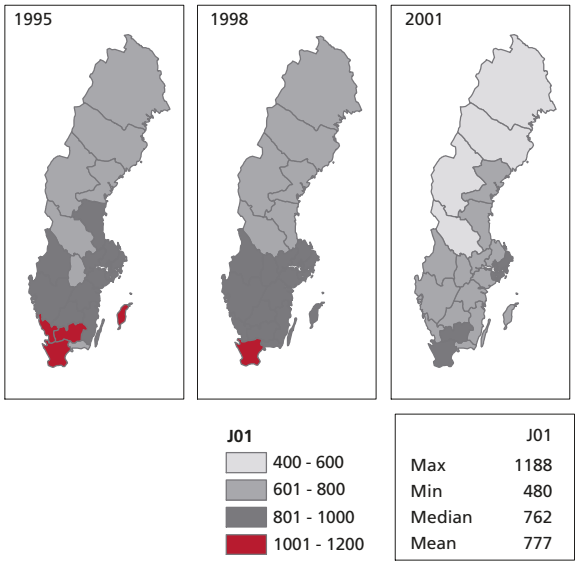


Figure 3.5. Different groups of antibiotics, age-group 0–6 years, 1993–2001, DDD/1000/day.

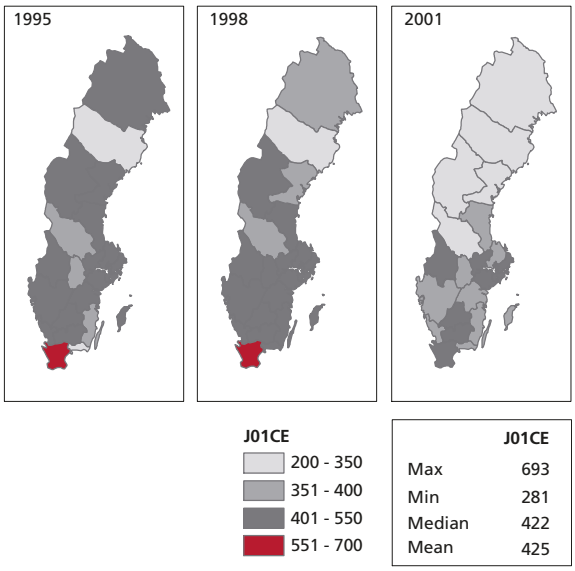
Table 3.2. Antibiotic utilisation in out-patient care, for different groups of antibiotics and different age-groups 1974, 1985, 1993 and 200 1.

	Women, DDD/1000/day				Men, DDD/1000/day			
Age-group (years)	1974	1985	1993	2001	1974	1985	1993	2001
Tetracyclines (J01A)								
0-6	0.01	0	0.01	0	0.05	0	0	0
7-19	1.02	1.52	2.2	1.97	0.89	1.27	2.3	2.2
20-60	3.06	3.93	5.82	4.3	2.49	3.26	3.85	2.91
61-79	2.32	2.47	5.15	3.91	2.16	3.05	5.04	3.83
80-99	1.16	1.6	3.13	2.61	3.16	2.07	4.76	3.63
Penicillins with extended spectrum (J01CA)								
0-6	0.51	0.86	2.59	1.43	0.55	0.85	2.63	1.58
7-19	0.72	0.77	0.87	0.72	0.37	0.2	0.59	0.41
20-60	1.04	1.77	1.55	1.46	0.56	0.6	0.68	0.61
61-79	0.84	2.47	1.76	2.4	1.07	1.39	1.05	1.52
80-99	1.82	3.99	1.82	3.94	3.17	3.98	1.47	2.62
Beta-lactamase sensitive penicillins (J01CE)								
0-6	4.28	4.97	6.26	4.33	4.9	5.11	6.21	4.96
7-19	4.63	5.15	6.39	4.65	3.63	4.51	5.06	4.08
20-60	4.32	6.68	7.69	5.81	3.33	4.77	5.16	4.16
61-79	1.84	3.13	4.25	4.1	2.03	2.98	3.62	3.74
80-99	1.79	2.84	3.1	3.35	2.5	3.66	3.56	3.73
Beta-lactamase resistant penicillins (J01CF)								
0-6	0.04	0.2	0.17	0.23	0.01	0.05	0.19	0.26
7-19	0.24	0.19	0.42	0.51	0.12	0.27	0.42	0.61
20-60	0.2	0.49	0.8	0.75	0.11	0.65	0.92	0.94
61-79	0.12	0.74	1.82	1.72	0.31	1.17	2.06	2.29
80-99	0.82	1.73	3.62	4.34	0.48	1.17	3.49	4.73
Trimethoprim and derivatives (J01EA)								
0-6	0	0.09	0.13	0.18	0	0.03	0.07	0.07
7-19	0	0.31	0.28	0.42	0	0.03	0.04	0.03
20-60	0	0.67	0.64	0.73	0	0.12	0.1	0.09
61-79	0	1.42	1.42	1.5	0.01	0.48	0.48	0.54
80-99	0	1.67	2.48	3.3	0	1.75	1.36	1.73
Macrolides and Lincosamides (J01F)								
0-6	0.76	3.69	3.69	1.08	1.42	3.47	3.68	1.2
7-19	0.7	1.75	1.91	1.06	0.71	1.56	1.72	0.98
20-60	0.57	1.96	2.02	1.15	0.37	1.14	1.07	0.67
61-79	0.43	0.92	1.24	0.95	0.54	0.8	0.96	0.9
80-99	0.16	0.8	0.93	0.94	0.69	0.48	0.74	1.04
Other beta-lactam antibacterials (J01D)								
0-6	0	1.1	0.5	0.6	0	1.0	0.6	0.6
7-19	0	0.3	0.4	0.4	0	0.2	0.4	0.3
20-60	0.1	0.4	0.7	0.5	0	0.2	0.4	0.3
61-79	0.1	0.5	0.8	0.5	0.2	0.5	0.7	0.6
80-99	0.2	0.3	0.7	0.9	0	0.6	1.0	1.0
Quinolone antibacterials (J01M)								
0-6	-	0	0	0	-	-	0	0
7-19	-	0	0.2	0.2	-	0	0.1	0.1
20-60	-	0.1	1.1	0.9	-	0.1	0.8	1.0
61-79	-	0.2	2.3	1.8	-	0.2	2.5	2.3
80-99	-	0.2	3.2	3.0	-	0.3	3.6	4.9

Total antibiotic use, J01, per 1000 inh./year. Age group 0-6 years.



Beta-lactamae sensitive penicillins, J01CE, per 1000 inh./year. Age group 0-6 years.



Macrolides, J01FA, per 1000 inh./year. Age group 0-6 years.

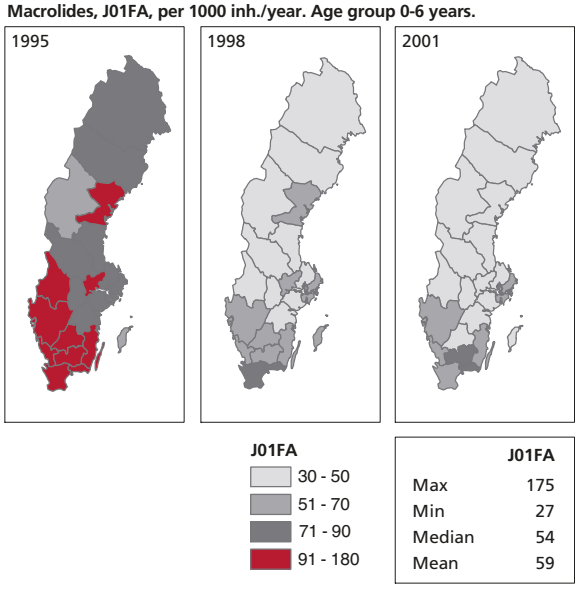


Figure 3.6. Total antibiotic use (J0v1), beta-lactamase sensitive penicillins (J01CE) and macrolides (J01FA), age-group 0-6 years, 1995, 1998 and 2001 (DDD/1000/day).

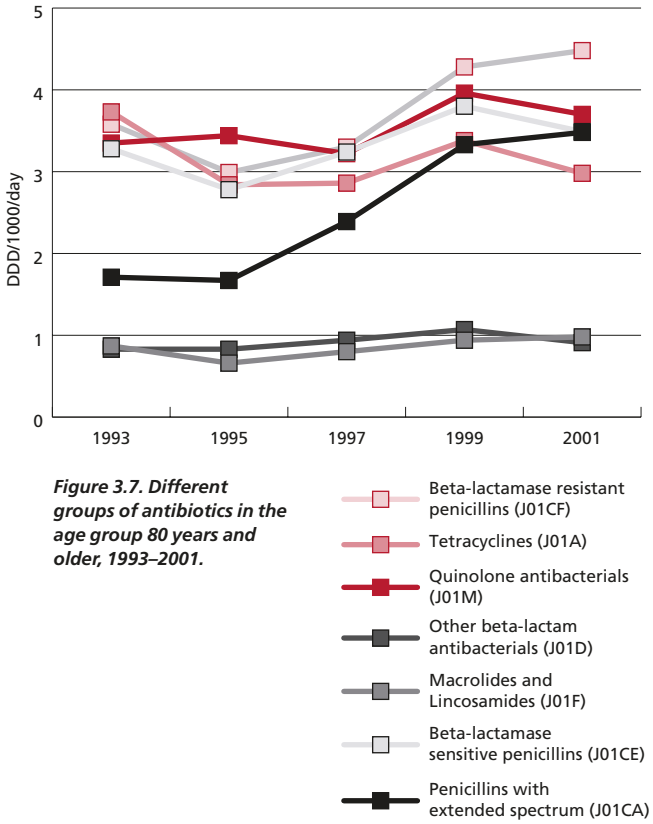


Figure 3.7. Different groups of antibiotics in the age group 80 years and older, 1993–2001.

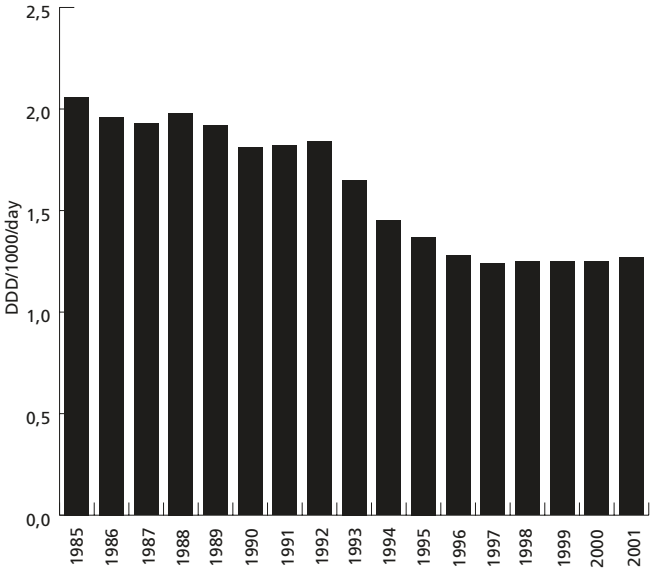


Figure 3.8. Antibiotic sales to hospitals (DDD/1000/day) in 1985–2001.

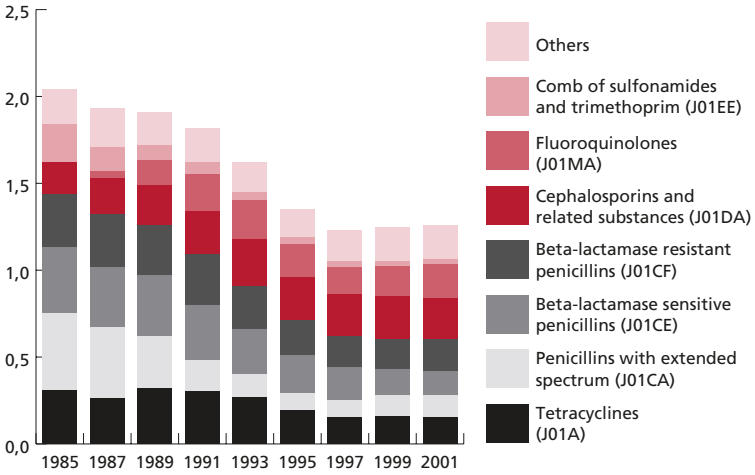


Figure 3.9. Antibiotic sales to hospitals (DDD/1000/day) in 1985–2001.

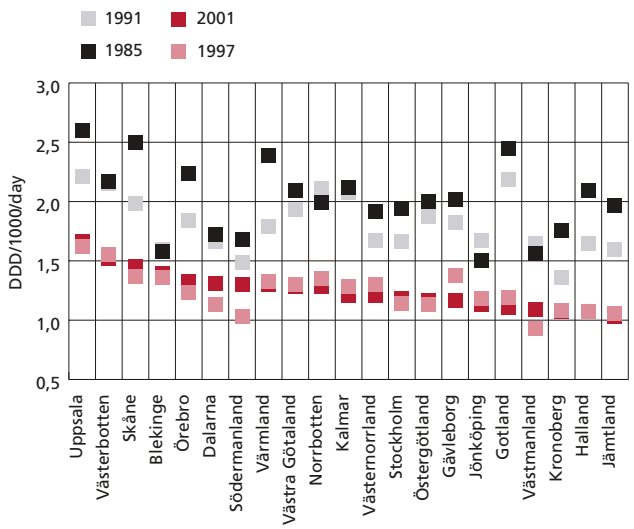


Figure 3.10. Antibiotic sales to hospitals (DDD/1000/day), per county in 1985, 1991, 1997 and 2001.

Hospital care

Data on antibiotics sales to hospitals are available from 1985 (Figure 3.8). That year, the total utilisation was 2.1 DDD/1000/day, followed by a decrease to 1.3 DDD/1000 /day in 2001 (38% decrease). During the same period the number of hospital beds administered by the county councils have been reduced with about 70% (approx. from 104.000 to 31.500), due to structural changes in the health care system. One major change took place in 1992 when more than 30.000 beds were transferred to the communities. Thus, the reduction in antibiotic utilisation during this period may partly be due to these changes since the drug use in the community care is registered as prescription sales and not as hospital data.

In 1985, penicillins with extended spectrum constituted 0.44 DDD/1000/day, and was thus the largest group, followed by beta-lactamase sensitive penicillins with 0.38 DDD/1000/day (Figure 3.9). For the year 2001, there has been a change; the largest group is now cephalosporins with 0.24 DDD/1000/day, followed by fluoroquinolones with 0.19 DDD/1000/day.

As in outpatient care, there is a large variation between the counties regarding antibiotic use in hospital care. In 2001, a difference of 0.7 DDD/1000/days was noted between the counties with the highest and the lowest values; 1.7 and 1.0 DDD/1000/day, respectively (Figure 3.10, Table 3.4).

Table 3.4. Antibiotic sales to hospitals (DDD/1000/day) in the county with the highest and lowest sale, respectively.

	County with the highest sale of antibiotics		County with the lowest sale of antibiotics	
	1991	2001	1991	2001
Cephalosporins and related substances (J01DA)	0.3	0.3	0.1	0.3
Beta-lactamase resistant penicillins (J01CF)	0.4	0.3	0.2	0.1
Fluoroquinolones (J01MA)	0.2	0.2	0.1	0.1
Tetracyclines (J01A)	0.4	0.2	0.3	0.1
Penicillins with extended spectrum (J01CA)	0.2	0.1	0.2	0.1
Beta-lactamase sensitive penicillins (J01CE)	0.3	0.1	0.2	0.1
Others	0.4	0.4	0.2	0.2
Total	2.2	1.6	1.3	1.0

Comments

As in other countries, the majority of antibiotic doses in Sweden are prescribed to outpatients.

In 2001 14.38 DDD/1000 were prescribed for out-patients and 1.27 for hospitalised patients (92 and 8%, respectively). Between 1986 and 1992 the antibiotic prescribing rates in out-patients increased from 12.28 DDD/1000/day to 17.5 1000/day (42%) (Figure 3.1.) There are no obvious medical reasons for the rapid and large increase. Thus, other explanations must be sought, e.g. increased number of primary care physicians, increased number of outpatients visits, introduction of new diagnostic methods, marketing of new antibiotics etc. From 1994 to 1997 a decline in the antibiotic prescribing rate in outpatients was seen and the level has then stabilised, although on a higher level than seen before 1986.

Published data on antibiotic prescribing linked to diagnosis have been scarce in Sweden. The alternative is examination of sales or prescription data without linkage to diagnosis which can only give a probable estimate of whether the consumption pattern is in concordance with therapeutic guidelines, or if implemented interventions to improve usage have been effective. Despite the limitations, it seems possible to draw some conclusions from the available data. The large reduction in the use of sulphonamides and combination of sulphonamides and trimethoprim (Figure 3.2) followed reports from the Medical Products Agency on severe adverse effects of these drugs. The reasons for reduction in antibiotic use from 1994 to 1997 are most likely multifactorial. The initiation of the STRAMA network (p. 23) and other initiatives drawing the attention to the problem of antibiotic resistance, led to an increased awareness among health care workers and the general public of the need to reduce inappropriate antibiotic use to minimise the risk of development of resistance. Local campaigns were initiated in many counties in Sweden regarding the importance of only prescribing antibiotics when necessary, especially to children. The reduction in total antibiotic use in children 0-6 years between 1993 and 1997 was 30 % (Table 3.3). Most prominent was the reduction in macrolides (69%) and broad spectrum penicillins (44%). The reduction in quinolone use in women above 20 followed a national recommendation to restrict their use in uncomplicated urinary tract infections. A corresponding increased use of trimethoprim was observed in this patient category. The increase in the use of quinolones in elderly men is of concern and the reasons remain unclear.

There is a large geographical variation in the total antibiotic use in Sweden. From the available statistics on antibiotic use and a recent antibiotic-diagnosis prescribing survey (p. 26) it can be hypothesised that, especially in some regions, unnecessary prescribing to a high extent consist of beta-lactamase sensitive penicillins in presumed bacterial throat infections (in children), tetracyclines in presumed acute sinusitis and lower respiratory tract infections (in middle aged patients) and beta-lactamase resistant penicillin and quinolones (in the elderly).

4. Antimicrobial resistance

In Sweden, routine susceptibility testing of clinical isolates is performed using well-standardised methods (Appendix 4). A national programme for surveillance has been designed, based to a large extent on such data (Appendix 5).

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). For many years, the percentage of PNSP isolates was well below 5% [Olsson-Liljequist et al, 1992], with the exception of Skåne Region in southern Sweden, where the rates increased in the early 1990s to about 8–15% [Ekdahl et al, 1994, Forsgren et al, 1994].

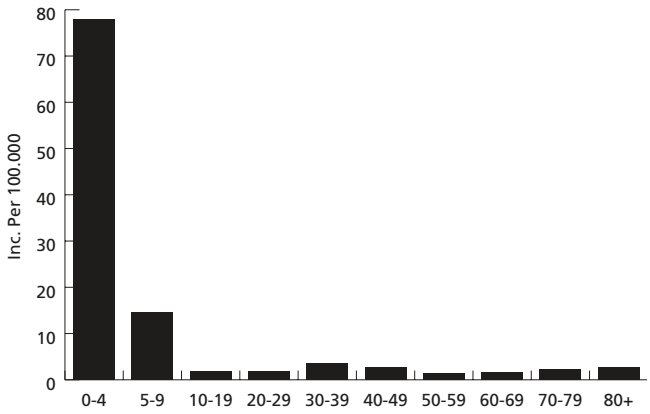


Figure 4.1. Number of notified cases with PRP (Penicillin G MIC ≥ 0.5 mg/L) 2001, by age group.

A large proportion of penicillin and multiresistant pneumococci belong to a limited number of international epidemic clones. In recent years, the dominant epidemic clone in Sweden has been of serotype 9V, resistant to penicillin G and also to trimethoprim-sulfonamide. This clone, which has been described in many parts of the world, was introduced in Skåne County in late 1994 [Melander et al, 1998], and has since spread to many other parts of Sweden as well [Kihlström et al, 1995].

Notifications according to the Communicable Disease Act

Since 1996, infection and carriage due to *S. pneumoniae* with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (henceforth designated PRP) has been notifiable according to the Communicable Disease Act (Appendix 5). The number of notified PRP cases has varied considerably (up to 20-fold) between the counties (Table 4.1). Most of the cases have been children aged 0–5 years, but small peaks have further been noticeable in the age groups 30–39 years and > 70 years, probably representing transmission from the small children to their parents and grandparents (Figure 4.1).

All but a few of the PRP-cases have been detected by nasopharyngeal culture. Since the culture rate (nasopharyngeal cultures per 1,000 inhabitants) has varied up to 25-fold between the counties, the PRP rate (percent PRP among pneumococcal isolates) is a better measure of the local burden of penicillin resistance (Figure 4.2).

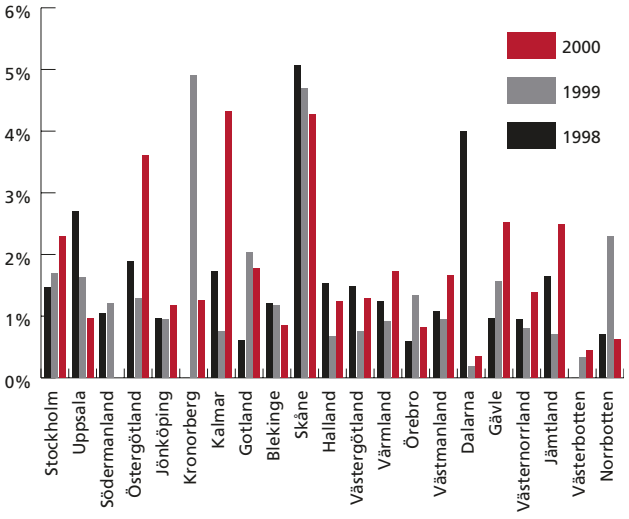


Figure 4.2. Rate of PRP (Penicillin G MIC ≥ 0.5 mg/L) in percent of all pneumococcal isolates by county 1998–2001.

Table 4.1. *Streptococcus pneumoniae* with reduced susceptibility to penicillin (penicillin G MIC ≥ 0.5 mg/L – PRP), notified by county according to the Communicable Disease Act .

	Number of notified cases					Incidence per 100,000 pop				
County	1997	1998	1999	2000	2001	1997	1998	1999	2000	2001
Stockholm	164	181	181	179	162	9.4	10.2	10.1	9.9	8.8
Uppsala	29	21	9	7	8	10.0	7.2	3.1	2.4	2.7
Södermanland	15	17	15	9	8	5.8	6.6	5.9	3.5	3.1
Östergötland	32	18	43	21	15	7.7	4.4	10.4	5.1	3.6
Jönköping	11	10	17	14	7	3.3	3.0	5.2	4.3	2.1
Kronoberg	0	42	8	2	8	0.0	23.5	4.5	1.1	4.5
Kalmar	23	10	40	15	10	9.5	4.2	16.9	6.4	4.3
Gotland	6	18	12	26	19	10.4	31.2	20.9	45.3	33.1
Blekinge	5	4	2	4	10	3.3	2.6	1.3	2.7	6.7
Skåne	434	408	278	301	228	38.9	36.5	24.8	26.7	20.1
Halland	17	6	8	13	13	6.3	2.2	2.9	4.7	4.7
V Götaland	67	28	39	40	52	4.5	1.9	2.6	2.7	3.5
Värmland	5	3	4	1	4	1.8	1.1	1.4	0.4	1.5
Örebro	11	25	9	11	4	4.0	9.1	3.3	4.0	1.5
Västmanland	13	10	11	13	7	5.0	3.9	4.3	5.1	2.7
Dalarna	33	1	1	3	3	11.5	0.4	0.4	1.1	1.1
Gävleborg	7	12	17	9	49	2.4	4.2	6.0	3.2	17.6
Västernorrland	10	6	13	9	3	3.9	2.4	5.2	3.6	1.2
Jämtland	7	4	8	3	4	5.2	3.0	6.1	2.3	3.1
Västerbotten	7	16	6	6	8	2.7	6.2	2.3	2.3	3.1
Norrbotten	0	2	3	1	2	0.0	0.8	1.2	0.4	0.8
Total	896	842	724	687	624	10.1	9.5	8.2	7.7	7.0

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 (Appendix 5) since 1994. In these studies, approximately 3000 consecutive clinical isolates of *S. pneumoniae*, 100 isolates from each of all clinical microbiology laboratories have been quantitatively tested for susceptibility to penicillin (by means of oxacillin 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 4.3.

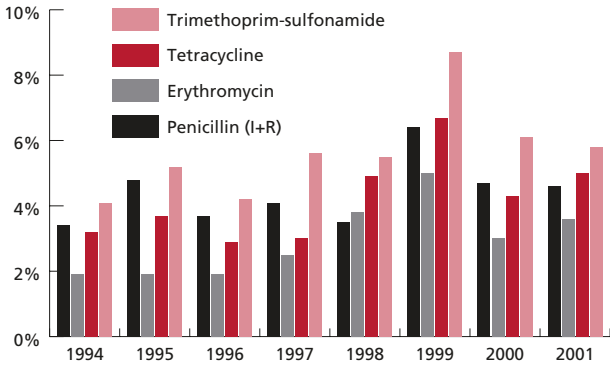


Figure 4.3. Overall national resistance rates (resistant isolates in percent of all pneumococcal isolates) for four different antibiotics 1994–2001 (data from the annual RSQC programme, approximately 3000 isolates per year).

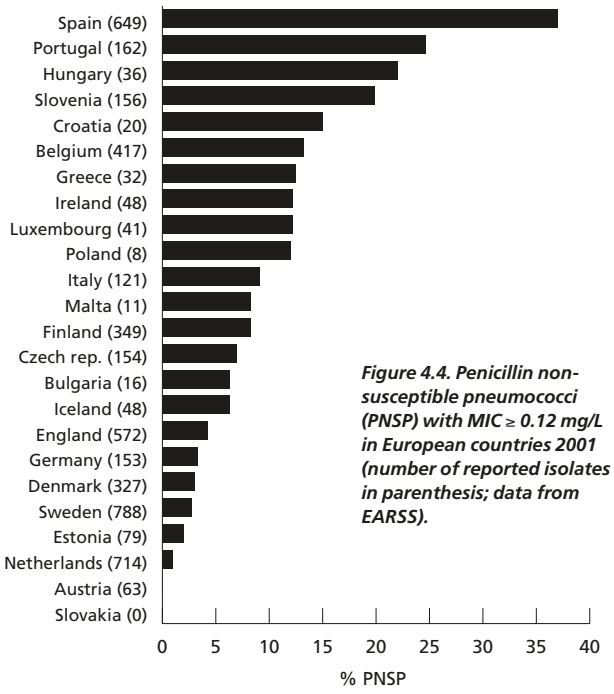


Figure 4.4. Penicillin non-susceptible pneumococci (PNSP) with MIC ≥ 0.12 mg/L in European countries 2001 (number of reported isolates in parenthesis; data from EARSS).

Data from the EARSS network

Twenty of the Swedish clinical microbiology laboratories, covering approximately 70% of the population, are reporting susceptibility data on invasive isolates of *S. pneumoniae* to the European Antimicrobial Resistance Surveillance System (EARSS) (Appendix 5). The Swedish data on susceptibility

Table 4.2. Invasive isolates of *Streptococcus pneumoniae* reported to EARSS.

Year		S	I	R	Total
1999	Penicillin*	793 (98.5%)	11 (1.4%)	1 (0.1%)	805
	Erythromycin	504 (94. 2%)	12 (2.2%)	19 (3.6%)	535
2000	Penicillin*	787 (98.0%)	16 (2.0%)	0 (0.0%)	803
	Erythromycin	622 (96.7%)	3 (0.5%)	18 (2.8%)	643
2001	Penicillin*	766 (97.2%)	18 (2.3%)	4 (0.5%)	788
	Erythromycin	623 (95.4%)	1 (0.2%)	29 (4.4%)	653

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

to penicillin and erythromycin is given in Table 4.2, and comparative figures for Europe in Figure 4.4. Overall resistance rates have been lower in invasive isolates, than in nasopharyngeal isolates which could partly be explained by a lower proportion of samples from children in the invasive isolates. Since 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, the figures from the different reporting systems are not comparable.

Staphylococcus aureus

Background

Staphylococcus aureus is a common pathogen which colonises nasal cavities of about 30% of 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. *S. aureus* is a Gram-positive microorganism that is traditionally treated with beta-lactamase stable beta-lactam antibiotics (e.g. methicillin, oxacillin, cloxacillin, dicloxacillin, flucloxacillin). Immuno-compromised patients are at highest risk to get *S. aureus* infection. Other risk factors for *S. aureus* infections are impaired cellular immunity (e.g., patients with diabetes mellitus or renal failure), and use of catheters or other invasive devices and presence of artificial grafts or other implants. *S. aureus* can cause a variety of infections.

Methicillin-resistant *S. aureus (*MRSA), although representing different clonal types, have the mecA gene in common. The presence of this gene renders them resistant, not only to methicillin, but to all currently available beta-lactam antibiotics. The first European isolate of MRSA was detected in 1960. MRSA has since become one of the leading causes of nosocomial infections worldwide, significantly reducing the number of treatment alternatives for serious staphylococcal infections. Spread of MRSA is favoured by poor hospital hygiene, crowding and inappropriate use of antibiotics.

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 (Chapter 5). The decision to include 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 and the Voluntary Laboratory Report System

Infection and colonisation with MRSA has been notifiable according to the Communicable Disease Act since January 2000. Previously, surveillance of the bacteria was done through the voluntary laboratory report system, where it could be monitored to some degree, but with little chance of determining the accuracy and coverage of these numbers.

The duration of MRSA carriage can be very long, complicating the statistics when reporting systems change. A case that was reported through the voluntary reporting system before or during 1999, would be considered as a new case if the person provided a new culture positive for MRSA from the year 2000, even though that person was already known by the local Communicable Disease Officers. This situation was relevant especially for the Västra Götaland Region, which had experienced a local outbreak of MRSA in the late 1990s, and screened many carriers from this outbreak in 2000. From 2001, however, no duplicate reports from the same patient have been included in the statistics.

Despite the uncertainty of the voluntary reporting system, making detailed comparisons between recent and retrospective data difficult, a clear increase in the number of reported cases can be seen (Figure 5). This increase could partly be attributed to increased awareness, resulting in better screening policies and contact tracing around existing cases, but mainly it represents an ongoing transmission in hospitals, nursing homes and in the community.

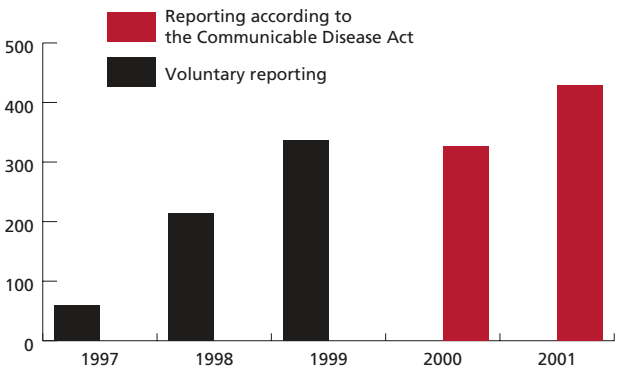


Figure 4.5. Reported MRSA cases 1997–2001.

Table 4.3. MRSA notified by county according to the Communicable Disease Act.

County	2000	2001
Stockholm	97	166
Uppsala	19	17
Södermanland	2	1
Östergötland	2	7
Jönköping	7	5
Kronoberg	1	0
Kalmar	3	2
Gotland	1	10
Blekinge	7	1
Skåne	22	76
Halland	10	26

County	2000	2001
Västra Götaland	114	56
Värmland	9	7
Örebro	8	7
Västmanland	3	8
Dalarna	0	5
Gävleborg	2	1
Västernorrland	14	12
Jämtland	0	0
Västerbotten	3	17
Norrbotten	3	5

Incidence data per county from the last two years show marked local differences and an increase in about one third of these (Table 4.3).

MRSA in 2001

During the year 2001, a total of 429 cases of MRSA were reported. Even though MRSA were reported from all age categories, the incidence was highest among the elderly (Figure 4.6). Carriage in the nose, throat and perineum together with colonisation or infections of wounds were by far the most common presentations, whereas invasive disease was rare (Figure 4.7).

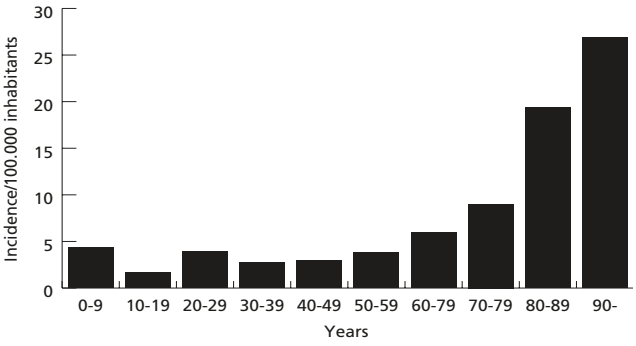


Figure 4.6. Age adjusted incidence of MRSA.

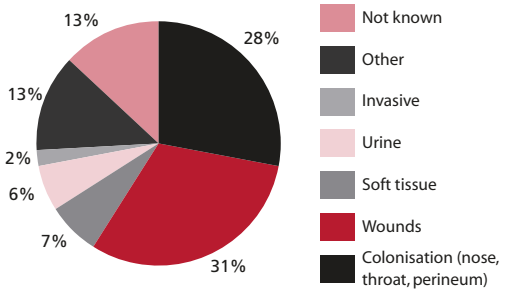


Figure 4.7. Site of isolation of MRSA 2001 (n = 429 patients).

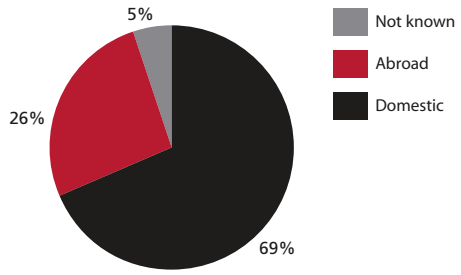


Figure 4.8. Reported origin of MRSA 2001 (n = 429 patients).

Out of the total number of reported cases in 2001, 69% were considered to have acquired MRSA within Sweden. The majority of the imported cases had acquired MRSA in health care settings abroad (Figure 4.8).

Among the domestic cases, the most common place of MRSA acquisition was reported to be health care facilities (Figure 4.9). Of the community-acquired infections, the majority seemed to have acquired MRSA from other family members (data not shown).

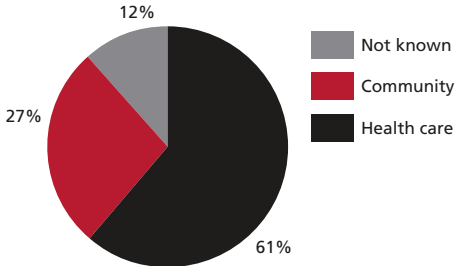


Figure 4.9. Reported place of acquisition for domestic MRSA-cases (n = 294 persons).

Most cases of health care related acquisition were reported to have taken place in in-patient care in hospital settings. Local outbreaks had also been noted outside such settings in nursing homes, primary care centres etc. (Figure 4.10). Many of the MRSA-cases in the older age-group has frequent contact with both in-patient and out-patient health care services and it can therefore be difficult to determine where the patient initially acquired MRSA. The multiple contacts with health care services for many of these patients pose a great challenge in information exchange between health care providers.

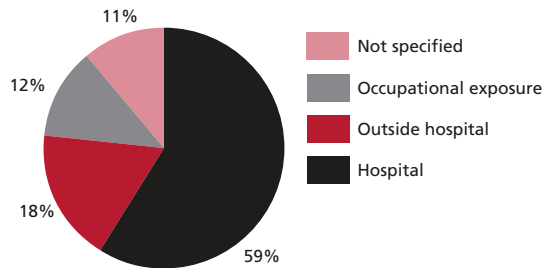


Figure 4.10. Reported way of domestic health care related acquisition (n = 180 persons).

Annual Resistance Surveillance and Quality Control (RSQC) programme

Staphylococcus aureus from wound infections were included in the annual RSQC programme (Appendix 5) in 2001. 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 the EARSS) are presented in Table 4.4.

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

	RSQC wound isolates		EARSS (Sweden), Invasive isolates	
Antibiotic	Total (n)	R (%)	Total (n)	R (%)
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

At the moment the quickly rising level of fusidic acid resistance with the spread of a clone of *S. aureus* causing impetigo in young children is of concern [Österlund A, et al, 2002]. Vancomycin-resistant *S.aureus* were not found among invasive nor among wound isolates.

Data from the EARSS network

Twenty of the Swedish laboratories (covering approximately 70% of the population) are reporting susceptibility data on invasive isolates of *S. aureus* to the EARSS (Appendix 5). On average 0.8% 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 three 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 the EARSS.

Year	S	R	Total
1999	1307 (99%)	13 (1.0%)	1320
2000	1469 (99.4%)	9 (0.6%)	1478
2001	1618 (99.1%)	14 (0.9%)	1632

Resistance to new antibiotics

As part of a methodological study in 2001 on susceptibility testing of Gram-positive bacteria against linezolid, vancomycin, and teicoplanin, 125 isolates of *S. aureus* from 25 laboratories were tested. None of the isolates were resistant to the three tested antibiotics.

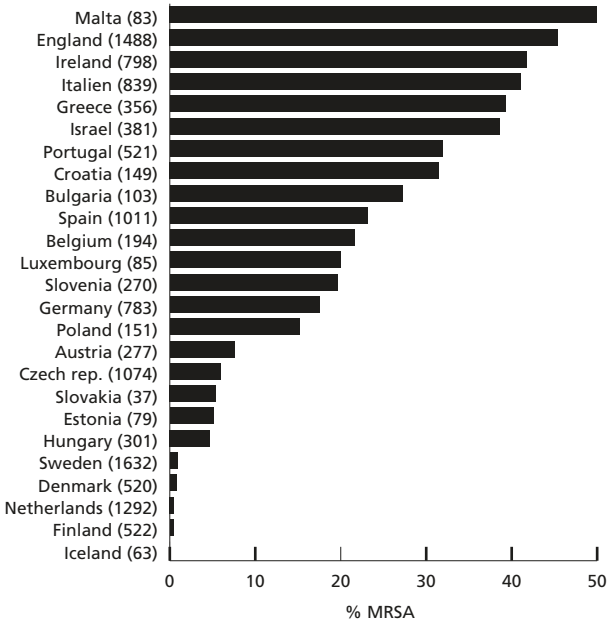


Figure 4.11. MRSA in Europe 2001 (data from EARSS).

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 bacteraemia. Most enterococcal infections are still caused by *Enterococcus faecalis* although the percentage of *E. faecium* 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) and was 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

immunosupressed and intensive care patients. Like MRSA, VRE were made notifiable pathogens according to the Communicable Disease Act in the year 2000. Surveillance of these pathogens was previously done through the voluntary laboratory reporting system.

Notifications of VRE according to the Communicable Disease Act and the Voluntary Laboratory Report System

The number of reported VRE cases remains very low (Figure 4.12). The older age group dominates among the reported (Figure 4.13).

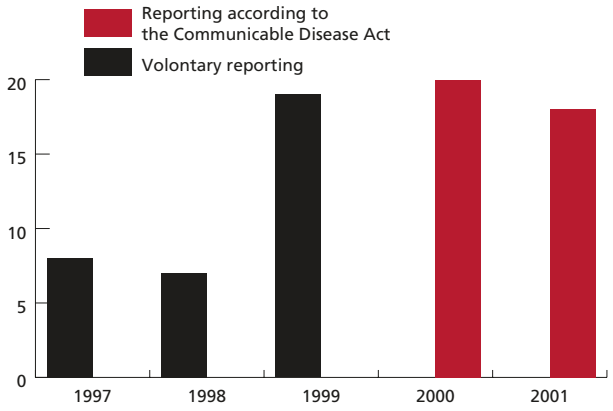


Figure 4.12. Reported VRE cases 1997–2001.

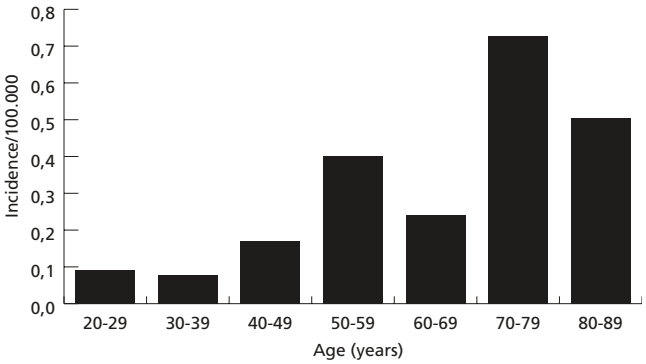


Figure 4.13. Reported VRE 2001, age adjusted incidence.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Enterococcus faecalis was one of six pathogens included in the annual RSQC programme (Appendix 5) in 1994. A follow-up was performed in 1997, when laboratories were asked to register quality assured routine disk diffusion data for three months. Eighteen laboratories were included in this survey. Vancomycin-resistance was extremely rare, whereas high-level resistance to aminoglycosides and fluoroquinolone resistance became prevalent during the three-year period (Figure 4.14).

In the enterococcal surveillance study in 1997 laboratories were also asked to register type of sample and routine quantitative susceptibility testing data on *E. faecium* judged to be of clinical relevance. The results showed that vancomycin-resistance again was extremely rare, but that high-level resistance against aminoglycosides and resistance to fluoroquinolones and betalactams was common (Table 4.6).

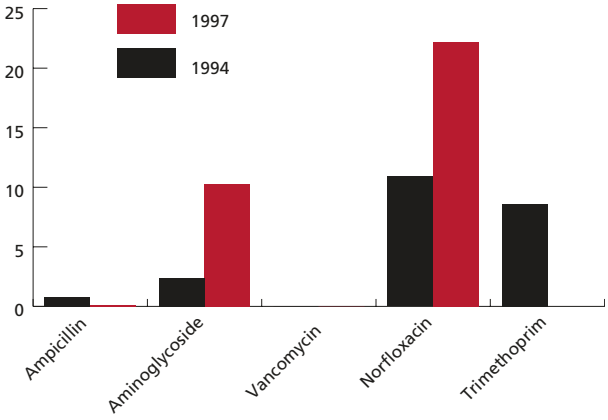


Figure 4.14. Enterococcus faecalis resistance rates (resistant isolates in percent of all isolates) for five different antibiotics 1994 (n = 3500 isolates) and 1997 (n = 8000 isolates). Data from the annual RSQC programme.

Table 4.6. *Enterococcus faecium* resistance rates (resistant isolates in percent of all isolates) for five antibiotics in 1997 (n = 900 isolates). Data from the annual RSQC programme.

	Resistance rates (percent of all isolates)				
Year	Ampi-cillin	Amino-glycoside	Vanco-mycin	Nor-floxacin	Cipro-floxacin
1997	70	22	<1	79	64

National study on the colonization of enterococci

In 1997 a national study of the colonisation of enterococci with acquired resistance to vancomycin (VRE) and ampicillin (ARE) was performed. Fecal samples from 670 non-hospitalised individuals and 841 patients in 27 major hospitals were obtained. Of the hospitalised patients, 181 (21.5%) were carriers of ARE and 9 (1.1%) carried VRE. All ARE and VRE isolates were *E.faecium*. All VRE were of *vanB* genotype and the patients were hospitalised at the same University hospital. Among the non-hospitalised individuals, the ARE carriage rate was significantly lower (6%) and only one person, recently returned from Africa, harboured VRE (*E. faecium, vanA*) [Torell et al, 1999].

Resistance to new antibiotics

As part of a methodological study in 2001 on susceptibility testing of Gram-positive bacteria against linezolid, vancomycin, and teicoplanin, 125 isolates of *E. faecium* from 25 laboratories were tested. None of the isolates were resistant to the three tested antibiotics.

Data from the EARSS network

Since the year 2001, invasive isolates of *E. faecalis* and *E. faecium* were included in the EARSS reporting (Appendix 5). The main focus was on vancomycin-resistance (Figure 4.15), 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 20 laboratories (covering approximately 70% of the population) contributed with quality assured routine disk diffusion data (Table 4.7).

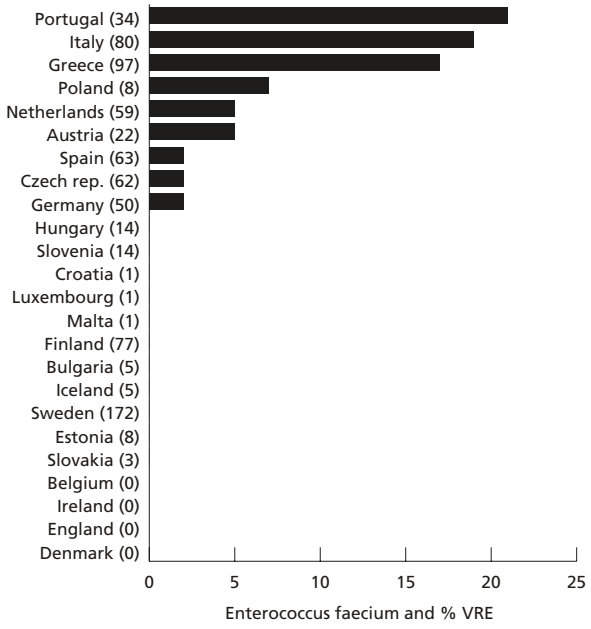


Figure 4.15. Proportion of vancomycin non-susceptible invasive E. faecium isolates reported by the participating countries in 2001 (data from EARSS; figures in parentheses after country names denote the number of contributed isolates).

Table 4.7. Resistance rates among invasive isolates of *Enterococcus faecalis* and Enterococcus faecium to three antibiotic groups in Sweden 2001 (data from EARSS).

	Enterococcus faecalis		*Enterococcus faecium*	
Antibiotic	Total (n)	R (%)	Total (n)	R (%)
Ampicillin	479	0	196	71
Aminoglycosides (gentamicin or tobramycin)	212	13	102	9
Vancomycin	396	0	172	0

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 annual RSQC programme since 1994 (Appendix 5). The antibiotics chosen for surveillance are those, which are considered as main treatment options, and for which resistance mechanisms have been described.

Resistance to erythromycin and other macrolide antibiotics is in some cases mechanistically related to clindamycin resistance (altered target, so called MLS-resistance) while in other cases it is unrelated and not affecting clindamycin (efflux mechanism). Summarized data for the years 1994–2001 shows a doubling of the tetracycline resistance rates and declining erythromycin resistance rates (Figure 4.16).

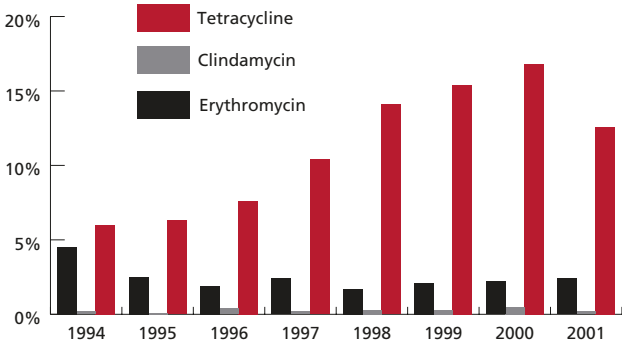


Figure 4.16. Resistance rates (resistant isolates in percent of all Streptococcus pyogenes isolates) for three major antibiotics 1994–2001 (data from the annual RSQC programme, approximately 3000 isolates per year).

Haemophilus influenzae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Haemophilus influenzae, primarily from nasopharyngeal swabs, have been part of the annual RSQC programme since 1994 (Appendix 5). 3000 isolates (100 consecutive clinical *H. influenzae* from each of 30 laboratories) have been screened annualy for resistance to beta-lactam drugs (beta-lactamase production and non-beta-lactamase penicillin/cephalosporin resistance), trimethoprim-sulfonamide and tetracycline (Figure 4.17). Approximately 10% of the strains were beta-lactamase producing and an additional 2-4% exhibited other beta-lactam resistance mechanisms. Trimethoprim-sulfonamide resistance at an average of 10% and tetracycline resistance at a low 1-2% have been stable over the years.

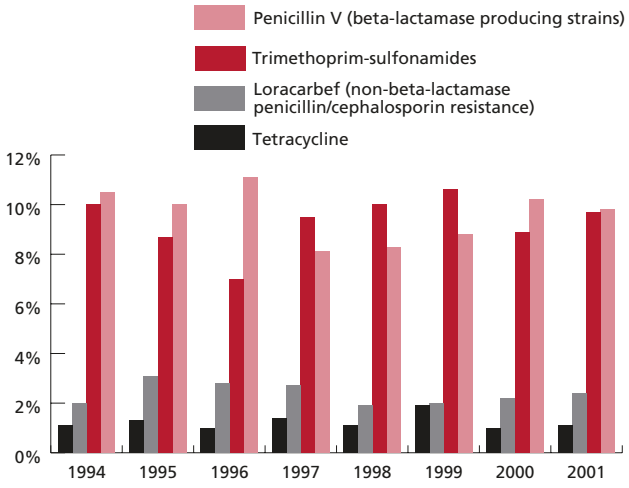


Figure 4.17. Resistance rates (resistant isolates in percent of all Haemophilus influenzae isolates) for four main antibiotics 1994–2001 (data from the annual RSQC programme, approximately 3000 isolates per year).

Escherichia coli

Annual Resistance Surveillance and Quality Control (RSQC) programme

Escherichia coli, mainly derived from urinary tract infections (UTI), has been included in the annual RSQC programme several times since 1996 (Appendix 5). Resistance to oral antibiotics, commonly prescribed for UTI, was tested each year. Resistance to ampicillin varied between 17 and 23%, and resistance to trimethoprim between 8% and 15%. Resistance to fluoroquinolones, represented by norfloxacin, has remained below 5%, but slowly increased, requiring special attention. Resistance to nitrofurantoin, mecillinam and cephalosporins have remained at resistance levels below 2% (Figure 4.18).

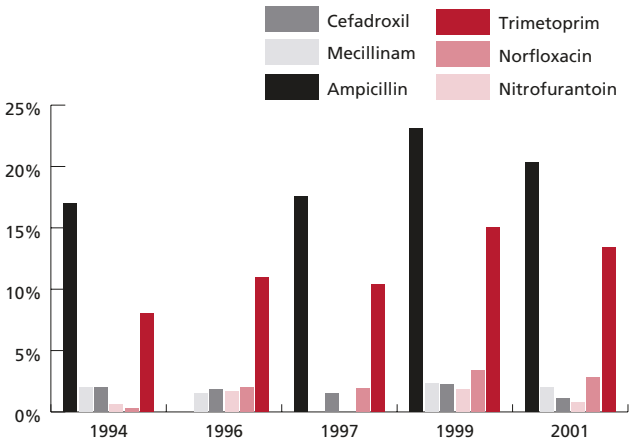


Figure 4.18. Resistance rates (resistant isolates in percent of all Escherichia coli isolates) for six different antibiotics 1994–2001 (data for 1996–2001 from the annual RSQC programme, approximately 3000 isolates per year; data for 1994 from Henning et al).

Data from the EARSS network

Escherichia coli derived from invasive infections (blood isolates) have been part of the EARSS-reporting since 2001 (Appendix 5). Focus for the surveillance activities has been on resistance to beta-lactam antibiotics, especially occurrence of strains producing betalactamases with so-called extended spectrum (ESBL), resistance to aminoglycosides and to fluoroquinolones.

Twenty Swedish laboratories have taken part also in this surveillance and delivered data on more than 1500 blood isolates. A summary of the EARSS results is presented in Table 4.8, and compared with the annual RSQC programme on UTI isolates from 2001. Results for the two different data sets were similar. Ampicillin resistance, caused by production of plasmid-mediated beta-lactamase (TEM-type most common) was slightly higher among blood than UTI 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 similar to that in other countries (Figure 4.19).

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

	Annual RSQC programme, urine isolates		EARSS (Sweden), Invasive isolates	
Antibiotic	Total (n)	R (%)	Total (n)	R (%)
Ampicillin	3803	20.3	1512	26.5
Cefotaxime (3rd generation cephalosporins.)	Nt	Nt	2500	0.5
Aminoglycosides (gentamicin, netilmicin, tobramycin)	Nt	Nt	2759	0.5
Fluoroquinolone (norfloxacin, ciprofloxacin)	3814	2.8 (nor)	2273	3.7 (cip)

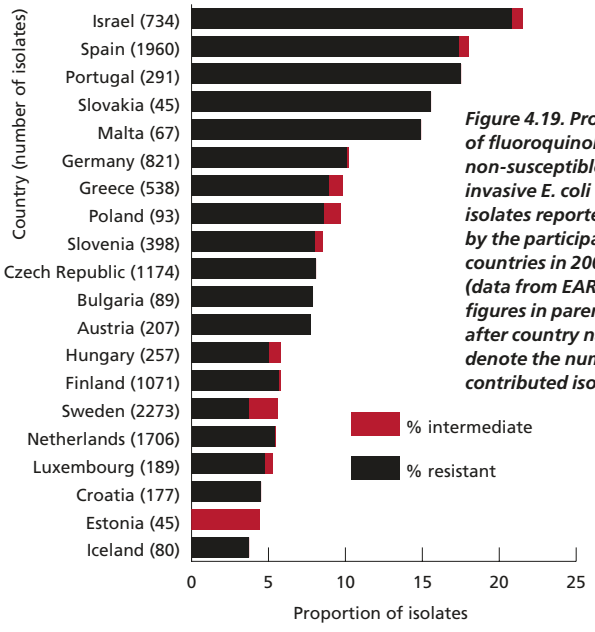


Figure 4.19. Proportion of fluoroquinolone non-susceptible invasive E. coli isolates reported by the participating countries in 2001 (data from EARSS; figures in parentheses after country names denote the number of contributed isolates).

Klebsiella pneumoniae

Annual Resistance Surveillance and Quality Control (RSQC) programme

In 1994 resistance in *Klebsiella pneumoniae* was monitored as part of the annual RSQC programme (Appendix 5). The results are shown in Table 4.9, and are compared with data from a study on Swedish blood isolates from 12 laboratories 1991–1998 (unpublished data G Kahlmeter et al).

Table 4.9. Resistance rates (percent) of *Klebsiella pneumoniae* for four antibiotics in 1994 (data from the annual RSQC programme and from G Kahlmeter et al).

	Cefuroxime	Cefotaxime	Ciprofloxacin	Trimethoprim
RSQC isolates (n=2500)	6.9	1.3	7	13.5
Blood isolates n=190	6	0	4	7

Voluntary reporting during recent years has revealed a small number of strains carrying beta-lactamase of SHV-type with extended spectrum (ESBL, resistance to 3rd generation cephalosporins).

Enterobacter species

Annual Resistance Surveillance and Quality Control (RSQC) programme

Antimicrobial resistance in *Enterobacter* spp. (unspecified infections) was monitored in 1997 through the RSQC programme, and data are compared with those from the Swedish blood isolate study from12 laboratories (unpublished data G Kahlmeter et al).

Table 4.10. Resistance rates (%) of *Enterobacter* spp for four antibiotics in 1997 (data from the annual RSQC programme and from G Kahlmeter et al.).

Year	Cefuroxime	Cefotaxime	Ciprofloxacin	Trimethoprim
RSQC isolates n=600	21	11	4	5
Blood isolates n=97	35	23	1	1

Helicobacter pylori

Annual Resistance Surveillance and Quality Control (RSQC) programme

Helicobacter pylori derived from gastric biopsies have not until 2001 been included in the annual RSQC program but has been monitored locally at a few laboratories. In vitro resistance against metronidazole has been reported in 10-40% of Scandinavian strains. Resistance to clarithromycin is less common (3%) but increasing and has not reached over 10%. Resistance to tetracycline is less than 1% and resistance to amoxycillin has only been described in a few strains and only outside Scandinavia. Resistance-figures from strains isolated in southwest of Sweden are presented. The population is about 300 000 and between 100-600 new Helicobacter strains are isolated yearly.

Mats Walder

Table 4.11. Resistance rates (%) of *Helicobacter pylori* for four antibiotics 1994-2001 (data from the annual RSQC programme, Malmö county.(- = not tested)

Year	Isolates	Claritro-mycin	Metroni-dazol	Tetra-cykline	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

Salmonella

Since antibiotic treatment is normally not used for uncomplicated gastrointestinal *Salmonella* infection, clinical isolates of *Salmonella* are not always tested for susceptibility to antibiotics. For comparison with veterinary reports, ten years of consecutive results from one laboratory (Department of Clinical Microbiology, Växjö County Hospital) is presented in Table 4.12. Recent data on *Salmonella* Typhimurium DT 104 from 1999-2001, originating in Sweden or abroad, analysed at the SMI, are also presented in Table 4.12.

Table 4.12. Resistance rates (%) for *Salmonella* (all serotypes) against 5 antibiotics in 1991-2000 in Sweden (Kronoberg county) and *Salmonella* typhimurium DT 104 1999-2001 (www.srga.org/BILDER/Resfaec.htm and national data, SMI).

Isolates	Year	Amp	Tet	Klo	TMP/ SMX	Cip	Nal	Str
Salmonella (all serotypes)	1991-2000	13	16	6	5	0		
DT 104 (n=281)	1999-2001	95	94	94	2.9/97	1.8	2.1	96

Other gastrointestinal pathogens

Gastrointestinal infections caused by *Shigella*, *Yersinia* or *Campylobacter* are usually not treated with antibiotics. The reported figures are based on consecutive clinical isolates from patients diagnosed in Kronoberg county. The majority of the strains are of foreign origin. The following table shows antibiotic resistance (%) in strains isolated in Sweden 1991-2000 (Table 4.13).

Table 4.13. Resistance rates (percent) of *Shigella, Yersinia* and *Campylobacter* for seven antibiotics in 1991-2000, Kronoberg county (www.srga.org/BILDER/Resfaec.htm).

Isolates	No of strains	Amp	Ctx	Ery	Klo	Cip	TMP/ SMX	Tet
Shigella species	128	37	0	-	16	0	57	60
Yersinia enterocolitica	207	-	0	-	1	0	0.5	0
Campylo-bacter jejuni	1040	-	-	1.6	0	31	1	24

Amp = Ampicillin, Ery= Erythromycin, Klo = Chloramphenicole, CTX = Cefotaxime, CIP = Ciprofloxacin, TMP/SMX = Trimetoprim/ Sulfamethoxazole, Tet = Tetracycline, STR = Streptomycin

Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pseudomonas aeruginosa was included in the first RSQC study in 1994 (Appendix 5). Those data are compared with two sentinel studies from 1984 and 1994, in which isolates were collected from eight and four laboratories respectively (total of 200 isolates in each collection) and tested at the SMI (Table 4.14). The most prominent increase in resistance between 1984 and 1994 was seen for ciprofloxacin.

Table 4.14. Resistance rates (percent) of *Pseudomonas aeruginosa* for four antibiotics in 1994 from the RSQC programme compared with sentinel studies in 1984 and 1994.

Year / study	Amino-glycoside	Cefta-zidime	Imipe-nem	Cipro-floxacin
Sentinel 1984 (n=200)	3.5	2	0.5	0.5
Sentinel 1994 (n=200)	No data	2.5	6	19
RSQC isolates 1994 (n=2800)	0.9	1.8	4.7	12.4

Stenotrophomonas maltophilia

Annual Resistance Surveillance and Quality Control (RSQC) programme

A total of 120 isolates of *Stenotrophomonas maltophilia* (formerly Pseudomonas maltophilia) were collected from all Swedish laboratories in 1995. Susceptibility to aminoglycosides was strongly influenced by the incubation temperature, and was only expressed at 30° C. This has lead to the recommendations from SRGA-M to classify *Stenotrophomonas maltophilia* as always resistant to aminoglycosides without prior testing. Results only need to be reported for the antibiotics included in Table 4.15.

Table 4.15. Resistance rates (%) of *Stenotrophomonas maltophilia* for four antibiotics in 1995 (data from the annual RSQC programme).

Year	Ceftazidime	Ciprofloxacin	TMP/SMX
RSQC isolates (n=120)	4	25	5

Neisseria gonorrhoeae

Notifications according to the Communicable Disease Act

Gonorrhoea is a notifiable disease, and in 2001 529 clinical cases of the disease were reported. Clinical isolates were analysed at the Reference Laboratory for pathogenic *Neisseria*, Department of Clinical Microbiology, University Hospital Örebro.

In 2001, 141 isolates were sent to the reference laboratory, representing 27% of notified cases. Isolates from large city areas were underrepresented in this material.

Susceptibility testing was performed according to standardized methodology using the E-test for determination of MIC of bensylpenicillin, ampicillin, cefuroxime, tetracycline, ciprofloxacin and spectinomycin. Production of beta-lactamase was detected using nitrocefin. Results for 2001 are compared with those from 1998 and 2000 in Table 4.16.

Hans Fredlund

Table 4.16. Resistance rates (%) of *Neisseria gonorrhoeae* for six antibiotics in 1998-2001 (data from the reference laboratory in Örebro).

	1998 (n=348)	2000 (n=131)	2001 (n=141
Penicillin G	31,6	42	38,3
Ampicillin	23,6	36,6	36,9
Cefuroxime	0	1,5	0
Tetracycline	31,9	52,3	56
Ciprofloxacin	9,5	28,2	42,6
Spectinomycin	0	0	0

Neisseria meningitidis

Notifications according to the Communicable Disease Act

Invasive meningococcal disease is a notifiable disease. In 2001 75 clinical cases of the disease were reported. A total of 58 clinical isolates from blood or cerebrospinal fluid were analysed at the Reference Laboratory for pathogenic *Neisseria*, Department of Clinical Microbiology, University Hospital Örebro.

Susceptibility testing was performed according to standardized methodology using the E-test for determination of MIC of bensylpenicillin, fenoxymethylpenicillin, cefotaxime, chlorampenicol, ciprofloxacin and rifampicin. Production of beta-lactamase was detected using nitrocefin.

None of the isolates produced beta-lactamase. Three isolates (5%) 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.

Hans Fredlund

Mycobacterium tuberculosis

Background

Specific antituberculosis drugs have been available since the 1940s. The first drugs, streptomycine and paraaminosalicylic acid (PAS) were synthesized in 1944 and 1946, followed by isoniazid (1952) and pyrazinamid (1954). Ethambutol was available from 1962 and rifampicin from 1969. Today there are four first line drugs included in the standard treatment of tuberculosis (TB) in Sweden – isoniazid, rifampicin, ethambutol, and pyrazinamid. The ability of mycobacteria to develop drug resistance has been known already from the beginning of the chemotherapeutic era. To prevent the survival and multiplication of resistant strains combined treatment with several different drugs is needed.

Drug resistant tuberculosis is the result of inappropriate drug therapy, poor compliance to recommended regimens or deficient absorption of the drugs. The risk of resistant strains is increased in cases with high bacillary load and in recurrent disease. Since the early 1990s, drug resistant tuberculosis has increased in many countries all over the world. Combined resistance against the two main drugs, isoniazid and rifampicin, defined as multidrug resistance (MDR), is an increasing serious problem, especially in developing countries in Asia, as well as in the Baltic Republics, Russia, and other newly independent states of the former Soviet Union.

Drug susceptibility testing

In Sweden there is one national reference laboratory for mycobacteria, located at the Swedish Institute for Infectious Disease Control (SMI), and five regional microbiological laboratories performing routine diagnostics of mycobacteria, including drug susceptibility testing (DST); in Stockholm, Göteborg, Malmö, Linköping and Umeå. All initial isolates of the *M. tuberculosis*-complex are tested against isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin (Appendix 4). One of the five laboratories did not perform DST for streptomycin during the end of 1999 and the whole of 2000. Since 1994 resistant TB strains are sent to SMI for epidemiological molecular typing.

Drug resistant TB in Sweden during the 1990s

During the 1990s drug resistance in TB has varied between five and ten percent of the annual number of patients diagnosed with culture confirmed *M. tuberculosis* or *M. africanum*. In 1999, there was a sharp increase to 14%. Thereafter, drug resistance has remained on a higher level than previously, with resistance to isoniazid being the most common (Figure 4.20).

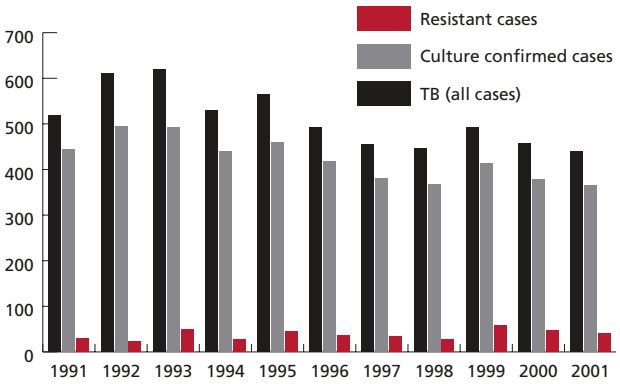


Figure 4.20. The number of reported TB cases (all, culture confirmed and resistant to at least one agent) 1991 – 2001.

MDR TB has so far been rare and has been reported in on average four cases per year or one percent of the patients (Figure 4.21). Resistant TB, including MDR, has mainly been found in patients born in other countries and in Swedes infected abroad, or older Swedish born patients with relapses of TB after previous treatment.

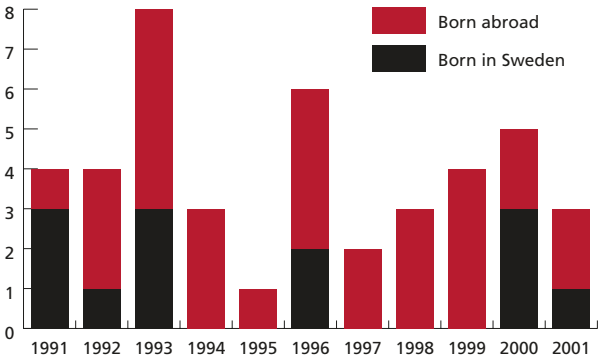


Figure 4.21. Number of reported MDR TB cases 1991 – 2001.

The average number of patients with resistant TB was 38 per year during 1991 to 2000, ranging from 23 in 1992 to 59 in 1999. This corresponds to 9% (range 4.6 – 14.3) of all patients with culture confirmed *M. tuberculosis* or *M. africanum*. The figure for 2001 is 42 resistant cases (11.7%) (Table 4.17). Resistance to isoniazid was most common, and increased from 2.9% in 1992 to 10.1% in 2000 (7.5% in 2001). Multidrug resistance was reported in on average four patients per year (1%).

Table 4.17. Drug resistant tuberculosis in Sweden. Resistance among initial isolates of Mycobacterium tuberculosis or *M. africanum* to at least one of the five drugs: isoniazid, rifampicin, ethambutol, pyrazinamide or streptomycin.

	Year of diagnosis				
	1991–1997	1998	1999	2000	2001
Culture confirmed *M. tuberculosis* or *M. africanum*	3 065	364	412	366	359
Any resistance total	7.9	7.7	14.4	12.9	11.7
Resistance to one drug only	5.5	5.8	10.0	9.6	6.4
Resistance to two or more drugs	2.3	1.9	4.4	3.3	5.3
Resistance to isoniazid	5.2	5.8	10.2	10.1	7.5
Resistance to rifampicin	1.1	1.4	2.2	1.4	1.4
Resistance to ethambutol	0.4	0.5	0.7	0.5	0.6
Resistance to pyrazinamide	1.2	1.6	3.2	3.0	1.7
Resistance to streptomycin	3.5	2.7	5.3	3.9	6.4
Resistance to isoniazid + rifampicin (MDR)	0.9	1.4	1.7	1.4	0.8

Resistant TB was more common in foreign-born TB patients, than in Swedish-borne, ratio 2.5 (11.7% vs. 4.7%) during the period 1991–2000 and ratio 3.2 (14.7 vs 4.6) in 2001. In 2001 resistance to isoniazid was reported in 2.8% of TB patients born in Sweden and in 9.6% of those born abroad. MDR TB was reported in on average 0.7% of the Swedish born patients and 1.3% of the foreign born patients during the period 1991–2000. Resistance to ethambutol remains rare, and is reported in only a few cases per year. Resistance to pyrazinamide increased from about 1% during the period 1991–1997 to about 3% of culture confirmed cases of *M. tuberculosis* during 1999 and 2000 and then fell to 1.7% in 2001. The proportion of isolates resistant to streptomycin increased from 3.5% in 1991–1997 to 5.3% in 1999 and 6.4% in 2001 (1.8% in Swedish born and 8.4% in foreign born patients). Resistance to streptomycin was most often associated with resistance to isoniazid.

Mycobacterium bovis is naturally resistant to pyrazinamide. During the period 1991 to 2000 M. bovis was identified in 72 patients, four with resistance to other drugs than pyrazinamide and one with MDR TB.

In the majority of patients with resistant TB, resistance has been identified in the initial isolates of *M. tuberculosis* (primary resistance). Resistant TB acquired during treatment has been reported in only a few cases. However, for TB patients previously treated in Sweden before 1989 or abroad, information is not available on the previous results of drug susceptibility tests. Transmission of resistant TB in Sweden has been confirmed in children born in Sweden to foreign-born parents, but also within the foreign-born population.

Victoria Romanus
Sven Hoffner

5. Interventions to minimise resistance

National Coordination: STRAMA

The responsibility for containment of the increasing problem with bacterial resistance to antimicrobial agents is shared between different authorities and organisations. The Swedish Institute for Infectious Disease Control (SMI) has the principal responsibility for surveillance of resistance, which is carried out in close collaboration with the regional microbiological laboratories (Appendix 4). The National Board of Health and Welfare supervises medical care and social services and The Medical Products Agency is responsible for establishing standards and requirements for the development, manufacturing and sales of drugs and other medicinal products. Data on sales and distribution of antimicrobials are provided by The National Corporation of Swedish Pharmacies. Health care is mainly organised and provided by the Swedish County Councils whereas nursing homes and similar forms of housing for the elderly often are run by local authorities. In addition, active participation of several professional organisations is essential to create the knowledge base, action programs and guidelines.

Because of the multi-faceted nature of the resistance problem and the need for cross-sectional national forum a network, the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA), was formed in 1994 [www.strama.org]. The STRAMA network consists of one national co-ordinating committee group and 25 regional groups. The national group is formed by clinical specialists appointed by the Swedish reference group for antibiotics (SRGA) and members representing the SMI, the Swedish Medical Products Agency, the National Board of Health and Welfare, the National Corporation of Pharmacies, the National Veterinary Institute, the Society of County Medical Officers for Communicable Disease Control, the Swedish Board of Agriculture, and the Swedish Network for Pharmacoepidemiology (NEPI). The main tasks of the national STRAMA group are to collect, analyse and share information, make national priorities and to suggest, initiate and co-ordinate nation-wide activities.

The County Medical Officers for Communicable Disease Control act as chairmen of the regional STRAMA groups, which include specialists from different medical fields e.g., general practice, infectious diseases, ENT, paediatrics, clinical microbiology, as well as pharmacists. The main objective of the regional groups is to evaluate the local utilisation of antibiotics and pattern of bacterial resistance. After identifying problem areas, the groups initiate activities to influence health care personnel to improve diagnostic procedures of infectious diseases and the prescribing pattern of antibiotics. In some counties with tertiary care hospitals, special groups are formed to influence the utilisation of antibiotics in hospitals. The STRAMA network should also stimulate an increased knowledge and understanding among both the medical profession and the public at large.

During the period 2000–2002 the STRAMA network has been supported financially by the Swedish Government with 3 million SEK annually.

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 intensive care demography, antibiotic policy, antibiotic use, antibiotic resistance and infection control policies, and to present this information on the home page according to each participating ICU (http://dior.imt.liu.se/icustrama/).The purpose is also to use data as "data for action" to optimise antibiotic use and infection control practices to reduce ICU-acquired infections and to minimise the emergence of antibiotic resistant strains within the units. 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. One important incentive for ICUs to participate has been the feed-back of statistics on 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.

Questionnaires have been sent by electronic mail, beginning in year 2000, to all Swedish adult intensive care units and departments of infectious diseases. Data from the first year was obtained for 38 ICUs providing services to a population of about 6 million and showed that the median antibiotic consumption was 1257 DDD/1000 bed days with a wide range (584-2415) and was positively correlated with mean length of stay but not with mean illness severity scores or ICU category (located in regional, county or local hospital). Antibiotic consumption was higher in ICUs lacking bedside devices for hand disinfection than in other units (2193 vs 1214 DDD/1000 beddays, p= 0.05). In ICUs having a specialist in infectious diseases responsible for antibiotic treatment the consumption pattern was significantly different only for use of glycopeptides (58% lower usage

than in other ICUs, 26 vs 11 DDD/1000 beddays, P=0.02). Only 21% of ICUs had a written guideline on the use of antibiotics, 57% received feedback on antibiotic usage at least every 3 months and 22% received aggregated resistance data annually from the local laboratory but such factors did not correlate with antibiotic usage. Clinically significant antimicrobial resistance were found among *Enterobacter* spp. to cephalosporins, and *Enterococcus* spp. to ampicillin. In order to reduce the time from data collection to publishing the results on the home page we are developing a web-based program, for the coordinated collection of all information. Starting 2002 questionnaires will be available on the Internet and data will be published on the home page, within 24 hours from submission.

Håkan Hanberger

Specific intervention strategies against the spread of penicillin-resistant pneumococci

Background

In 1994, the National Board of Health and Welfare formed an Expert Committee in response to an increasing prevalence of penicillin non-susceptible *Streptococcus pneumoniae* (PNSP – Penicillin G MIC ≥ 0.12 mg/L) in Southern Sweden. The task of the Expert Committee was to identify intervention strategies to limit the spread in Southern Sweden [Ekdahl et al 1994, Forsgren et al 1994], and to prevent a similar situation in other parts of Sweden.

The recommendations of the Expert Committee were presented in 1996 [Socialstyrelsen 1997]. Based on existing knowledge of the MICs of international epidemic PNSP clones, penicillin resistant pneumococci with Penicillin G MIC ≥ 0.5 mg/L (PRP) were targeted for intervention. The proposed intervention activities were focused on children attending group day-care, and included repeated cultures, contact tracing, and exclusion from group day-care, whenever a child carrying PRP was identified.

In January 1996, carriage/infection with PRP (MIC ≥ 0.5 mg/L) became mandatory notifiable by law.

The South Swedish Pneumococcal Intervention Project

The first large-scale attempt to implement these recommendations started in March 1995 in Malmöhus County (from 1998 part of the larger Skåne Region). The South Swedish Pneumococcal Intervention Project, which is still running, has the aim to reduce the spread of PRP (Penicillin G MIC ≥ 0.5 mg/L). It is a community-based project combining the STRAMA initiative with interventions focused on children [Ekdahl et al 1998].

Since March 1995, all PRP are directly reported from the three microbiology laboratories in the county to the county Office of Communicable Disease Control (OCDC) in Malmö. Whenever an individual with an infection due to PRP is identified ("index case"), the county OCDC contacts the local health-care centre of that patient. The local physician is then responsible of securing nasopharyngeal specimens from family members and other close contacts (e.g. day-care group) of the index case, in order to identify additional carriers in the surrounding population ("contact cases").

All carriers (index cases as well as contact cases) are followed with weekly nasopharyngeal cultures, until two consecutive negative specimens have been obtained (defined as PRP negative). All control cultures, and other health care contacts due to the project are free of charge for the individual patient. If an identified carrier is a child participating in any form of child day-care, nasopharyngeal specimens are also obtained from the staff and other children in that day-care group. If more carriers are found, the screening procedures could be extended to the whole day-care centre. Repeated cultures are then obtained every 1–2 weeks from the children and staff, until no more carriers are identified.

Pre-school children that are identified as carriers must refrain from group day-care until PRP-negative. The parents of these children are able to abstain from work with full reimbursement from the social security system, if the day-care could not be arranged in any other way. In a limited number of children with prolonged PRP carriage, eradication treatments with rifampicin in combination with amoxicillin, erythromycin, or clindamycin, have been used successfully [Ekdahl et al 1997A]. However, such treatments should be given with caution due to the risk of selecting rifampicin-resistant strains.

The parents of PRP-carrying small children are urged to have them avoid close indoor contacts with other small children or frail elderly people. Out-door play or other activities (shopping, visit at the library etc.) are considered to constitute such a small risk of transmission that no limitations are recommended in these cases. PRP-carrying school children and adults are recommended to stay home from school or work only if having symptoms of an acute respiratory tract infection.

During the seven years the project has been running, data from Skåne has increased the knowledge of the epidemiology of PRP [Ekdahl et al 1997B]. The much-feared exponential increase in the PRP prevalence, noted in other countries, have not been observed in Southern Sweden. Instead the PRP prevalence has remained on the same or slightly lower levels than when the project started. Since the antibiotic consumption has decreased during the same period as the day-care interventions have been in place, it is hard to single out the impact of each of these factors.

The results from investigations within the frames of the project have further shown the importance of antibiotics as a risk factor for the spread of PRP [Melander et al 1998, Gunnarsson et al 1998].

Intervention strategies in other counties

In the years after the issue of the Expert Committee recommendations, all Swedish counties have adopted local strategies against the spread of PRP. However, these strategies have differed considerably, especially with regard to day-care interventions.

To map current intervention activities, a questionnaire was sent to all 21 County Medical Officers for Communicable Disease Control during the spring of 2001 to map the current local control strategies against PRP. Questions were asked on the extent of contact tracing, culture follow up on identified carriers, and intervention measures in day-care centres.

Local strategies varied considerably, but three main approaches could be identified: 1) A more individual approach, where no general actions were taken when a PRP case was identified, and contact tracing was rarely done. 2) Large scale interventions including consistent contact tracing, repeated cultures in day-care centres with identified cases, and exclusion of carriers from group day-care until one or two negative cultures has been obtained. 3) A middle way approach, with comprehensive contact tracing, repeated cultures in day care centres, but exclusion only of PRP carrying children with ongoing upper respiratory tract infection (Figure 5.1).

Community prevalence studies have been performed in child welfare centres clinics in Gothenburg [Borres et al 2000] and in day-care centres in Stockholm [Christenson et al 1997].

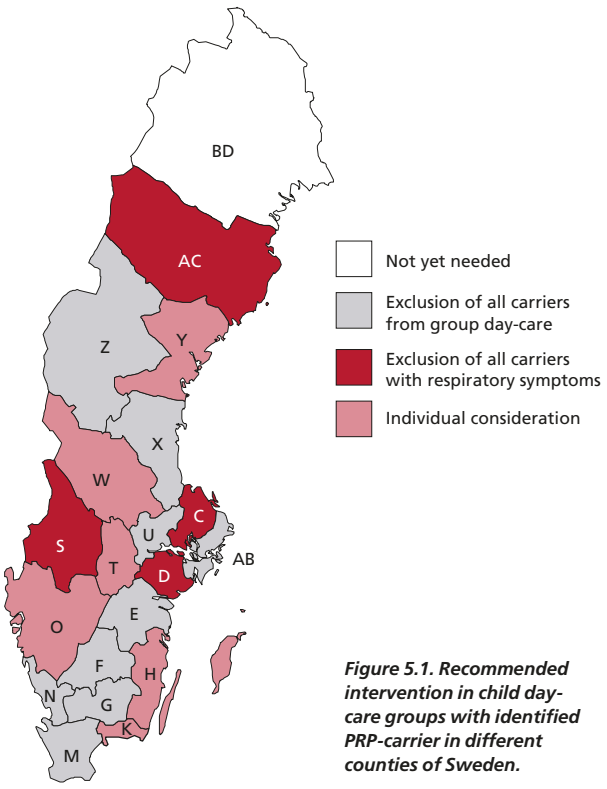


Figure 5.1. Recommended intervention in child day-care groups with identified PRP-carrier in different counties of Sweden.

A policy program for detection and prevention of dissemination of multiresistant bacteria in Swedish health care institutions.

Multiresistant bacteria are rare in hospitals in Sweden and other Nordic countries. The frequencies of MRSA, VRE and multiple resistant Gram-negative bacteria in Sweden are below 1%, only interrupted by short term local outbreaks of primarily MRSA and occasionally VRE. So far these outbreaks have been successfully combated. Hospital and community infection control units make every effort to prevent the introduction and spread of these bacteria in the hospital and nursing home environment. Following the joint initiative of the Swedish Reference Group of Antibiotics, the STRAMA network and the Swedish Society for Hospital Infection Control, a guideline was published on the Internet (http://www.srga.org/mrb/index.html). It is available to all concerned parties and contains sections addressing personnel and patients in hospital and community health care, personnel in hospital and community infection control and microbiological laboratory personnel.

In essence, all patients who have been hospitalised (or regularly received treatment in a hospital) outside the Nordic countries during the last 6 months prior to their admission to a Swedish hospital, are screened for multiresistant bacteria (in 2002 defined as MRSA, VRE, multiple resistant Gram-negative bacteria) immediately on admission to the ward. Similarly, all hospital personnel (Swedish or foreign) who have worked in health care institutions abroad during the last 6 months are screened for multiresistant bacteria. A set of samples taken from the nose, the perineum and faeces from patients and from the nose and perineum from personel is screened for MRSA, VRE and multiresistant Gram-negative bacteria (resistance to three or more of the following: piperacillin, ceftazidime, imipenem, aminoglycoside, quinolone). Additional samples from catheters, eczema, skin lesions etc are taken if relevant. Screening samples should be negative before the patient is allowed in general wards and personnel allowed in direct patient care.

The same rules apply to patients and personnel that have been in contact with multiresistant bacteria within the Swedish health care sector and to all parts of the health sector. The program further contains Swedish and English information to patients and personnel on multiresistant bacteria and was recently updated with strategies for community institutions and homes for the elderly.

MRSA intervention strategies in the Västra Götaland Region

In the fall of 1997, an increase in the incidence of MRSA was observed in the Västra Götaland Region, especially at the Sahlgrenska University Hospital (SUH) in Gothenburg, an outbreak mainly caused by an international epidemic MRSA clone (E-MRSA 16). The outbreak reached its peak in 1999, when 134 new MRSA cases were registered, 88 of which belonged to the E-MRSA 16 clone. This clone has since caused several smaller outbreaks in 1998–2000, the most recent at the SUH in May 2000.

Due to increased awareness, intensive contact tracing, and liberal indications for culturing, also in outpatients, an increase in other, less epidemic, MRSA strains have been noted. In 2001, altogether 56 patients were notified with MRSA in the region, belonging to several different clones, and consisting both of locally contracted and imported infections. Only three patients at the SUH, and seven in the rest of the region were found with E-MRSA 16. The cost of MRSA cultures in 1997–2000 has been 9.3 million SEK.

A cornerstone in the strategy has been that every MRSA-case should have a responsible doctor with the specific task to inform the patient, the patient's family, and when the patient is staying at a nursing home, also the staff. Of strains, other than E-MRSA 16, only a few clusters of cases have been noted in outpatients, with no previous hospital contacts, being treated for wound infections or furuncles. When such patients later have been treated in hospital no secondary spread has been noted.

It has been considered important that the initial management of MRSA patients has been the same for all cases. After the result of the initial investigation and genotyping of the MRSA strain, an individual management has been adopted, especially in those cases where the MRSA have been isolated only from the nares or from the throat. A number of patients with transient carriage at these sites have been noted. This carriage has often been successfully terminated after treatment with topical mupirocin.

The strategy against MRSA is based on:

- routine screen cultures of all patients with a history of hospital care in another country, and of all staff that have worked abroad;.
- liberal indications for culturing before initiation of antibiotic treatment;
- control program for known MRSA patients;
- training programs in hygiene for staff in hospitals and municipality health care;
- close collaborations between the patients' "MRSA doctors" and those responsible for communicable disease control and hospital hygiene.

An action plan for MRSA in municipality health care and primary care, as well as a report for the period 1998–2000, are both available at the website [http://www.vastragotaland.net/zv0011].

Describing, analysing and influencing antibiotic prescribing practices

Through its regional groups, the STRAMA network is involved in many projects to describe, analyse and influence prescribing practices. Some recent examples of such projects are presented below.

The STRAMA diagnosis-antibiotic prescribing survey

Published data are scarce on the proportion of patients with different diagnoses that are given antibiotic treatment except for a few local projects. On a national level information on the antibiotic prescription pattern for various diagnoses has so far been limited to data from the annual, national diagnosis and therapy survey [The National Corporation of Swedish Pharmacies, 1990-2000]. However, in recent years low participation rates have been noted, especially among general practitioners, and the survey has now been terminated.

Therefore, a focused diagnosis-antibiotic prescribing survey was initiated by STRAMA. It was performed in November 2000 in five counties, comprising almost 1.3 million inhabitants [Stålsby Lundborg et al 2002]. Physicians in primary care and outpatient clinics in ENT, paediatrics, and infectious diseases completed a one-page form for all patients seeking care for an infectious complaint. 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 by the patient, diagnosis by the doctor, diagnostics used, and if an antibiotic was prescribed, the drug, and duration of treatment. In addition information was collected on factors such as chronic diseases or requests by the patient, that were believed to have influenced the choice of treatment. Altogether 7 029 forms concerning patients with infectious complaints (with a suggested diagnosis) were returned to the research group and were thus included in the analysis.

Ninety-two percent of the forms emanated from primary care. Twenty-five percent concerned children below eight years of age. Respiratory tract infections were most common (70% of the cases), followed by urinary tract infections and skin and soft-tissue infections (14% and 10%, respectively). Overall an antibiotic was prescribed in 59% of the cases, varying from 5% of unspecified upper respiratory tract infections to 97% of tonsillitis (Figure 5.2). The number of cases per diagnosis and the proportion of these receiving an antibiotic are shown.

Penicillin V was the most commonly prescribed antibiotic,

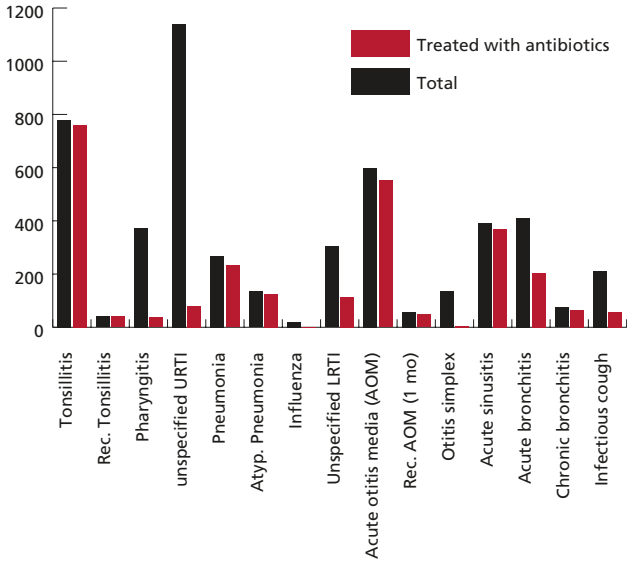


Figure 5.2. The number of cases per diagnosis and the number of these receiving an antibiotic in the 2000 diagnosis-antibiotic prescribing study.

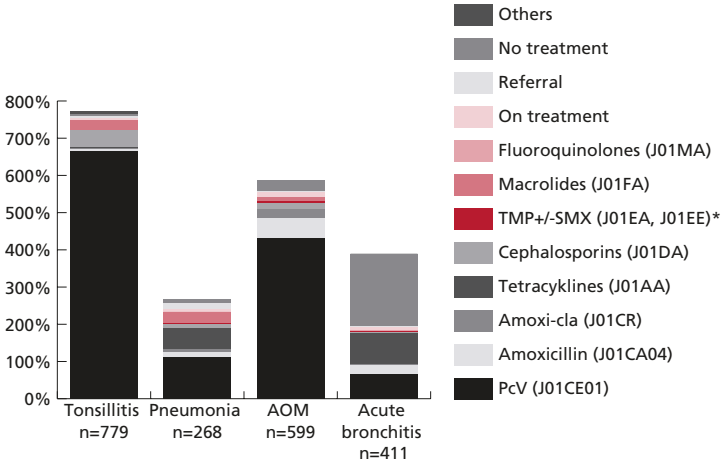


*Figure 5.3. The pattern of antibiotics for some of the respiratory tract infections in the 2000 STRAMA diagnosis-antibiotic prescribing study. * Almost exclusively J01EA trimethoprim alone.*

used in 62% of the respiratory tract infections, and dominated particularly in tonsillitis (88%), whereas tetracycline was the leading agent for bronchitis. The pattern of antibiotics for some of the respiratory tract infections is shown in Figure 5.3.

About six month before the study new guidelines regarding treatment of acute otitis media in children were distributed [Swedish Medical Research Council, online]. These guidelines recommend in children above two years of age as an alternative to immediate antibiotic prescribing, two days of expectancy for a possible spontaneous decline of symptoms. This alternative treatment strategy had had little impact at the time of the study (Figure 5.4).

A similar study will be performed in November 2002 to follow treatment patterns and to gather more data fore discussions regarding actual and recommended practices.

Influencing prescribing practices

Changing prescribing behaviour is a complex process focusing on the individual and involving several steps – from learning about a new strategy to an individual persuasion into a decision to change practices. After that a process to establish the new prescribing practice, involving some kind of effort on the part of the prescriber takes place. The body of knowledge on the methods to influence prescribing practices is continuously growing. The current state of knowledge could be summarised as follows. Distribution of printed material alone has small and uncertain clinical significance. Also didactic sessions alone are unlikely to change professional practice. On the other hand, it has repeatedly been shown in randomised controlled trials that to be effective in changing prescribing behaviour multifaceted strategies are needed. The strategies should preferably include the following parts:

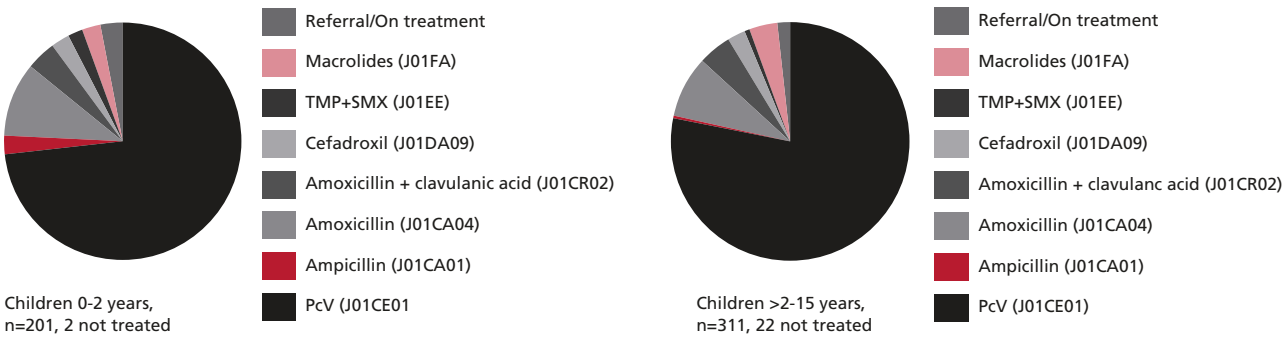


Figure 5.4. Treatment of acute otitis media (AOM) in children 0–2 years and children >2–15 years of age from the 2000 diagnosis-antibiotic prescribing study.

1) educational outreach/academic detailing (an external credible facilitator visiting individual practitioners or small groups of practitioners);
2) they should be based on problem based learning of a limited content;
3) small group peer discussions should be used
4) preferably also some kind of feed-back should be included

In addition, use of available guidelines and a combination of different strategies is recommended.

The National Corporation of Swedish Pharmacies has since more than 10 years each year focused information and communication campaigns to the general public and health professionals on various themes e.g. Diabetes, Pain, Cardiovascular Diseases, etc. During 2000–2001, the focus was "Infections". This year activities were done in close collaboration with the STRAMA network. One educational material that was developed was a series of fictitious cases that could be used during educational outreach sessions by pharmacists in collaboration with general practitioners or infectious disease specialists. This form of educational outreach had previously been proven effective for uncomplicated urinary tract infection in Sweden [Stålsby Lundborg, 1999B]. Altogether 12 different cases series were developed. One example of a case in the urinary tract infection (UTI)-case series is shown in Figure 5.5.

A female patient visits your office. She complains of painful and frequent micturition since the day before yesterday. She has no fever and on physical examination there are no abnormal findings indicating pyelonephritis. Urine examination shows a positive nitrite test and a positive test for leukocyturia. Your diagnosis is lower uncomplicated UTI.

A. Age: 25 years (not pregnant).
B. Previous episodes of lower uncomplicated UTI: Occasional episodes, last episode two months ago (treated with trimethoprim)
C. Severity of symptoms: Moderate pain; micturition twice hourly or more
D. Circumstances: Your own patient on a Tuesday morning

Questions:

1. Would you prescribe a drug for this patient? ❑ No ❑ Yes
2. If yes, which drug would you prescribe? Please motivate.
3. For how long?

Figure 5.5. Fictitious UTI-case for educational outreach sessions.

Educational days for local STRAMA representatives on how to use the case series in educational outreach were held and later this method was used in small groups around Sweden. More than 200 general practitioners participated in such educational sessions. In the sessions individual feedback was given on decisions on the cases series and in many cases also on which factors influenced the decision. In addition local guidelines, when available, were discussed and feedback on prescribing patterns were presented when possible. The advantage of using also feedback from decisions on the fictitious cases are that all doctors in a group then has taken decisions on the same patients, thus showing more differences in decisions between doctors rather than differences in the patients lists etc. The differences in decisions between individual doctors are usually clear and immediately elicit a lively discussion. The participants completed a questionnaire in connections with the discussions. More than 80% of the participants thought that the method was useful and would like to use the same method also for other areas. In one part of Sweden the method will be continuously used in a project to follow its impact on prescribing practices.

Audit Project Odense

The method of Audit Project Odense (APO) has been widely used in primary care to improve treatment of respiratory tract infections. In APO, a special form for registering patients is developed by the participating physicians and used before and after an intervention. Such educational outreach, including individual feed back, has shown to be effective. The method of registering patients has also been used in other areas, e.g. urinary tract infections in the elderly and infections diseases in nursing homes, both examples where interventions seem necessary.

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
PRP	Penicillin-resistant pneumococci
RFLP	Restriction fragment length polymorphism
RSQC	Resistance Surveillance and Quality control programme
SMI	Swedish Institute for Infectious Disease Control
SRGA	The Swedish Reference Group for Antibiotics
SRGA-M	The Swedish Reference Group of Antibiotics- subcommittee on Methodology
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. Average population by county and age group 2001.

County	0–6 years	7–18 years	19–65 years	> 65 years	Total
Blekinge (Blek)	10 265	22 517	89 927	27 659	150 368
Dalarna (Dlrn)	18 736	45 019	161 940	52 104	277 799
Gotland (Gotl)	3 941	9 735	34 075	9 766	57 517
Gävleborg (Gävl)	18 484	42 899	165 346	52 151	278 880
Halland (Hall)	21 686	45 849	162 854	45 603	275 992
Jämtland (Jmtl)	8 509	20 339	75 878	24 506	129 232
Jönköping (Jkpg)	25 171	54 747	190 967	57 108	327 993
Kalmar (Kalm)	15 768	37 569	136 855	45 003	235 195
Kronoberg (Kron)	12 663	27 876	104 868	31 370	176 777
Norrbotten (Nbtn)	17 633	39 963	154 567	43 488	255 651
Skåne (Skån)	84 524	172 450	686 440	189 760	1133 174
Stockholm (Sthm)	150 814	264 347	1170 978	245 074	1831 213
Södermanland (Södm)	18 467	41 419	152 424	44 477	256 787
Uppsala (Upps)	23 104	47 369	185 127	39 977	295 577
Värmland (Vrml)	18 903	42 190	161 626	51 909	274 628
Västerbotten (Vbtn)	18 267	41 092	154 070	41 964	255 393
Västernorrland (Vnrl)	16 433	36 886	145 729	47 106	246 154
Västmanland (Vstm)	18454	40 689	154 525	43 925	257 593
Västra Götaland (Vgöt)	113 610	233 223	907 449	243 641	1497 923
Örebro (Öreb)	20 221	42 311	163 141	47 869	273 542
Östergötland (Östg)	30 289	64 124	248 848	68 745	412 006
All counties	665 942	1 372 613	5 407 634	1 453 205	8 889 394

Table App 2.2. Population of Sweden 1997 – 2001 (December 31).

	1997	1998	1999	2000	2001
Population (thousands)	8 846	8 851	8 861	8 882	8 908

More detailed demographic data is available at the Internet web page of Statistics Sweden (http://www.scb.se/eng/befovalfard/befovalfard.asp).

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 (x 1000)	Blood (pairs of bottles)	Cerebro-spinal fluid (CSF)	Nasopharynx	Throat	General culture	Faeces SSYC	Screen MRB / MRSA	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Enterococcus sp*	*Enterococcus faecalis*	*Enterococcus faecium*
Borås	Southern V Götaland	273	8985	208	5456	9433	12913	7058	2696*	4214	1006		2234	323
Eskilstuna	Södermanland	257	5547	105	6352	7968	4859	5800		3036	1050		2191	101
Falun	Dalarna	278	7123	166	2095	2365	7536	3332	1000	3281	414		1460	178
Gävle	Gävleborg	273	4062	360	4003	3069	9419	5847	515	2950	615		1483	238
Göteborg	Southern Bohuslän + Gothenburg	700	21974	1115	3962	5778	18544	14963	-	2526	931		375	92
Halmstad	Halland	275	5472	131	3861	5292	9155	5039		3237	646		1181	263
HS, Stockholm	Southern Stockholm	900	19807		23342	11182	26655	14817	2336	9330	3806		4400	834
Jönköping	Jönköping	340												
Kalmar	Kalmar	235												
Karlskrona	Blekinge	152	3141	63	1351	2151	4863	2772	203	1977	305		1190	190
Karlstad	Värmland	274	10562	130	934	2333	9066	3684	2252	3825	309		1872	266
Kristianstad	North-Eastern Skåne	260	6389		6515	8088	12143	7731	263	5180	1314		2788	325
KS, Stockholm	Northern Stockholm	900	21387	4208	31531	17058	33258	16750	307**	10514	3764	6278	310	647
Linköping	Östergötland	412	12295	444	5861	4437	14532	8657	1226	4652	1040		697	113
Lund	Lund, Landskrona, Orup, NW Skåne	520	13809		12056	8348	26587	15292	7964	6908	2812		5303	356
Malmö 2001	Malmö, Trelleborg	346	10246	260	6429	8673	15332	9040	6153	5377	1535		3616	339
Skövde	Skaraborg	260	7803	143	3543	3758	8038	4841		3421	904		3218	9
St Göran NMAB	St Göran hospital+ private GPs		3227		8874	7648	7784	8948		3141	1289		2811	81
Sunderby (Luleå)	Norrbotten	260												
Sundsvall	Västernorrland	254	7278		4300	3033	10179	5022	1130	3448	734	2011	11	108
Uddevalla	Parts of V Götaland	280	10558	113	2437	4299	7773	6609	2745	3968	535		2947	296
Umeå	Västerbotten													
Uppsala	Uppland	300	11695		5362	2845	15673	7597	4018	4317	812	3655		
Visby	Gotland	58												
Västerås	Västmanland	265	6904	177	3732	4006	7622	4863	881	3045	672		2186	109
Växjö	Kronoberg	190	3552	93	2135	3306	5103	4113	629	1657	327		668	80
Örebro	Örebro	274	11557	202	8793	2238	11549	4899	1145	5262	1142		3113	202
Östersund	Jämtland	128	4059		2269	2222	4692	2392	392	2102	455		1341	119

* Wound cultures included.

** Most MRSA cultures included in General cultures.

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. This 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.

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 packs.

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 packs and number of defined daily doses.

The national diagnosis and therapy survey

Since 1978 prescribing among general practitioners and specialists has been studied in Sweden in the National Diagnosis and Therapy Survey. This study enables analyses of diagnoses for which a specific drug is prescribed – its diagnoses profile and also the spectrum of drugs that are prescribed for a certain diagnosis/symptom – its drug profile. The study is based on a current sample of practising physicians in Sweden. In year 2000, 1257 physicians participated. Since the validity of the data from this study is uncertain we have chosen not to present them in this report. Due to the low participation rate, the survey in its previous form has been terminated. A new form for this kind of survey is presently under development.

In Sweden, the Anatomic Therapeutic Chemical (ATC) classification system as defined by the WHO Collaborating Centre, is used for drug statistics methodology. Due to a reclassification in the ATC classification system, methenamine is since 2000 included in the ATC group J01. In 2001, on a national level, methenamine accounted for 1.6 DDD/1000/day. Methenamine is mostly prescribed in the age-group 80 years or older – patients who often get their drugs by a dose-system (Apodos) managed by the local pharmacy. The system started in 1993 but was not included in the statistics until 1999 (Figure Appendix 3.1). For historical comparisons we have excluded methenamin from the presentations in this report.

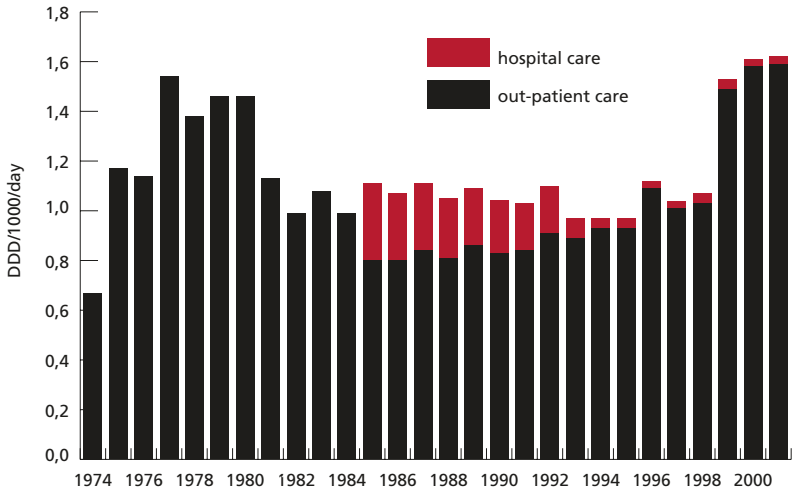


Figure Appendix 3.1. Methenamine sales 1974-2001

ATC-code	Antibiotics registered in Sweden 2001
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

Table Appendix 3.1. ATC-codes and drug names in Sweden 2001

Appendix 4 – Antibiotic Susceptibility testing

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

The Swedish clinical microbiology laboratories, in collaboration with the SRGA-M, have successfully standardised the disk diffusion method. It is used as the routine method for susceptibility testing, and as a screening method. In some instances the disk diffusion method 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 E-test (beta-lactam resistance in pneumococci, chromosomally mediated beta-lactam resistance in *Haemophilus influenzae*). In still other instances methods for enzyme detection (beta-lactamase detection in *Haemophilus influenzae*, *Neisseria gonorrhoeae* and others) are used.

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 corresponding antibiotic containing paper disks, interpretive criteria for SIR-categorization are provided by the SRGA-M. They are regularly updated and available through the Internet web site [http://www.srga.org].

Each laboratory performs internal and external quality assurance and quality control of susceptibility testing. Internal quality control includes using international quality control 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, as presented by the ResNet (Figur Appendix 5.1).

External quality control is often done by participation in UK-NEQAS and other international programs, whereas quality assurance is one of the features of the Swedish annual RSQC programme.

For in vitro susceptibility testing of *M. tuberculosis* other techniques must be used. There are four generally accepted reference techniques, three based on culture on solid medium, and one based on a liquid culture. The later (the radiometric BACTEC 460-TB method) is the one used in Sweden. In this assay the tested strain is grown in a radiolabelled broth and growth/growth inhibition, in the presence of a defined concentration of the drug to be tested, is measured as the production of $^{14}CO_2$. An antibiogram could be achieved within a week, compared to three-four weeks for the reference techniques based on solid culture. For the testing of second line drugs there are still no reference techniques acknowledged. Such testing should be centralised to experienced reference laboratories and the current WHO recommendations should be considered, (Guidelines for drug susceptibility testing for second-line anti-tuberculosis drugs for DOTS-Plus, WHO/CDS/TB/20012.288).

A national system for quality assurance organised from SMI was established in 1998.

Appendix 5 – National surveillance of antibiotic resistance

Components of the national surveillance of antibiotic resistance

The Swedish national surveillance of antibiotic resistance currently rests on:

1. The statutory notification of penicillin-resistant pneumococci (PRP), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE), regulated in the Communicable Disease Act;
2. Voluntary reporting of some specified unusual or newly identified resistances;
3. The long tradition of combined resistance surveillance and quality control, carried out by the Swedish microbiology laboratories, the Swedish Reference Group of Antibiotics – subcommittee on Methodology (SRGA-M), and the Swedish Institute for Infectious Disease Control (SMI);
4. The Swedish commitment to report resistance in certain bacteria isolated from invasive disease to the European Antimicrobial Resistance Surveillance System (EARSS);
5. Sentinel surveillance of resistance in certain pathogens (e.g. *Salmonella, Shigella, Campylobacter, Helicobacter*, *Neisseria gonorrhoeae, Neisseria meningitidis*) by certain dedicated laboratories.

Surveillance regulated in the Communicable Disease Act

Statutory notifications of certain communicable diseases are regulated in the Communicable Disease Act of 1988. With the exception of certain sexually transmitted infection (STI), both the clinician caring for a patient with a notifiable disease (clinical notification) and the laboratory diagnosing the pathogen causing the disease (laboratory notification) are obliged to notify. This double notification significantly enhances the sensitivity of the surveillance system.

Notification shall be done within 24 hours, in duplicate to the County Medical Officer for Communicable Disease Control and to the 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 antibiotic resistant pathogens are presently included in the list of notifiable diseases. Penicillin-resistant *Streptococcus pneumoniae* with Penicillin G MIC > 0.5 mg/L (PRP) have been notifiable since 1996. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE) have been notifiable since 2000. The 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 published annually 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 between 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 newly detected) pathogen-resistance combinations is under construction. The pathogens are so selected that each finding should trigger some action (either confirmation testing or infection control measures). To make the system comprehensive, the identification and reporting of these pathogens from the local laboratory computer systems to the SmiNet must be automated.

Annual Resistance Surveillance and Quality Control (RSQC) programme

In 1994, a model for the concomitant surveillance of antimicrobial resistance and quality of antimicrobial susceptibility testing was devised [Kahlmeter et al, 1997]. 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 routine antimicrobial susceptibility testing methods of the laboratories are strictly standardized and controlled through the combined work of the SRGA-M (Appendix 4).

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100 consecutive clinical isolates of a number of species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this annual programme. On one or several occasions *Escherichia coli*, *Enterococcus faecalis/faecium, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella* and *Enterobacter* spp. have been part of these surveys. The number of commonly used antibiotics tested for each pathogen has varied between 4 and 6.

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

A typical result for nine laboratories is shown in Figure Appendix 5.1.

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 instantly permit web feed-back in the form of resistance rates for 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 data are available to the profession and to the public on < http://www4.smittskyddsinstitutet.se/index.html >.

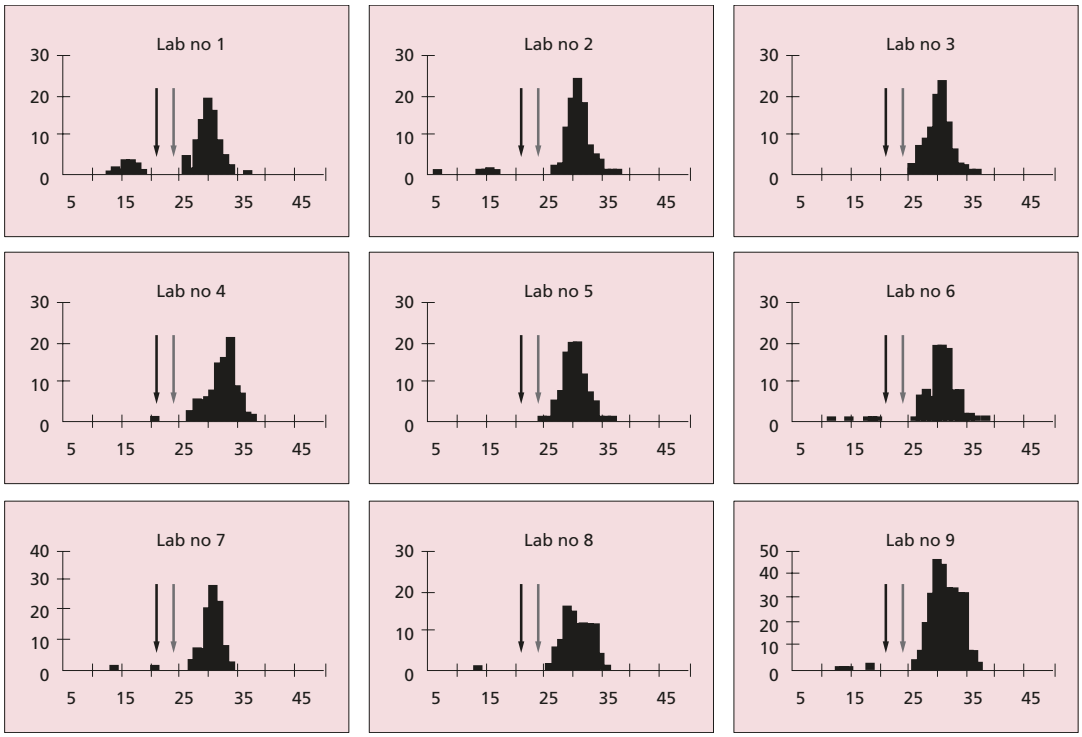


Figure App 5.1. Individual laboratory zone diameter distributions and breakpoints for Streptococcus pyogenes and erythromycin. Each laboratory tested 100 consecutive patient isolates using an erythromycin 15 µg disk. The zone diameter distributions were processed by the SRGA-M. National Breakpoints S/R 23/19 mm [www.srga.org].

EARSS

EARSS, funded by the Health and Consumer Protection Directorate-General 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 to invasive infections of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis/faecium* isolates, and monitors variations in antimicrobial resistance over time and place.

Participation in the 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 regularly provided susceptibility data. Information about EARSS, as well as a database yielding information about the susceptibility results for each country, year and pathogen, is available through an Internet web site < http: //www.earss.rivm.nl >.

Data collected by the EARSS should be routinely generated quantitative data (MICs or inhibition zones), but the data presented are only in susceptibility categories (S I R). External quality assurance exercises have been carried out by the EARSS, in cooperation with UK-NEQAS and the EARSS Advisory Board, in 2000 and 2001. 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 antibiotic resistance, yet could and should be extended and improved.

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

Sentinel surveillance

Susceptibility testing of gastrointestinal pathogens such as *Salmonella, Shigella, Campylobacter jejuni/coli, Clostridium difficile* 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) will be made available also for data on these pathogens, as well as for national quantitative data on *Neisseria gonorrhoeae* and *N. meningitidis* performed by the Reference Laboratory in Örebro. Also collections of quantitative susceptibility data on other pathogens or sets of isolates of general interest are suitable for entering and displaying in the ResNet.

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Appendix 4

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Appendix 5

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