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**A Report on Swedish Antimicrobial Utilisation
and Resistance in Human Medicine**




Strama

Swedish Strategic Programme
against Antibiotic Resistance



SMITTSKYDDSIINSTITUTET

Swedish Institute for Infectious Disease Control



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



Strama, The Swedish Strategic Programme against Antibiotic Resistance was founded in 1995. The remit from the Government is to collaborate interdisciplinary on issues aiming to preserve the effectiveness of antibiotics.

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Content

1 Preface.....	3
2.1 Summary	4
2.2 Sammanfattning.....	6
3. Use of antimicrobials	8
3.1 Use of antibiotics	8
3.2 Use of antifungals	17
4. 1. Antimicrobial resistance.....	18
<i>Staphylococcus aureus</i>	18
<i>Streptococcus pneumoniae</i>	21
<i>Enterococcus faecium</i> and <i>Enterococcus faecalis</i>	23
<i>Streptococcus pyogenes</i>	24
<i>Streptococcus agalactiae</i>	24
<i>Haemophilus influenzae</i>	24
<i>Clostridium difficile</i>	25
Extended spectrum beta-lactamase-producing <i>Enterobacteriaceae</i> (ESBL)	25
<i>Escherichia coli</i>	26
<i>Klebsiella pneumoniae</i>	26
<i>Pseudomonas aeruginosa</i>	27
<i>Helicobacter pylori</i>	28
<i>Salmonella</i> and <i>Shigella</i> spp.	28
<i>Campylobacter</i> spp.....	28
<i>Neisseria gonorrhoeae</i>	28
<i>Neisseria meningitidis</i>	29
<i>Mycobacterium tuberculosis</i>	29
4.2. Antifungal resistance.....	31
Appendix 1: Contributors	33
Appendix 2: Abbreviations.....	34
Appendix 3: Demographics and denominator data	35
Appendix 4: Surveillance of antibiotic consumption	37
Appendix 5: Antibiotic Susceptibility testing	38
Appendix 6: National surveillance of antibiotic resistance.....	38
Appendix 7: Recent publications (2005-2007).....	40

1 Preface

WELCOME to the eighth Swedish report combining results from the monitoring of antimicrobial resistance and antimicrobial usage in both human and veterinary medicine: SWEDRES and SVARM. These joint reports facilitate comparisons of resistance levels and incidence of use in the two areas.

International reports of transmission of MRSA between pigs and humans and our own experience of outbreaks affecting dogs and personnel in small animal hospitals further emphasize the zoonotic potential of antibiotic resistance and need for continuous close collaboration between human and veterinary medicine. Many questions remain to be answered such as the potential importance of transmission of some types of resistance via the food-chain or the environment. The installation of a “Strama VL” focussing on veterinarian and food-related aspects on antimicrobial resistance will obviously strengthen this process.

In human medicine it became evident in 2007 that the occurrence of enteric bacteria producing ESBLs (extended spectrum beta-lactamases) rapidly has developed into an endemic situation reaching beyond the healthcare sector out in the community and emerging as an obvious threat to public health. In response to this Strama developed and distributed a suggestion for a national action plan. A newly detected major outbreak of vancomycin-resistant *Enterococcus faecium* (*vanB*-genotype) affecting several counties may call for similar action.

The good news is that, even if figures must be interpreted with caution, the domestic transmission of MRSA appears to have levelled out in the health-care sector. At best, this is a result of

intensive infection control efforts and screening programmes within the health-care sector and long-term care facilities. As community acquisition now seems to dominate, this will call for complementary strategies.

Antibiotic consumption increased for the third year in a row. This is worrisome since reasons are not fully understood, although under investigation. There is still a wide variation in consumption of different antibiotics between counties and municipalities that cannot be explained by differences in disease burden. Particularly worrying is an overall high consumption of quinolones (as compared to neighbouring Scandinavian countries) despite an improved compliance to guidelines for treating lower urinary tract infections among women, and a high use of cephalosporins in hospital care. This profile of consumption may enhance the spread of the quinolone-resistant hypervirulent strain of *Clostridium difficile* ribotype 027/nap1, if introduced. This strain has not yet been found in Sweden but systems for detection and surveillance are insufficient and urgently need to be improved.

Fighting antibiotic resistance and development of new antibacterial drugs is a global concern. This is becoming increasingly evident as Strama's and SMI's expertise support is increasingly asked for at an international level. The topic has also reached the political agenda internationally. A European Antibiotic Awareness Day will be held in November 2008 and different aspects on antibiotic resistance will be a continuous topic through the French, Czech and Swedish EU-presidencies in 2008-2009.

2.1 Summary

Use of antimicrobials

The use of antibiotics in Sweden has increased during the last three years, particularly in children. During 2007, penicillin V and tetracyclines were the most prescribed antibiotics in community care, representing about 50% of the antibiotic use measured in defined daily doses. An increase in antibiotic use was seen in almost all 21 counties. Uppsala county was the only one to show a decline over the last two years. Stockholm had the highest use with 485 prescriptions/1000/year and Västerbotten the lowest with 346 prescriptions/1000/year.

According to the individual-based Prescribed Drug Register, supplied by the Swedish National Board of Health and Welfare, more than one quarter of the Swedish population took antibiotics in the community in 2007 (254 users/1000 inhabitants and year).

The difference between counties was considerable when comparing antibiotic use within community care in children aged 0–6 years. Children in Halland received almost twice the amount of antibiotics per 1000 inhabitants that children in Jämtland received. A comparison between municipalities reveals an even greater difference. Generally, antibiotics were prescribed less often in northern Sweden than in the southern parts. This is also true for antibiotics commonly used for respiratory tract infections. The use of these antibiotics in Stockholm was nearly twice that in Västerbotten.

The use of antibiotics in hospital care has increased continuously since the end of the 1990s. Cephalosporins are the most commonly used. Together with beta-lactamase resistant penicillins, tetracyclines and fluoroquinolones they account for more than half of inpatient prescribing. Over the last three years, increases were seen primarily in tetracyclines and the various types of penicillins. A slight dip in the use of cephalosporins was seen during 2007.

The hospital care use of cephalosporins and carbapenems per county is analysed in this Swedres report. Uppsala county showed a distinct decrease in cephalosporin prescribing and a large increase in carbapenem prescribing. This is probably the consequence of new recommendations in response to an outbreak of ESBL producing *Klebsiella pneumoniae*. Östergötland and Västerbotten also had a relatively high use of carbapenems per 100 patient-days compared to other counties.

The large increase in tetracyclines in hospital care is probably partially explained by the increasing number of genital infections caused by *Chlamydia trachomatis* reported to the Swedish Institute for Infectious Disease Control during 2007. Increasing prescribing rates per county correlate well with the increasing number of reported cases of *Chlamydia* per county.

Antibiotic resistance

While a few forms of antibiotic resistance are notifiable under the Communicable Disease Act the vast amount of data on

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

Staphylococcus aureus: A total of 1128 cases of MRSA were notified in 2007, a 7% increase compared to 1057 cases in 2006. More than half of the reported cases (608 cases) had acquired MRSA in Sweden, and one-third (376 cases) had been acquired abroad, the remaining having several alternatives or lacking data. Five of the Swedish counties had an incidence of notified MRSA cases above the average country incidence of 12.3 cases/100 000 inhabitants. These counties were all but one the same as in 2006.

Invasive isolates of MRSA were fewer in 2007 (n=11/2173, 0.5%) than in 2006 (n=16/1865, 0.9%) and thus Sweden is still one of the few countries having less than 1% of MRSA among invasive *Staphylococcus aureus*, as reported in the European surveillance network EARSS.

Epidemiological typing of all MRSA isolates has been performed by spa-typing since 2006. The five most commonly encountered spa-types in 2007 were t032 (n=105), t008 (n=102), t044 (n=87), t002 (n=69), t037 (n=29). The prevalence of MRSA with PVL toxin was slowly increasing. PVL-positive isolates with PFGE-type SE03-5 (spa-type t008) showed the most rapid increase. This PFGE pattern was identical to the one of USA300, an MRSA-type described as being rapidly spreading internationally in the community.

Staphylococcus aureus from wound infections (RSQC programme) were susceptible to antibiotics in >95% of the cases, the only exception being fusidic acid resistance which was decreasing but still above 5%.

Streptococcus pneumoniae: In 2007 there were 672 notifications of PNSP (*Streptococcus pneumoniae* with MIC of penicillin > 0.5 mg/L) in Sweden. PNSP have decreased in annual incidence rate from 10.1 in 1997 to values between 6 and 8 per 100 000 population since 2000. Most cases were identified through nasopharyngeal culture. The majority of PNSP cases, independent of year observed, were found in the age group 0–4 years. In 27 cases (4%) the PNSP isolates were derived from invasive sites, i.e. blood and/or spinal fluid. The most common serotypes/groups found were 19F, 14, 9V, 6B, 23F and 19A. For all four antibiotics tested on *Streptococcus pneumoniae* in the yearly RSQC programme the rates of resistance were

1-2% lower in 2007 than in 2006. Multiresistance (resistance to penicillin and at least two more antibiotics) was common among PNSP. Levels of non-susceptibility to penicillins in *Streptococcus pneumoniae* (=PNSP) were lower among invasive isolates than in the nasopharyngeal isolates from the RSQC programme.

Enterococci, and more specifically vancomycin resistant enterococci (VRE), have become important causes of nosocomial outbreaks in many parts of the world, but are still rare in Sweden. Still, there were 53 notified cases of VRE during 2007, the highest number since the mandatory notifications begun. This was attributable to the investigation of an outbreak of *vanB*-carrying *Enterococcus faecium* in the Stockholm county. Not more than ten invasive VRE isolates have been reported to the EARSS network 2001-2007. A common feature among vancomycin-susceptible invasive isolates of *Enterococcus faecium* was high-level aminoglycoside resistance (HLAGR) with 16% and 15%, respectively.

Streptococcus pyogenes: Data from the RSQC programme and from a sample of invasive isolates in 2007 (data derived from eleven laboratories using ADBact laboratory information system) showed similar patterns with low rates of macrolide/clindamycin-resistance (2-2.5%), mainly caused by efflux mechanisms (*mef* genes). Resistance to tetracycline is still above 10% but slowly decreasing since the year 2000.

Streptococcus agalactiae: From a total of 9585 positive blood cultures during 2007 137 (1.4%) were *Streptococcus agalactiae* (GBS). Twelve of the isolates (8.8%) were resistant to erythromycin and clindamycin. This was a considerable increase since 2006, from 4.4% to 8.8%.

Haemophilus influenzae: *Haemophilus influenzae* was only found in 51 blood isolates (0.5% of all blood isolates) in 2007. Three of these were beta-lactamase producing. No chromosomally mediated beta-lactam resistance was detected in this limited material.

Enterobacteriaceae producing extended spectrum beta-lactamases (ESBL) were made notifiable by the laboratories from February 2007. A total of 2099 persons were notified during the period, including 100 with a positive blood culture. This makes ESBL our most prevalent form of notifiable antibiotic resistance, about twice as commonly reported as MRSA. Most ESBLs were found in urine samples (70%) and the most commonly reported species was *E. coli* (77%).

Escherichia coli, mainly derived from urinary tract infections, has been included in the RSQC programme since 1996, and invasive isolates have been included in the EARSS network since 2001. Ampicillin resistance, caused by production of plasmid-mediated beta-lactamase (most often of TEM-type), was slightly higher in blood isolates than in the urine isolates (33% vs. 27%) in 2007. The level of resistance to third generation cephalosporins among blood isolates increased to 2.2%, and the majority of the cases was caused by plasmid-mediated ESBLs of CTX-M type. Such resistance was often accompanied by resistance to many other antibiotics, e.g. aminogly-

cosides, fluoroquinolones and trimethoprim. Resistance to fluoroquinolones has increased every year and was almost the same in urine as in blood isolates (12 vs. 13.3%) in 2007.

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

Helicobacter pylori has been monitored locally at a few laboratories. Resistance to clarithromycin (and erythromycin) has been steadily increasing but did not exceed 10% when tested at one laboratory. In *Campylobacter jejuni/coli* high levels of resistance were seen for fluoroquinolones (> 40%) and tetracyclines (> 30%) and lower but increasing levels for erythromycin (7%) in 2007.

Neisseria gonorrhoeae. Gonorrhoeae is a notifiable disease. Isolates from 404/642 (63%) of the notified clinical cases were completely characterised at the Swedish Reference Laboratory for Pathogenic Neisseria, Örebro University Hospital, and at the Division of Clinical Bacteriology, Karolinska University Hospital Huddinge, Stockholm. In 2007 30% of these isolates were beta-lactamase producing and ampicillin resistant, and 70% were resistant to ciprofloxacin.

Mycobacterium tuberculosis. Totally 497 new cases of TB were diagnosed and notified in Sweden 2007. Resistance to isoniazid was reported in 12.7% of the isolates, followed by rifampicin in 4.2%, pyrazinamid in 3.0% and ethambutol in 1.9%. Resistance against at least isoniazid and rifampicin (=MDR-TB) was diagnosed in 4.2% (15/361) of all culture confirmed TB patients, but in only 1.3% of those born in Sweden as compared to 7% of those born in Somalia and 4% of those born in other countries. By genetic typing of all resistant strains of *Mycobacterium tuberculosis* with RFLP (restriction fragment length polymorphism) isolates from 15 of the 49 patients were identified to belong to 13 different clusters with two or more patients in each cluster. One patient with MDR-TB was infected with three different strains of *M. tuberculosis*.

Every fourth candidemia episode in Sweden (102/402, 25.4%) was caused by *Candida* spp. strains with decreased susceptibility or resistance, as assessed in vitro, to one or more of the compounds fluconazole, itraconazole, voriconazole, amphotericin B and caspofungin, representing >99% of the total antifungal drugs used for systemic treatment in hospital care.

2.2 Sammanfattning

Antibiotikaförbrukning

Antibiotikaförbrukningen i Sverige har ökat under de senaste tre åren, särskilt bland barn. Under 2007 var penicillin V och tetracykliner de vanligaste antibiotika i öppenvården och stod tillsammans för cirka 50 procent av antibiotikaförbrukningen mätt i antalet definierade dygnsdoser (DDD). Ökningen av antibiotikaförbrukning ses i nästan alla 21 län. Uppsala är det enda län som uppvisar en minskning under de senaste två åren. Den högsta förbrukningen ses i Stockholms län och den lägsta i Västerbottens län, 485 respektive 346 recept per tusen invånare och år.

Enligt data från Socialstyrelsens individbaserade läkemedelsregister fick 25,4 procent av den svenska befolkningen minst en kur antibiotika i öppenvård under 2007. Detta motsvarar en ökning med 1,7 procent jämfört med året innan.

Det råder stora skillnader mellan länen vid jämförelser av öppenvårdsförbrukningen av antibiotika. I Stockholms län var 2007 års förbrukning av luftvägsantibiotika nästan dubbelt så stor som i Västerbottens län. Antibiotikaförbrukningen bland barnen i Halland var nästan dubbelt så hög som bland barnen i Jämtland. Vid jämförelse på kommunnivå blir skillnaderna ännu mer uttalade. Generellt sett är förbrukningen lägre i de norra och högre i de södra delarna av Sverige.

Antibiotikaförbrukningen inom svensk slutenvård har ökat för varje år sedan slutet av 1990-talet. Vanligast är användningen av cefalosporiner. Tillsammans med betalaktamasresistenta penicilliner (isoxazolyl-penicilliner), tetracykliner och fluorokinoloner står de för mer än hälften av slutenvårdsförbrukningen. Under de senaste tre åren ökade förbrukningen av tetracykliner och olika slag av penicilliner. Förbrukningen av cefalosporiner minskade något under 2007.

I denna upplaga av Swedres görs en länsvis jämförelse av slutenvårdsförbrukningen av cefalosporiner och karbapenemer. Uppsala län uppvisar en uttalad minskning av cefalosporinförbrukning och en ökad förbrukning av karbapenemer. Detta är troligtvis en följd av nya rekommendationer som svar på ett utbrott av ESBL-producerande *Klebsiella pneumoniae*. Även Östergötland och Västerbotten hade en relativt hög förbrukning av karbapenemer per hundra vård dagar jämfört med andra län.

Förbrukningen av tetracykliner har ökat inom slutenvården, särskilt under det senaste året. Ökningen kan troligen delvis förklaras av ett ökat antal fall av genital infektion orsakad av *Chlamydia trachomatis* inrapporterade till Smittskyddsinstitutet under år 2007. Den ökade tetracyklinförbrukningen per län stämmer väl överens med det ökade antalet inrapporterade klamydiafall.

Antibiotikaresistens

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

Staphylococcus aureus: Totalt 1128 fall av MRSA anmäldes 2007, en ökning med 7 procent från 2006 då 1057 fall noterades. Mer än hälften av fallen hade blivit smittade i Sverige (608 fall), och cirka en tredjedel (376 fall) hade blivit smittade utomlands. Jämfört med övriga länder i Europa är förekomsten av MRSA låg i Sverige. Antalet invasiva isolat av MRSA var färre 2007 ($n=11/2173$, 0,5 procent) än 2006 ($n=16/1865$, 0,9 procent), vilket medför att Sverige fortfarande är ett av de få länder i Europa som ännu ej nått nivån 1 procent av alla invasiva *Staphylococcus aureus* enligt rapportering till den europeiska resistensövervakningen EARSS.

I fem län/regioner var incidensen av MRSA-fall högre än riksgenomsnittet (12,3 procent). Fyra av dessa fem län hade också en hög incidenssiffra 2006. Från och med 2006 har spa-typning utgjort den primära typningsmetoden. De fem vanligast förekommande spa-typerna var t032 ($n=105$), t008 ($n=102$), t044 ($n=87$), t002 ($n=69$), t037 ($n=29$). Förekomsten av MRSA med PVL-toxin ökade långsamt. Den PVL-positiva MRSA-stam som ökat mest hade PFGE-mönster SE03-5 och spa-typ t008. PFGE-mönstret har visats vara identiskt med det hos USA300, beskriven som den snabbast ökande samhällsförvärvade stammen i USA under senare år.

Staphylococcus aureus i sårinfektioner (data från ResNet) var i mer än 95 procent av fallen känsliga för antibiotika med undantag för fusidinsyra. Fortfarande var mer än 5 procent av isolaten resistent.

Streptococcus pneumoniae: Under 2007 noterades 672 fall med nedsatt känslighet för penicillin (MIC av penicillin $> 0,5$ mg/L, definierade som PNSP). Incidensen PNSP per 100 000 invånare har minskat från 10,1 1997 till 6-8 sedan år 2000. De flesta fallen identifierades genom nasofarynxodling. Majoriteten av PNSP-fall var i åldersgruppen 0-4 år. I 27 fall (4 procent) påvisades PNSP från blod och/eller spinalvätska. Multiresistens (resistens mot penicillin och minst två ytterligare antibiotika) var vanlig hos PNSP. De vanligast förekommande serotyperna/grupperna var 19F, 14, 9V, 6B, 23F and 19A.

Enligt data rapporterade i ResNet sågs en trend av minskande resistens mot samtliga de typer av antibiotika som testades (penicilliner, makrolider, tetracykliner och trimetoprim-sulfa).

Enterokocker, särskilt de med resistens mot vankomycin (VRE), har ökat i betydelse vid sjukvårdsrelaterade utbrott i många delar av världen och ofta omfattat riskpatienter, men de är fortfarande ovanliga i Sverige. Under 2007 rapporterades dock 53 fall, den högsta siffran sedan anmälningsplikten infördes 2000. Den fördubblade anmälningsfrekvensen kunde tillskrivas Stockholms län, där spridning av *vanB*-innehållande *Enterococcus faecium* upptäcktes inom sjukvården. Majoriteten av rapporterade VRE under hela perioden 2000-2007 var *Enterococcus faecium* med *vanB*-gen.

Bland invasiva enterokock-isolat rapporterade till EARSS 2001-2007 har endast 10 varit VRE. Högggradig aminoglykosidresistens (HLAGR) var vanligare hos invasiva isolat av både *Enterococcus faecalis* och *Enterococcus faecium*, 15,8 procent och 14,8 procent, respektive.

Streptococcus pyogenes: Data från ResNet och från ett urval av invasiva isolat (konsekutiva isolat från elva ADBakt-laboratorier) under 2007 visade likartade resistensmönster med låg frekvens makrolid/klindamycin-resistens (2-2,5 procent) och högre frekvens tetracyklin-resistens (>10 procent) även om den visade en minskande trend.

Invasiva isolat av *Streptococcus agalactiae* 2007 var makrolid-resistent i 8,8 procent av fallen, vilket var en fördubbling från 2006.

Haemophilus influenzae var ett sällsynt fynd bland invasiva isolat. Bland isolat från elva ADBakt-laboratorier återfanns bara 51 fall (0,5 procent) 2007. Tre av dessa producerade betalaktamas, men ingen kromosomalt medierad betalaktamresistens påträffades.

Tarmbakterier tillhörande *Enterobacteriaceae* som bildar "Extended Spectrum Beta-Lactamases" (ESBL) blev anmälningspliktiga för laboratorierna februari 2007. Sammanlagt rapporterades 2099 personer, varav 100 med positiv blododling. Det innebär att ESBL är vår vanligaste anmälningspliktiga form av antibiotikaresistens, c:a dubbelt så många fall rapporterades av ESBL som av MRSA. ESBL-bildande bakterier påträffades oftast i urinodlingar (70 %). Den vanligaste bakteriearten var *E. coli* (77%).

Escherichia coli, huvudsakligen från urinvägsinfektioner, har övervakats enligt det nationella programmet (ResNet) sedan 1996, och blodisolat har inkluderats i EARSS sedan 2001. Ampicillinresistens, orsakad av plasmidmedierad betalaktamasproduktion av TEM-typ, återfanns i något högre frekvens än bland blodisolat som bland urinisolat 2007 (32,9 respektive 27 procent). Förekomsten av blodisolat med resistens mot tredje generationens cefalosporiner hade ökat till 2,2 procent, och hos majoriteten av dessa var resistensen orsakad av plasmidmedierade ESBL av CTX-M-typ. Dessa stammar var också ofta resistenta mot andra antibiotikagrupper som exempelvis aminoglykosider och kinoloner. Resistens mot kinoloner har ökat årligen och var ungefär samma hos urinisolat som bland blodisolat (12 respektive 13,3 procent).

Andra gram-negativa bakterier som övervakats nationellt och/eller internationellt är *Klebsiella pneumoniae* och

Pseudomonas aeruginosa, och båda inkluderades i EARSS-programmet från juli 2005. Resistensnivåerna hos respektive patogen var desamma oberoende av övervakningsprogram och typ av prov. Hos *K. pneumoniae* var cirka 2 procent resistenta mot cefalosporiner och ESBL-producerande, och resistens mot fluorokinoloner förekom i 8-13 procent. Hos *P. aeruginosa* var karbapenemresistensen cirka 5 procent och kinolonresistensen 10 procent.

Helicobacter pylori har övervakats vid några laboratorier. Resistens mot klaritromycin har ökat stadigt men nådde vid ett lokalt laboratorium bara 9,8 procent under 2007. Hos *Campylobacter jejuni/coli* var kinolonresistensen högre än 40 procent, tetracyklinresistensen högre än 20 procent, och erytromycinresistensen hade ökat till 7 procent 2007.

Gonorré är en anmälningspliktig sjukdom och 2007 rapporterades 642 kliniska fall. Isolat från 404 av dessa (63 procent av fallen) har undersökts antingen vid det svenska referenslaboratoriet i Örebro eller vid laboratoriet för klinisk bakteriologi, Karolinska Universitetssjukhuset Huddinge, Stockholm. Trettio procent av isolaten var beta-laktamasproducerande och därmed ampicillinresistenta, och 70 procent var resistenta mot ciprofloxacin.

Mycobacterium tuberculosis. Antalet anmälda nya fall av tuberkulos var 497 under 2007. Hos de isolat som undersöktes var resistens mot isoniazid vanligast (12,7 procent av fallen), följt av rifampicin (4,2 procent), pyrazinamid (3 procent) och etambutol (1,9 procent). *Mycobacterium tuberculosis* med resistens mot minst två antibiotika (MDR-TB) rapporterades hos 4,2 procent (15/361 fall). Epidemiologisk typning med RFLP av alla resistenta TB-isolat visade att de tillhörde 13 olika kluster med två eller fler patienter i varje. En patient med MDR-TB var infekterad med tre olika stammar av *Mycobacterium tuberculosis*.

3. Use of antimicrobials

3.1 Use of antibiotics

Statistics on antibiotic sales have been obtained from The National Corporation of Swedish Pharmacies. Sales data are expressed either as defined daily doses, DDD, per 1000 inhabitants and day (DDD/1000/day), or as prescriptions per 1000 inhabitants and year (prescriptions/1000/year). Since July 2005, the Swedish National Board of Health and Welfare has supplied an individual-based register on all drugs prescribed and dispensed in community care. Among other things, this Prescribed Drug Register provides information on the number of individuals treated with at least one course of antibiotics during a specific period of time, i.e. the number of users per 1000 inhabitants and year (users/1000/year). Data on number of admissions and patient-days derives from The Swedish Association of Local Authorities and Regions. For further details on sales statistics see Appendix 3.

Total sales of antibiotics

Total sales of antibiotics are increasing in Sweden. This has been the case for the last three years as shown in Table 3.1.1.

Table 3.1.1. Total sales of antibacterial drugs for systemic use in Sweden 2000-2007, DDD/1000/day. Methenamine is an antiseptic and therefore of no interest regarding antibiotic resistance, even though the WHO Collaborating Centre for Drug Statistics methodology classifies it as an antibacterial drug.

	2000	2001	2002	2003	2004	2005	2006	2007
J01 excl methenamine	15.2	15.3	14.8	14.6	14.3	14.8	15.2	15.6
Methenamine	1.6	1.5	1.6	1.7	1.9	1.9	1.9	1.8
Total J01	16.8	16.8	16.4	16.3	16.2	16.6	17.1	17.4

Community care

Antibiotic use in community care in 2007 shows an increase of 2.7% over 2006. The same rate of yearly increase has been seen for the last three years. Antibiotic sales are now at the same level as in the late 1990's (Figure 3.1.1.).

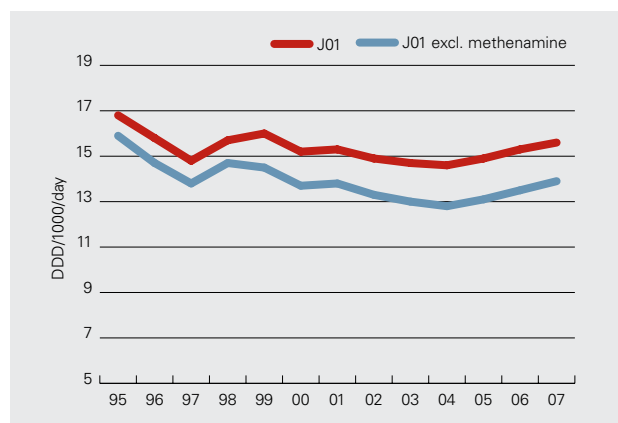


Figure 3.1.1. Antibiotics in community care, DDD/1000/day, with and without methenamine.

The distribution between different classes of antibiotics is shown in Figure 3.1.2. Beta-lactamase sensitive penicillins and tetracyclines still predominate.

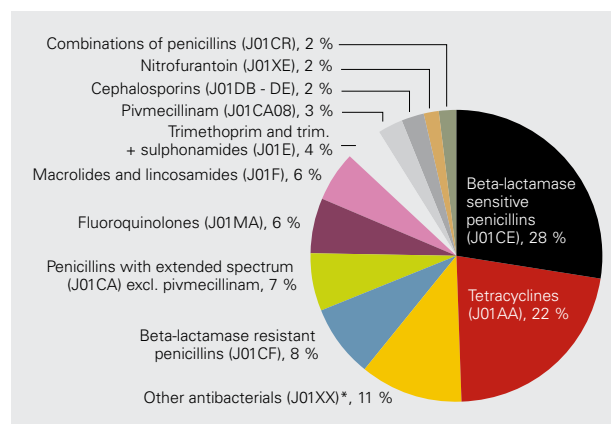


Figure 3.1.2. Antibiotics in community care 2007, percent of total DDD/1000/day. *Methenamine represents more than 99% of the group "Other antibacterials".

Figure 3.1.3 shows antibiotic consumption in the period 2005 – 2007. During the last year, the use of nitrofurantoin increased by 24%. Calculated as a percentage, this is the most pronounced increase. It indicates improved compliance with guidelines on the treatment of lower urinary tract infections. In 2007, trimethoprim shows the largest decrease in use, 12%. In the same period, decreases in use are also seen for cephalosporins and fluoroquinolones, 6% and 5.5%, respectively.

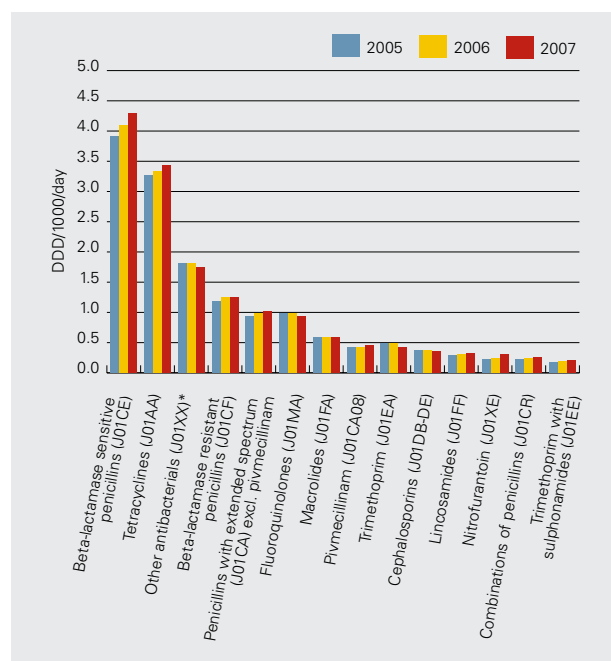


Figure 3.1.3. Antibiotics in community care 2005-2007, DDD/1000/day. *Methenamine use represents more than 99% of the group "Other antibacterials".

Table 3.1.2. Antibiotics in community care, different groups of antibiotics and different age groups. DDD/1000/day and Prescriptions/1000/year, 2003–2007. Users/1000/year in 2006 and 2007 is presented as well.

Age group (years)	DDD/1000/day					Prescriptions/1000/year					Users/1000/year	
	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2006	2007
Tetracyclines (J01AA)												
0-6	0.00	0.00	0.00	0.00	0.00	0.1	0.1	0.1	0.1	0.0	0.1	0.0
7-19	2.29	2.36	2.71	3.12	3.23	24.7	25.4	28.9	32.7	33.9	20.4	21.5
20-59	3.34	3.36	3.52	3.56	3.68	64.2	62.9	67.2	66.3	68.3	51.8	53.4
60-79	3.80	3.90	4.15	4.11	4.29	90.9	91.7	99.7	96.3	99.3	71.6	74.4
80 -	2.90	2.83	3.04	2.89	2.93	78.3	75.8	82.6	76.4	77.8	60.1	62.0
All age groups	3.04	3.06	3.26	3.33	3.44	59.2	58.6	63.2	62.6	64.3	46.9	48.6
Penicillins with extended spectrum (J01CA) excl. pivmecillinam												
0-6	1.34	1.25	1.41	1.59	1.74	91.1	84.7	85.0	86.9	95.2	64.6	70.5
7-19	0.37	0.32	0.38	0.45	0.46	13.1	10.8	12.5	14.1	14.5	12.4	12.8
20-59	0.65	0.64	0.72	0.72	0.77	17.2	16.8	18.3	18.4	19.4	16.0	16.7
60-79	1.35	1.43	1.56	1.59	1.62	37.4	39.3	41.2	41.4	42.0	32.3	32.9
80 -	1.54	1.65	1.80	1.81	1.79	43.2	45.3	47.5	47.3	46.8	38.3	38.0
All age groups	0.85	0.84	0.94	0.98	1.02	28.2	27.4	29.0	29.6	31.0	23.4	24.5
Pivmecillinam (J01CA08)												
0-6	0.01	0.01	0.01	0.01	0.01	0.2	0.3	0.4	0.5	0.5	0.4	0.5
7-19	0.13	0.14	0.15	0.17	0.19	6.4	7.4	8.7	10.7	12.4	9.6	11.0
20-59	0.31	0.32	0.31	0.34	0.36	14.7	15.4	16.9	20.1	22.2	17.3	19.0
60-79	0.70	0.72	0.70	0.71	0.74	32.4	33.4	36.2	40.3	43.0	31.2	33.1
80 -	2.04	2.05	1.90	1.84	1.84	96.4	97.4	100.0	106.7	109.3	80.1	81.8
All age groups	0.41	0.43	0.42	0.43	0.46	19.6	20.5	22.3	25.5	27.6	20.7	22.3
Beta-lactamase sensitive penicillins (J01CE)												
0-6	3.78	3.32	3.35	3.59	4.03	347.5	307.9	310.5	327.3	350.7	230.8	244.3
7-19	3.50	2.92	3.01	3.38	3.68	149.9	120.6	121.5	135.0	142.5	113.1	117.3
20-59	4.34	4.16	4.18	4.28	4.49	111.5	105.5	105.2	107.9	112.8	91.6	95.2
60-79	4.10	4.33	4.27	4.46	4.57	100.1	104.8	102.9	107.0	109.0	88.0	89.4
80 -	3.37	3.32	3.39	3.33	3.36	89.7	86.8	87.1	84.2	84.2	71.4	72.2
All age groups	4.10	3.90	3.92	4.09	4.30	132.9	122.6	122.5	128.1	134.3	104.0	108.1
Beta-lactamase resistant penicillins (J01CF)												
0-6	0.38	0.33	0.31	0.35	0.33	38.5	34.3	32.2	35.6	32.9	26.7	25.2
7-19	0.74	0.67	0.65	0.70	0.69	35.9	32.0	30.7	33.6	31.9	27.5	26.4
20-59	0.90	0.88	0.88	0.95	0.96	32.5	31.7	31.7	33.5	33.3	26.9	26.7
60-79	1.98	1.94	1.91	2.04	2.04	55.5	54.5	54.4	57.4	56.3	37.7	37.1
80 -	4.55	4.47	4.38	4.44	4.40	129.3	124.2	122.0	123.4	122.6	68.7	67.9
All age groups	1.21	1.18	1.18	1.25	1.25	42.6	40.9	40.5	42.9	42.2	31.2	30.7
Combinations of penicillins (J01CR)												
0-6	0.77	0.68	0.73	0.73	0.75	55.1	48.5	51.8	51.2	52.7	34.4	35.2
7-19	0.21	0.17	0.20	0.22	0.21	6.5	5.1	6.0	6.4	6.4	5.1	4.9
20-59	0.15	0.15	0.17	0.18	0.20	3.4	3.3	3.8	3.9	4.4	3.5	3.9
60-79	0.15	0.17	0.20	0.22	0.25	3.2	3.5	4.2	4.5	5.1	3.6	4.1
80 -	0.11	0.11	0.15	0.15	0.17	2.5	2.4	3.0	3.0	3.4	2.3	2.7
All age groups	0.20	0.19	0.22	0.24	0.26	7.6	6.9	7.8	8.0	8.5	6.1	6.5
Cephalosporins (J01DB-DE)												
0-6	0.59	0.53	0.50	0.52	0.52	55.5	49.7	46.4	49.0	49.7	37.6	38.0
7-19	0.35	0.30	0.29	0.30	0.29	24.3	20.9	19.6	20.6	20.2	17.4	17.2
20-59	0.32	0.30	0.30	0.29	0.28	18.0	16.9	16.6	16.8	16.2	14.2	13.7
60-79	0.51	0.48	0.47	0.46	0.40	24.3	23.6	23.1	22.6	20.2	17.1	15.5
80 -	0.85	0.79	0.77	0.73	0.65	45.9	42.6	42.3	40.5	35.4	30.9	27.4
All age groups	0.44	0.40	0.38	0.37	0.35	25.5	23.4	22.5	22.5	21.5	17.9	17.2

Age group (years)	DDD/1000/day					Prescriptions/1000/year				Users/1000/year		
	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2006	2007
Trimethoprim (J01EA)												
0-6	0.12	0.12	0.11	0.12	0.12	16.2	15.6	14.8	16.0	15.4	11.1	10.6
7-19	0.21	0.21	0.20	0.21	0.18	13.0	12.4	11.9	12.4	10.9	10.8	9.5
20-59	0.39	0.36	0.33	0.33	0.29	20.2	18.7	17.3	17.4	14.6	14.7	12.4
60-79	0.99	0.92	0.86	0.84	0.76	47.9	44.6	41.7	40.7	35.2	29.7	25.6
80 -	2.62	2.48	2.28	2.19	1.91	146.4	136.0	125.6	120.1	104.5	73.3	61.6
All age groups	0.56	0.53	0.49	0.49	0.43	30.1	28.2	26.4	26.3	22.8	19.8	16.9
Trimethoprim with sulphonamides (J01EE)												
0-6	0.16	0.15	0.15	0.16	0.16	20.0	18.4	18.1	18.1	18.8	13.2	13.5
7-19	0.09	0.09	0.10	0.10	0.10	4.2	4.0	4.1	4.0	4.1	2.7	2.6
20-59	0.12	0.12	0.12	0.13	0.14	2.6	2.7	2.8	2.9	3.0	1.9	1.9
60-79	0.28	0.33	0.34	0.36	0.39	7.3	8.2	8.4	8.8	9.2	5.8	6.1
80 -	0.31	0.35	0.34	0.36	0.39	10.7	11.8	11.5	11.7	12.2	8.8	9.1
All age groups	0.16	0.18	0.18	0.19	0.20	6.2	6.2	6.2	6.3	6.4	4.0	4.1
Macrolides (J01FA)												
0-6	0.78	0.73	0.80	0.80	0.85	36.3	34.5	37.4	37.3	38.1	29.6	30.4
7-19	0.65	0.62	0.72	0.76	0.74	19.7	18.1	21.0	22.1	21.7	17.9	17.2
20-59	0.57	0.54	0.56	0.54	0.55	17.2	16.3	16.8	16.3	16.5	13.0	13.2
60-79	0.47	0.49	0.51	0.50	0.50	14.2	14.1	14.8	14.5	14.6	11.0	11.0
80 -	0.32	0.31	0.34	0.34	0.32	10.0	9.7	9.8	9.3	8.7	7.2	6.8
All age groups	0.57	0.55	0.59	0.58	0.59	18.2	17.3	18.4	18.2	18.4	14.4	14.4
Lincosamides (J01FF)												
0-6	0.03	0.02	0.02	0.02	0.03	5.4	4.1	4.5	5.0	5.3	3.6	3.9
7-19	0.09	0.09	0.10	0.11	0.12	6.9	6.5	6.9	7.8	8.3	6.2	6.7
20-59	0.23	0.24	0.25	0.28	0.29	12.3	12.6	13.0	14.3	15.6	11.1	12.2
60-79	0.49	0.51	0.53	0.55	0.55	20.1	21.1	22.1	23.7	24.4	15.3	15.9
80 -	0.69	0.71	0.77	0.75	0.74	29.8	30.0	32.2	32.6	32.8	18.1	18.6
All age groups	0.27	0.27	0.29	0.31	0.32	13.4	13.5	14.1	15.4	16.3	10.9	11.7
Fluoroquinolones (J01MA)												
0-6	0.01	0.01	0.02	0.01	0.01	0.7	0.4	0.8	0.8	0.8	0.4	0.4
7-19	0.12	0.12	0.12	0.12	0.13	5.8	5.5	5.5	5.5	5.5	4.7	4.4
20-59	0.83	0.81	0.81	0.80	0.76	35.0	33.1	31.9	30.2	27.8	22.0	20.3
60-79	2.08	2.07	2.08	2.05	1.93	91.8	88.0	84.6	80.2	73.7	52.7	48.7
80 -	3.31	3.14	3.13	3.00	2.74	172.6	158.4	149.4	136.8	119.7	92.5	81.5
All age groups	1.00	0.98	0.99	0.98	0.93	44.8	42.5	41.0	39.0	35.7	27.0	24.9
Nitrofurantoin (J01XE)												
0-6	0.08	0.07	0.07	0.07	0.07	6.9	6.9	6.4	6.3	6.3	4.2	4.2
7-19	0.10	0.11	0.12	0.12	0.14	4.3	4.9	5.3	5.2	6.7	4.4	5.8
20-59	0.16	0.17	0.19	0.20	0.24	6.8	7.4	8.5	8.5	11.0	7.0	9.1
60-79	0.24	0.29	0.34	0.36	0.46	9.4	11.7	14.1	14.6	19.4	10.7	14.3
80 -	0.58	0.68	0.78	0.78	0.97	26.6	31.0	36.5	37.2	46.7	24.0	30.3
All age groups	0.18	0.20	0.23	0.24	0.30	7.9	9.0	10.3	10.5	13.5	8.0	10.3
All agents (J01 excl. methenamine)												
0-6	8.06	7.23	7.49	7.98	8.62	674.2	605.9	608.8	634.7	666.8	335.6	348.5
7-19	8.86	8.13	8.76	9.79	10.18	315.5	274.1	283.4	311.1	319.8	204.5	208.1
20-59	12.33	12.09	12.37	12.63	13.04	356.4	344.2	350.9	357.6	366.1	223.9	228.7
60-79	17.22	17.66	18.02	18.34	18.58	537.2	541.0	550.0	554.5	553.7	288.8	289.6
80 -	23.32	23.01	23.20	22.74	22.33	886.2	856.3	854.2	833.3	807.9	379.4	372.5
All age groups	13.02	12.77	13.13	13.51	13.87	437.6	418.2	425.6	436.1	443.8	249.8	254.1

Table 3.1.2 shows the sales of different groups of antibiotics in different age groups. Since 2004, the use of antibiotics measured as DDD/1000/day has increased in all age groups, except for patients aged over 80 years. The younger the patients, the more pronounced the increase. The use of antibiotics seems to be decreasing in the oldest patients. This might be an actual decrease in antibiotic use, but it may also be caused by changes in drug purchase procedures. Residents of Swedish nursing homes can obtain drugs on individual prescription (data shown in Table 3.1.2) or they can obtain them from the nursing home's drug stock. In the latter case, sales data will not be included in the community prescription data but are included in hospital care or total use data. The way drugs are purchased for these patients is inconsistent.

In 2007, more than a quarter of the Swedish population received at least one course of antibiotics in community care (254 users/1000). This is an increase of 1.7% on the previous year. The highest rates of antibiotic use are seen in children aged 0-6 years and in the elderly aged over 80 years, 349 and 373 users/1000 respectively. As mentioned above, the true number of users among the elderly may be even higher.

Comparison of the number of antibiotic users and the number of prescriptions shows that in children and elderly, it is quite common for one patient to receive more than one course of antibiotics during one year. In children the number of prescriptions is almost twice the number of users. This is even more pronounced in the elderly, where the number of prescriptions is more than twice the number of users.

County data

The increased use of antibiotics can be seen in most counties in Sweden as shown in Figure 3.1.4. The only county where the use has decreased over the last two years is Uppsala. In 2007, Stockholm county had the highest use and Västerbotten the lowest, 485 and 346 prescriptions/1000/year, respectively.

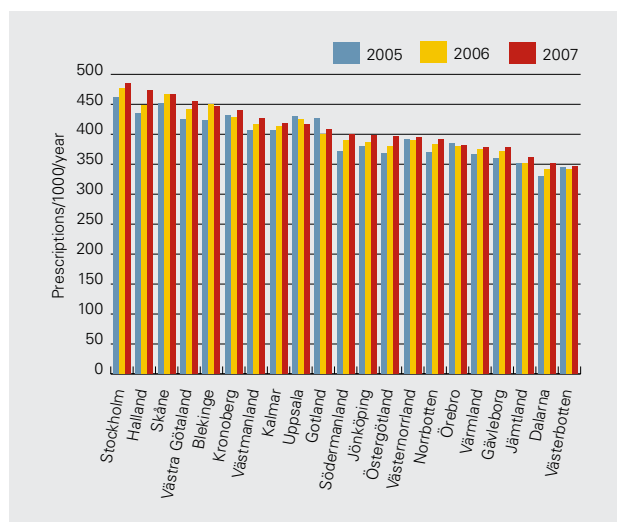


Figure 3.1.4. Antibiotic use in community care in the 21 counties of Sweden. Prescriptions/1000/year, 2005 – 2007, J01 excl methenamine.

Figure 3.1.5. presents the age and gender standardized fraction of the population treated with at least one course of antibiotics in community care in 2007, i.e. the number of

users/1000 inhabitants. Like the previous figure, this analysis reveals the highest number for Stockholm and the lowest for Västerbotten, 280 and 202 users/1000 respectively. The average number of users/1000 inhabitants for the whole country was 254 as shown in Table 3.1.2.

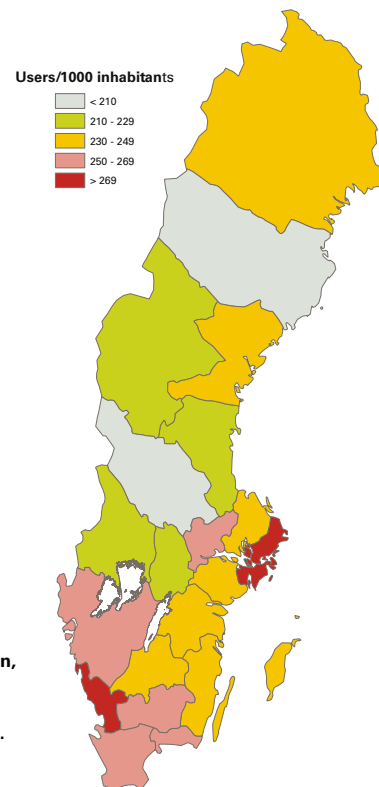


Figure 3.1.5. Fraction of the population treated with at least one course of antibiotics (J01 excl methenamine) in community care in 2007. The 21 counties of Sweden, all ages, users/1000 inhabitants. Age and gender standardized data.

Antibiotic consumption in children

Antibiotic consumption in children is presented in Figure 3.1.6. There are great variations within the country and an increase could be seen for almost all 21 counties last year. Measured in prescriptions/1000 inhabitants, the children of the counties of Halland, Stockholm, Skåne and Kronoberg received almost twice as much antibiotics as the children in the county of Jämtland in 2007.

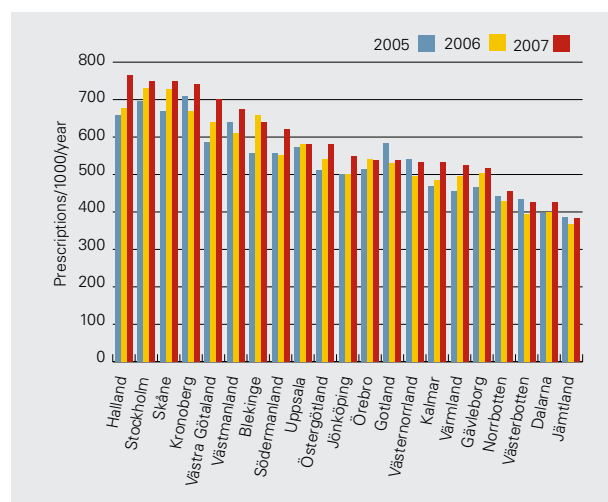


Figure 3.1.6. Sales of antibiotics (J01 excl methenamine) in the 21 counties of Sweden 2005 – 2007. Children aged 0 – 6 years, community care, prescriptions/1000/year.

The fraction of children given at least one course of antibiotics in community care in each county of Sweden is presented in Figure 3.1.7. The number of users per 1000 children ranges from 233 in Jämtland to 393 in Halland. Generally speaking, the fraction of children treated with antibiotics is higher in the southern part of Sweden than in the north.

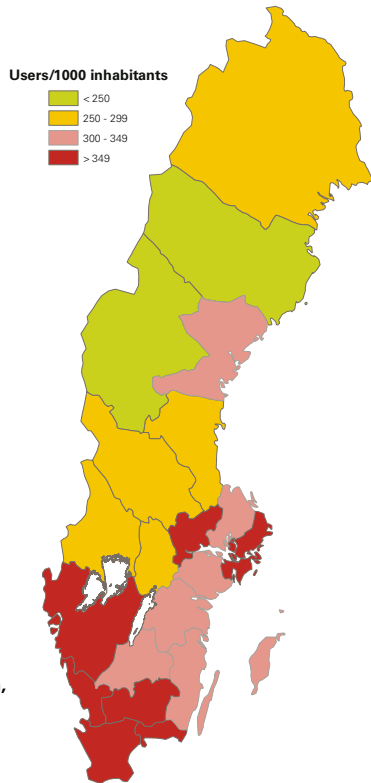


Figure 3.1.7. Fraction of the population treated with at least one course of antibiotics (J01 excl methenamine) in community care in 2007. The 21 counties of Sweden, children aged 0-6 years, users/1000 children.

There are 290 municipalities in Sweden. Figure 3.1.8 presents the ten highest and ten lowest ranking municipalities with regards to fraction of children treated with antibiotics in community care during 2007. Analysis of antibiotic use at municipality level, produces even more pronounced differences than at the county level. The number of users per 1000 children ranges from 165 in Bjurholm in Västerbotten county, to 463 in Ljungby in Kronoberg county. All ten lowest ranking municipalities are classified as small towns and all but Hällefors, Örebro county, are situated in the northern part of Sweden. The ten municipalities with the highest use of antibiotics in children are municipalities of varying sizes. Three of them, Kävlinge, Vellinge and Åstorp, are situated in the county of Skåne. Sigtuna and Lidingö are both municipalities in Stockholm county.

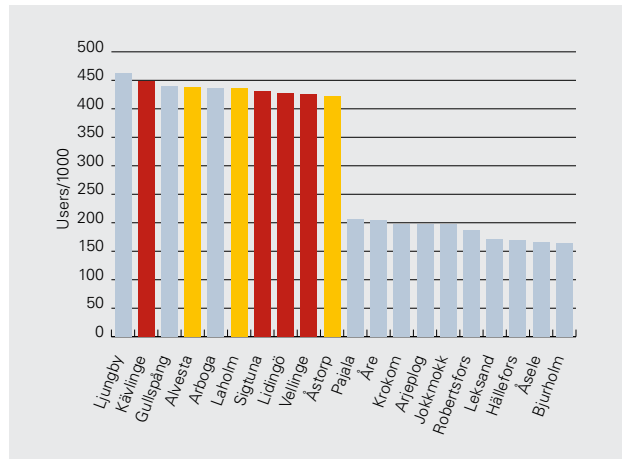


Figure 3.1.8. Swedish municipalities with the highest and lowest fraction of children treated with at least one course of antibiotics (J01 excl methenamine) in community care in 2007. Children aged 0-6 years, users/1000. Red coloured municipalities are large in size, yellow coloured are of medium size and blue coloured are small municipalities.

Antibiotics commonly used for respiratory tract infections

The use of antibiotics for respiratory tract infections, RTIs, decreased in the early 2000's as shown in Figure 3.1.9. However, since 2004, the use has increased for all classes but cephalosporins. In the last three years, measured as prescriptions/1000/year, the use of penicillin V and doxycycline has increased by 10%, amoxicillin by 18%, macrolides by 6% and amoxicillin with clavulanic acid by 23%. In November 2007, Strama and the Swedish Medical Products Agency organised a workshop on the treatment of lower RTIs. According to the workshop, antibiotics for lower RTI should only be used on strict indications. If a patient with indistinct lower RTI is not generally affected, expectancy or delayed antibiotic prescribing is recommended. The workshop also concluded that there is no documented benefit of antibiotic treatment of acute bronchitis. Furthermore, according to these guidelines, antibiotics should not be used for acute exacerbation of chronic bronchitis or chronic obstructive pulmonary disease without discoloured sputum.

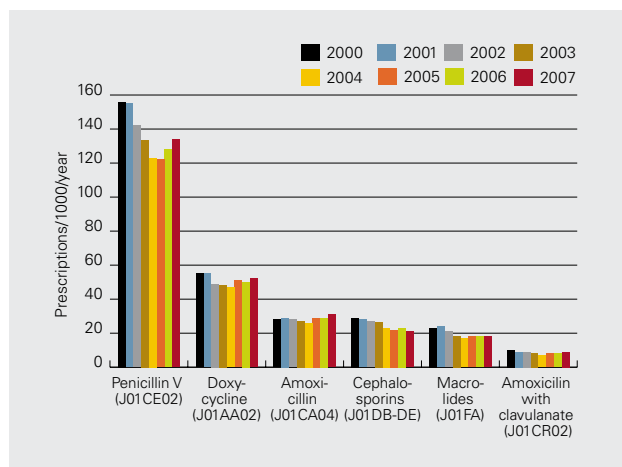


Figure 3.1.9. Antibiotics commonly used for respiratory tract infections. Prescriptions/1000/year, community care, 2000-2007.

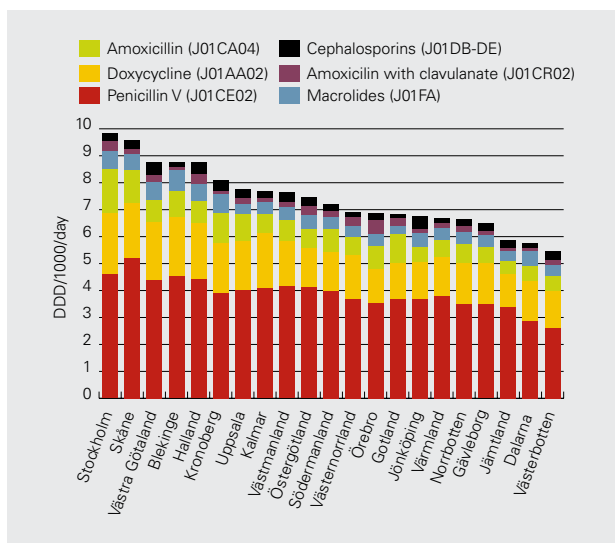


Figure 3.1.10. Antibiotics commonly used for respiratory tract infections, community care 2007. DDD/1000/day, age and gender standardized data.

Measured as DDD/1000/day, a great variation is seen between counties in the use of antibiotics for respiratory tract infections. When standardized with regards to age and gender, the numbers range from 5.5 in Västerbotten to 9.9 in Stockholm as presented in Figure 3.1.10. The proportion of penicillin V, which is the recommended first choice antibiotic for respiratory tract infections in need of antibiotic treatment, varies from 47% in Stockholm to 58% in Jämtland.

Antibiotics commonly used for urinary tract infections (UTI) in women

In Swedish guidelines for the treatment of lower UTIs in women, the first choices are pivmecillinam or nitrofurantoin. Trimethoprim is the second-line choice. Figure 3.1.11 indicates that compliance with these guide-lines is increasing.

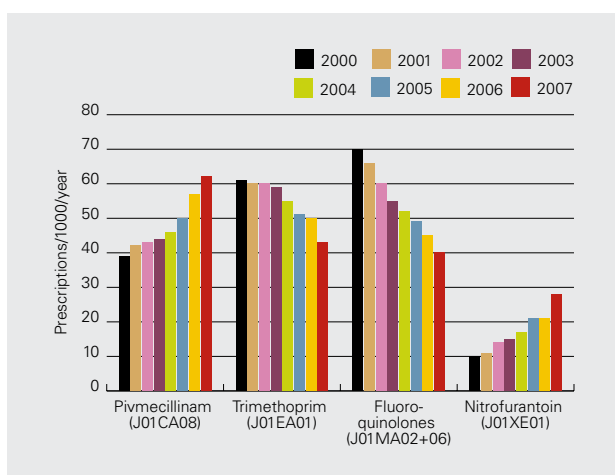


Figure 3.1.11. Antibiotics commonly used for urinary tract infections. Women aged 18 years or older, 2000 – 2007, prescriptions/1000/year.

Hospital care

The use of antibiotics in hospital care has continuously increased since the end of the 1990s. About 10% of the total antibiotic use is prescribed for inpatients. In Table 3.1.3 the antibiotic use in hospitals, with and without methenamine, is listed.

Table 3.1.3. Antibiotic use in hospital care, 2000 – 2007, DDD/1000/day.

	2000	2001	2002	2003	2004	2005	2006	2007
J01 excl methenamine	1.26	1.26	1.27	1.33	1.37	1.43	1.50	1.55
Methenamine	0.03	0.03	0.03	0.05	0.07	0.07	0.07	0.07
Total J01	1.30	1.29	1.30	1.38	1.44	1.50	1.57	1.62

Cephalosporins is the group of antibiotics which is used the most and together with beta-lactamase resistant penicillins, tetracyclines and fluroquinolones they constitute more than half of the use within hospital care. Figure 3.1.12 shows the distribution of antibiotics within hospital care.

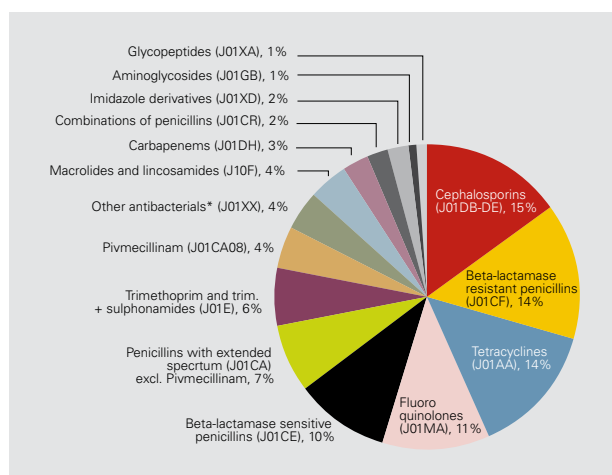


Figure 3.1.12. Antibiotics in hospital care 2007, percent of total DDD/1000/day. *Methenamine represents more than 98% in the group "other bacterials".

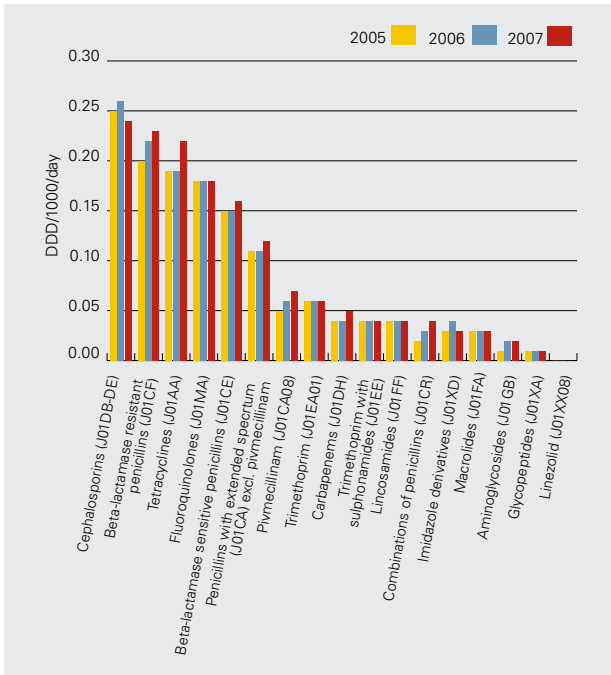


Figure 3.1.13. Antibiotics in hospital care 2005-2007, DDD/1000/day.

Figure 3.1.13 shows all classes of antibiotics used in hospital care the last three years. The most pronounced increases are seen in tetracyclines and the various types of penicillin. The use of cephalosporins in 2007 is lower than previous years. New recommendations for the treatment of uncomplicated community acquired pneumonia were published by the Swedish Society of Infectious Diseases a few years ago. Beta-lactamase sensitive penicillins were suggested as first choice and the use of cephalosporins should be reduced. These recommendations were also disseminated by all local Strama-groups. This is a possible explanation to the decrease in cephalosporins and increase in beta-lactamase sensitive penicillins in 2007. An increasing number of infections involving ESBL-producing bacteria may be another reason for the lower use of cephalosporins. Stramas proposed action plan “ESBL resistance in enteric bacteria” recommends the reduction in cephalosporins in favour of penicillins (<http://www.strama.se/dyn//,33,18.html>).

Beta-lactamase resistant penicillins represents another group of antibiotics showing an upward trend. This group is often used as peroperative prophylaxis and for the treatment of skin infections as well as bone and joint infections. Three point prevalence studies carried out in Swedish hospitals in 2003, 2004 and 2006 indicate that the duration of prophylaxis has shortened which contradicts the increase. The point prevalence studies do not show any increase at all of beta-lactamase resistant penicillins. This suggests that the explanation for the increase is to be sought elsewhere, maybe within the departments not participating in the point prevalence studies.

The use of tetracyclines has increased within hospital care and in some counties the increase is considerable. Doxycycline tablets 100 mg account for the whole increase. One possible explanation is the increase of genital infection caused by *Chlamydia trachomatis* reported to the Swedish Institute for Infectious Disease Control during 2007. Genital Chlamydia is a notifiable disease and the patient receives treatment free of

charge. According to some outpatients’ departments for young people the drug is often handed over directly by the doctor/nurse in the clinic and the prescription is classified as hospital prescription. Figure 3.1.14 shows the use of tetracyclines per county within hospital care and Figure 3.1.15 the number of reported cases of Chlamydia. The common treatment of genital Chlamydia is doxycycline 100 mg, 10 tablets, which corresponds to 10 DDD.

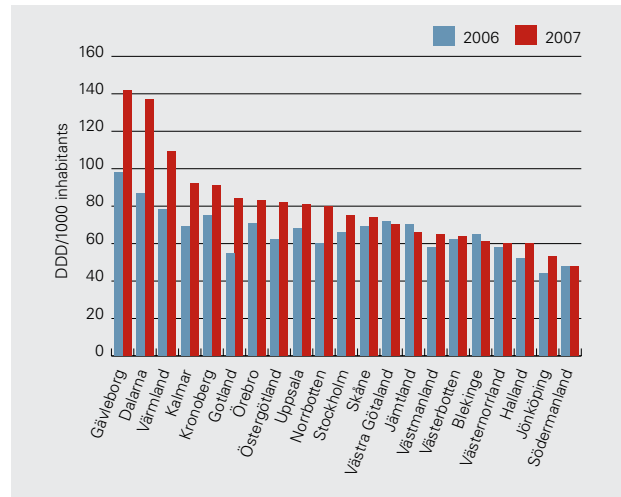


Figure 3.1.14. Tetracyclines (J01AA) in hospital care, all counties 2006-2007, DDD/1000 inhabitants.

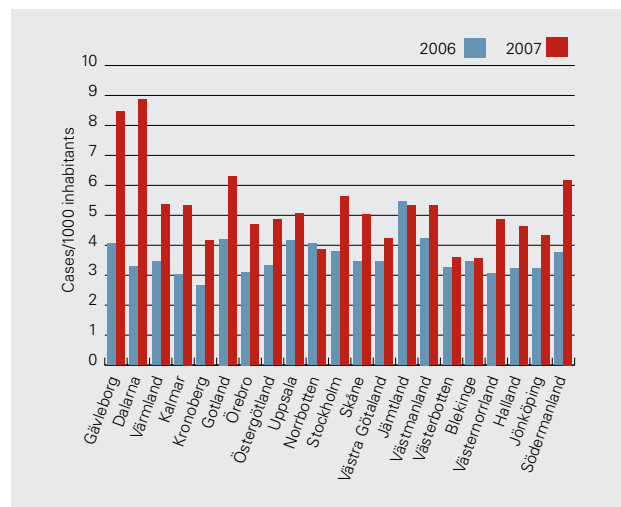


Figure 3.1.15. Incidence of genital Chlamydia, all counties 2006-2007, number of cases/1000 inhabitants. Sorted as Figure 3.1.14.

Table 3.1.4 and 3.1.5 show antibiotic use in relation to number of admissions and number of patient days in hospital care during 1997-2006. A difficulty in the interpretation of these data is that the conditions of the numerator in relation to the denominator have changed over the years. Antibiotic sales data include all health-care providers ordering drugs per requisition. Data concerning number of admissions and patient-days are reported only by the county councils and thus do not include patients in municipal care. Organizational changes explain why the increase in DDD/100 admissions and DDD/100 patient-days are much larger than the increase in DDD/1000/day.

Table 3.1.4. Antibiotics in hospital care 1997-2006. DDD/100 admissions.

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Tetracyclines (J01AA)	31.8	33.1	34.9	34.8	33.6	34.3	34.9	36.4	42.2	43.5
Penicillins with extended spectrum (J01CA)	21.6	22.9	24.8	26.8	28.0	29.3	31.8	34.7	36.3	38.9
Beta-lactamase sensitive penicillins (J01CE)	38.8	33.1	31.9	31.7	30.5	30.4	30.7	29.5	33.8	34.7
Beta-lactamase resistant penicillins (J01CF)	37.9	36.9	36.9	37.9	40.2	41.4	42.3	42.5	44.4	48.3
Combinations of penicillins (J01CR)	1.9	2.1	2.3	2.8	2.8	3.2	4.0	4.7	5.2	6.4
Cephalosporins (J01DB-DE)	49.8	52.7	53.4	54.6	54.0	55.0	56.4	55.6	57.3	57.3
Carbapenems (J01DH)	5.2	6.1	6.5	7.0	7.1	7.4	8.2	8.7	9.4	10.1
Trimethoprim (J01EA)	6.8	6.5	7.0	7.4	7.7	8.5	10.0	10.4	13.5	13.4
Trimethoprim with sulfonamides (J01EE)	5.9	6.0	6.1	6.6	6.6	6.9	7.2	7.7	8.2	8.2
Macrolides (J01FA)	6.5	6.4	6.5	6.3	6.3	5.9	5.5	5.4	5.8	6.0
Lincosamides (J01FF)	5.3	6.1	6.1	7.0	7.6	7.1	8.2	8.1	8.1	8.4
Aminoglycosides (J01GB)	2.9	2.8	2.9	3.1	3.0	2.9	3.0	3.2	3.3	3.5
Fluoroquinolones (J01MA)	33.5	34.9	35.5	36.5	37.4	37.1	39.4	38.9	41.2	41.2
Glycopeptides (J01XA)	1.9	2.3	2.2	2.3	2.5	2.5	2.8	3.0	3.1	3.3
Imidazole derivatives (J01XD)	7.0	7.4	7.6	8.1	8.1	8.5	8.3	8.1	7.9	8.0
Methenamine (J01XX05)	5.8	7.3	8.0	7.1	6.9	6.4	10.0	14.6	16.5	15.2
Linezolid (J01XX08)	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.2	0.2	0.3
All agents (J01)	264.1	268.5	274.9	282.2	284.5	288.9	305.5	314.6	340.1	351.1

Table 3.1.5. Antibiotics in hospital care 1997-2006. DDD/100 patient-days.

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Tetracyclines (J01AA)	4.73	4.99	5.41	5.65	5.44	5.62	5.80	6.20	7.32	7.5
Penicillins with extended spectrum (J01CA)	3.22	3.45	3.84	4.35	4.54	4.81	5.29	5.91	6.29	6.7
Beta-lactamase sensitive penicillins (J01CE)	5.79	5.00	4.95	5.14	4.94	4.98	5.11	5.02	5.85	6.0
Beta-lactamase resistant penicillins (J01CF)	5.65	5.56	5.72	6.15	6.52	6.80	7.05	7.23	7.70	8.3
Combinations of penicillins (J01CR)	0.28	0.32	0.36	0.45	0.46	0.52	0.66	0.81	0.90	1.1
Cephalosporins (J01DB-DE)	7.42	7.96	8.28	8.86	8.75	9.02	9.38	9.46	9.92	9.8
Carbapenems (J01DH)	0.77	0.92	1.00	1.13	1.16	1.21	1.36	1.48	1.62	1.7
Trimethoprim (J01EA)	1.01	0.98	1.09	1.21	1.26	1.39	1.66	1.76	2.34	2.3
Trimethoprim with sulfonamides (J01EE)	0.89	0.91	0.95	1.07	1.07	1.14	1.20	1.31	1.42	1.4
Macrolides (J01FA)	0.96	0.97	1.01	1.02	1.03	0.96	0.91	0.92	1.00	1.0
Lincosamides (J01FF)	0.80	0.92	0.95	1.14	1.23	1.17	1.36	1.37	1.40	1.4
Aminoglycosides (J01GB)	0.43	0.43	0.45	0.50	0.49	0.47	0.50	0.55	0.57	0.6
Fluoroquinolones (J01MA)	4.99	5.27	5.50	5.92	6.07	6.08	6.56	6.62	7.13	7.1
Glycopeptides (J01XA)	0.28	0.34	0.35	0.37	0.40	0.40	0.46	0.51	0.54	0.6
Imidazole derivatives (J01XD)	1.05	1.11	1.18	1.32	1.32	1.40	1.39	1.37	1.36	1.4
Methenamine (J01XX05)	0.86	1.11	1.23	1.16	1.12	1.04	1.67	2.48	2.85	2.6
Linezolid (J01XX08)	0.00	0.00	0.00	0.00	0.00	0.02	0.03	0.03	0.04	0.0
All agents (J01)	39.37	40.53	42.64	45.81	46.14	47.38	50.82	53.54	58.91	60.2

Figure 3.1.16 shows the use of cephalosporins per county 2005-2007 and Figure 3.1.17 the distribution of cefuroxime, ceftazidime and cefotaxime in each county in 2007. The dramatic dip in Uppsala county is probably explained by new recommendations in response to an outbreak of ESBL-producing *Klebsiella pneumoniae* in accordance with Stramas proposed action plan mentioned above.

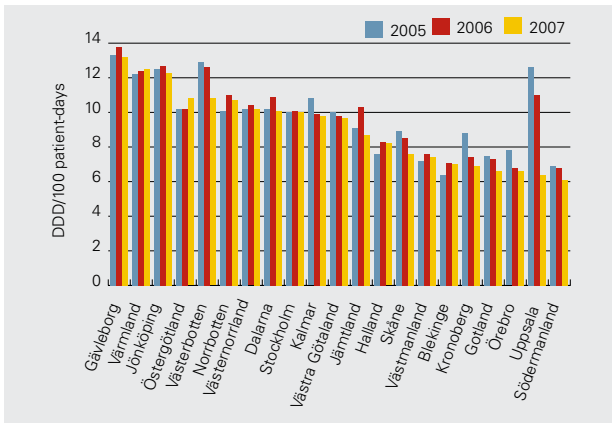


Figure 3.1.16. Cephalosporins (J01DB-DE) in hospital care, all counties 2005-2007, DDD/100 patient-days. Denominator data for 2006 is also used for 2007, see Appendix 3.

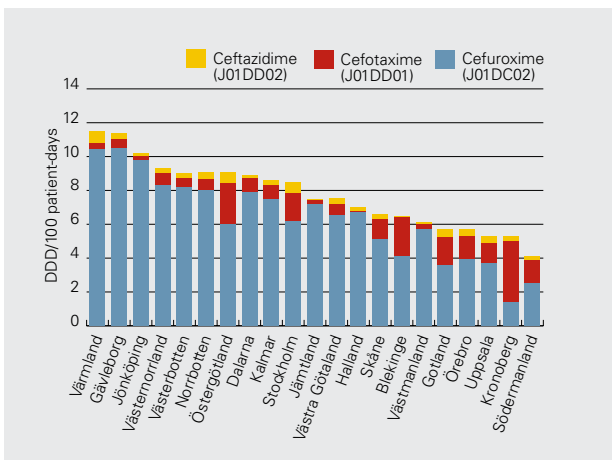


Figure 3.1.17. Cephalosporins in hospital care, all counties 2007 (denominator data from 2006), DDD/100 patient-days.

The use of carbapenems differs significantly between the counties as shown in Figure 3.1.18. Why the use of carbapenems is so much higher per 100 patient-days in Uppsala, Östergötland and Västerbotten than in the other counties is not known. One explanation might be that these three counties have major tertiary care hospitals serving patients from neighbouring counties.

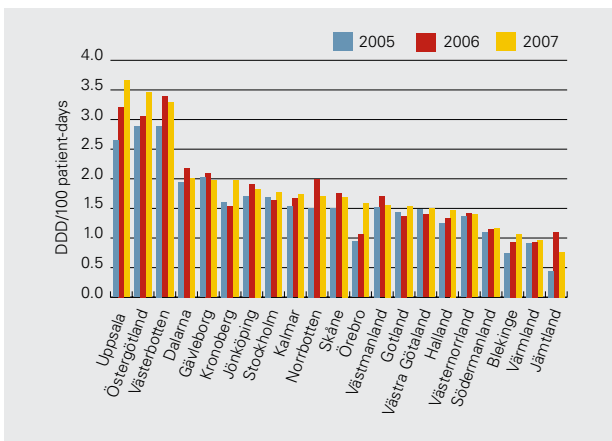


Figure 3.1.18. Carbapenems (J01DH) in hospital care, all counties 2005-2007, DDD/100 patient-days. Denominator data for 2006 is also used for 2007, see Appendix 3.

Antibiotic consumption in Europe

Sweden participates in the European Surveillance of Antimicrobial Consumption project, ESAC. Sales data have been collected since 1997. In Figure 3.1.19 the total community use (excluding methenamine) for some European countries during the period 1999-2006 is presented. A large difference is seen between the lowest and the highest prescribing country. France uses nearly three times more antibiotics than the Netherlands but shows a distinct downward trend.

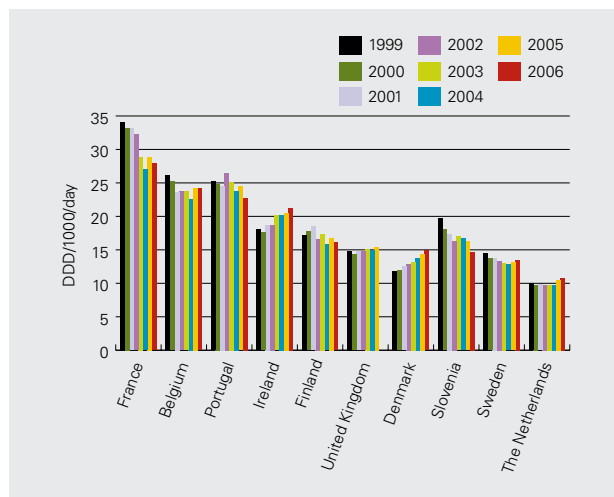


Figure 3.1.19. Total community antibiotic use (methenamine excluded) in some European countries, 1999-2006. DDD/1000/day. Source: ESAC.

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Adverse reactions related to antibiotic use

Spontaneously reported drug-related adverse reactions are continuously registered in SWEDIS, a national database administered by the Swedish Medical Products Agency. The reports originate from healthcare professionals. The frequencies of antibiotic-related adverse reactions, adjudged as probably drug-related, during the last five years (2003–2007) were analysed for various groups of agents. The six most commonly reported categories of adverse reactions, adjudged as probably related to the use of systemic antibiotic drugs (J01), in the period 2003–2007 were skin- and subcutaneous tissue disorders (n=452), gastrointestinal disorders (n=194), hepatobiliary disorders (n=192), general disorders (n=159), blood disorders (n=158), and musculoskeletal disorders (n=156). The majority of the reports (61%) concern female patients. The ten antibiotic substances most commonly associated with adverse reactions, in the last five years, unadjusted for the consumption and regardless of the cause of the report are shown in Table 3.1.6.

Table 3.1.6. Number of reports to the Swedish Medical Products Agency 2003–2007

Antibiotic	Total number of ADR reports 2003 to 2007	Number of 'serious' reports	Number of fatal cases (causal relationship possible)
Ciprofloxacin	190	96	1
Flucloxacillin	110	77	3
Trimethoprim	102	45	0
Nitrofurantoin	98	51	1
Clindamycin	84	40	1
Fenoxymethylpenicillin	77	34	0
Doxycyclin	67	27	3
Sulphamethoxazol + trimethoprim	64	40	1
Norfloxacin	54	26	2
Levofloxacin	51	31	0

Following the amendment of treatment recommendations there was a change in prescription patterns for uncomplicated urinary tract infections during this period. Consumption of fluoroquinolones decreased, which was reflected in a decrease in reported adverse events. In the latter years this decline in reporting seems to have levelled out, Table 3.1.7. For nitrofurantoin which has been increasingly prescribed in recent years a slight corresponding increase in the reporting of adverse reactions was noted. Due to the low number of reports and to the fact that data are based on spontaneous reporting, no clear conclusions can be made with regards to these trends.

Table 3.1.7. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin during the period 2003–2007.

	2003	2004	2005	2006	2007	2003-2007
Fluoroquinolones						
Total adverse events	84	75	77	78	72	386
Musculoskeletal	22	34	24	19	22	121
tendinitis	14	15	13	11	10	63
tendon rupture	5	12	5	3	6	31
Skin- and subcutaneous tissue	16	7	11	6	17	57
Psychiatric disorders	9	4	10	8	4	35
Nitrofurantoin						
Total adverse events	32	48	26	38	39	183
Respiratory system	10	10	8	12	3	43
dyspnoea	4	3	2	4	0	13
interstitial pneumonia	4	2	2	2	2	12
lung fibrosis	0	1	0	2	0	3
Skin- and subcutaneous tissue	5	7	1	7	8	28
General disorders	9	11	7	8	7	42
fever	5	6	6	4	3	24

Charlotta Edlund, Bengt Lindeskog

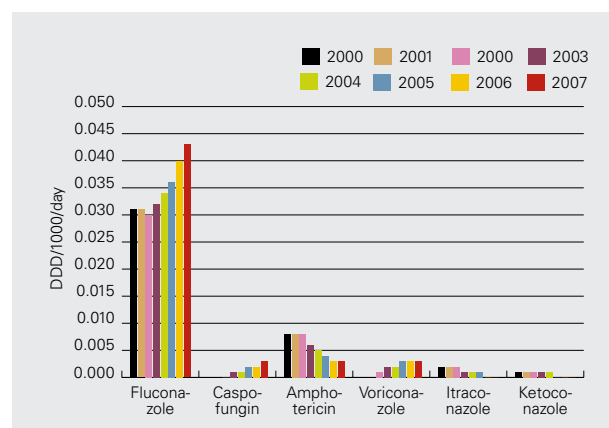
3.2 Use of antifungals

Community care

Measured as number of packages/1000 inhabitants, 95% of the total consumption of antimycotics takes place in community care. Imidazoles for gynecological use are mostly sold over the counter as well as antifungals for topical use, 92% and 63% respectively. During 2007 the rate of community care antifungal prescription was highest for fluconazol (J02AC01) and miconazol plus hydrocortisone for topical use (D01AC52), 18 and 17 prescriptions/1000/year respectively. These two groups represented nearly 50% of all antifungal prescriptions.

Hospital care

The total use of antifungals administered systemically in hospital care increased by nearly 5% (from 0.050 to 0.053 DDD/1000/day) from 2006 to 2007. Fluconazole accounts for most of the rise and constitutes 82% of the total antifungal use, administered systemically, in hospital care. The use of caspofungin also showed an increase during the last year. Following the trend observed in recent years the use of amphotericin B decreased by 17% from 2006-2007. Since 2001 the reduction has been 66%.

**Figure 3.2.1. Use of antifungals in hospital care, 2000-2007.**

Gunilla Skoog

4.1. Antimicrobial resistance

IN SWEDEN, testing of clinical isolates for antibiotic susceptibility is routinely performed using standardized methods (Appendix 4). The first finding of methicillin resistant *Staphylococcus aureus* (MRSA), pneumococci with decreased susceptibility to penicillin G (PNSP, MIC $\geq 0,5$ mg/L) or vancomycin resistant enterococci (VRE) in a patient is notifiable for the clinician and the laboratory under the Communicable Disease Act, regardless of whether it is a clinical infection or asymptomatic carriage. ESBL-producing *Enterobacteriaceae* became notifiable by the laboratories under the Communicable Disease Act February 1st 2007. In addition to these mandatory notifications a national programme for the surveillance of resistance, RSQC, was initiated in 1994 (Appendix 5). Well-characterised data on resistance in many bacterial pathogens are available since several years both at regional and national level.

Twenty-one of the Swedish laboratories, covering approximately 75% of the population, report susceptibility data on invasive isolates for seven species to EARSS. Eleven of these laboratories, using the same laboratory information system, also deliver invasive isolates on all positive blood cultures (Appendix 5).

One of the cornerstones in the battle against antibacterial resistance in Sweden has been early identification of cases via screening programmes and contact-tracing around cases with notifiable resistance. The annual number of samples specifically registered to be analysed for screening for (multi-) resistant bacteria, MRB, is shown in Figure 4.1.1. Even if the screening programmes and criteria for registering analyses under this heading may vary somewhat between laboratories, they are fairly constant within each laboratory. In 2007 all laboratories reported data for the first time.

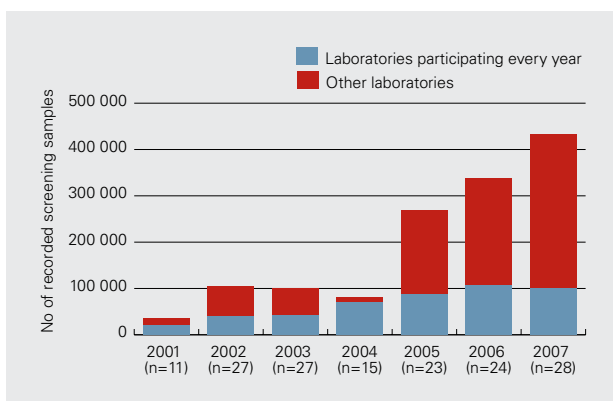


Figure 4.1.1. Annual number of recorded screening samples, 2001-2007.

Staphylococcus aureus

Background

Following an extensive regional outbreak and increasing alertness responding to the situation seen in other European countries MRSA was made mandatory notifiable in the year 2000. Compared to some other European countries, where the proportion of MRSA approaches 40% of invasive *S. aureus* isolates, the prevalence of MRSA among such isolates is still below 1% in Sweden (see details on EARSS data in the following text). Infection control programmes have been developed and implemented locally under supervision of the County Departments for Communicable Disease Control (CDCDC) and infection control teams. These programmes are based on early case-finding through extensive screening of patients with risk factors and contact tracing combined with infection control measures such as isolation of MRSA positive cases and intensive campaigns on basic hygiene precautions.

Notifications of MRSA under the Communicable Disease Act

The following presentation is based on data collected in the web-based notification system "SmiNet 2" as recorded at county level. An active effort has been made to collect missing data for 2006 and 2007. The notifications have been reviewed and complemented with available relevant information in collaboration with the CDCDCs. A total of 1128 cases of MRSA were notified in 2007, an increase with 7% as compared to the 1057 cases 2006, Figure 4.1.2.

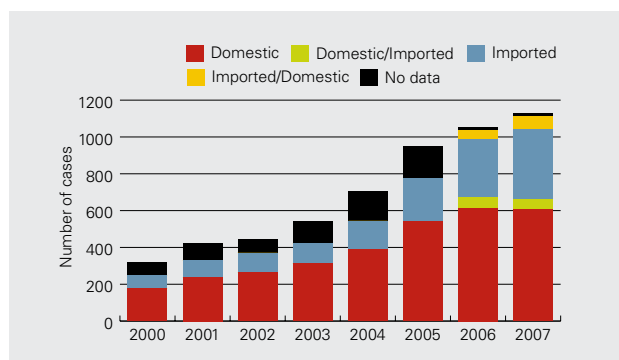


Figure 4.1.2. Number of MRSA notified annually by country of acquisition, Sweden 2000-2007. Domestic/Imported and Imported/Domestic means both alternatives possible, given in that order.

Table 4.1.1. MRSA notified in 2000-2007 by county under the Communicable Disease Act

County	2000		2001		2002		2003		2004		2005		2006		2007	
	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *
Stockholm	97	5.3	166	9	205	11.1	228	12.3	277	14.8	315	17.1	356	18.9	351	18.0
Uppsala	19	6.5	17	5.7	10	3.3	12	4	26	8.6	28	9.2	24	7.9	33	10.2
Södermanland	2	0.8	1	0.4	4	1.5	2	0.8	8	3.1	11	3.8	9	3.4	26	9.8
Östergötland	2	0.5	7	1.7	7	1.7	14	3.4	14	3.4	101	24.3	48	11.5	49	11.6
Jönköping	7	2.1	6	1.5	5	1.5	24	7.3	14	4.3	40	12.1	44	13	17	5.1
Kronoberg	1	0.6	0	0	4	2.3	5	2.8	17	9.5	11	6.1	14	7.8	13	7.2
Kalmar	3	1.3	5	0.9	5	2.1	6	2.6	16	6.8	23	9.7	26	11.1	36	15.4
Gotland	1	1.8	10	17.5	3	5.3	2	3.5	1	1.7	10	17.3	4	6.9	8	14.0
Blekinge	7	4.7	1	0.7	3	2	2	1.3	3	2	9	5.9	4	2.7	16	10.5
Skåne	22	1.9	76	6.7	68	5.9	104	9.1	128	11.3	162	13.9	179	15.5	166	13.8
Halland	10	3.6	26	9.4	13	4.7	13	4.6	9	3.2	21	7.4	23	8.1	18	6.2
Västra Götaland	114	7.6	56	3.7	48	3.2	63	4.2	118	7.8	125	8.1	177	11.6	178	11.5
Värmland	9	3.3	7	2.6	6	2.2	11	4	18	6.6	9	3.2	13	4.8	32	11.7
Örebro	8	2.9	7	2.6	16	5.9	8	2.9	11	4	16	5.8	35	12.8	25	9.1
Västmanland	3	1.2	8	3.1	6	2.3	11	4.2	12	4.6	35	13.4	48	18.4	54	21.7
Dalarna	0	0	5	1.8	1	0.4	2	0.7	3	1.1	6	2.1	11	4	15	5.4
Gävleborg	2	0.7	1	0.4	12	4.3	5	1.8	5	1.8	24	8.6	17	6.1	12	4.4
Västernorrland	14	5.7	12	4.9	7	2.9	10	4.1	5	2	4	1.6	9	3.7	22	9.0
Jämtland	0	0	0	0	2	1.6	5	3.9	1	0.8	8	6.2	4	3.1	24	18.9
Västerbotten	3	1.2	17	6.7	10	3.9	13	5.1	16	6.2	10	3.8	7	2.7	23	8.9
Norrbottnen	3	1.2	5	2	7	2.8	9	3.6	7	2.8	8	3.1	5	2	10	4.4
Total, Sweden	327	3.7	429	4.8	442	4.9	549	6.1	709	7.8	975	10.8	1057	11.7	1128	12.3

* = Incidence / 100 000 inhabitants in Sweden.

In 2007, six of the Swedish counties had a higher incidence than the total national incidence of 12.3 cases/100000 inhabitants, Table 4.1.1. During 2007 minor outbreaks were reported from several counties.

Fifty-four percent (n=608) of all MRSA cases reported 2007 were domestically acquired. One third (376 cases) were acquired abroad. The Philippines, with 24 reported cases, former Serbia/Montenegro (23 cases), China, (21 cases), Thailand (20 cases) and the USA (20 cases) made up the five most common countries for imported MRSA infection during 2007. In 12% of the cases Sweden and/or at least one other country were mentioned as possible countries for acquisition of MRSA. These cases were divided between “domestic/imported” or “imported/domestic” depending on the order of listing of the countries. In only 1% of all MRSA was no source country of infection reported or reported as “unknown”. Figure 4.1.3 shows that the age groups below 50 years of age increased most among domestic cases during recent years.

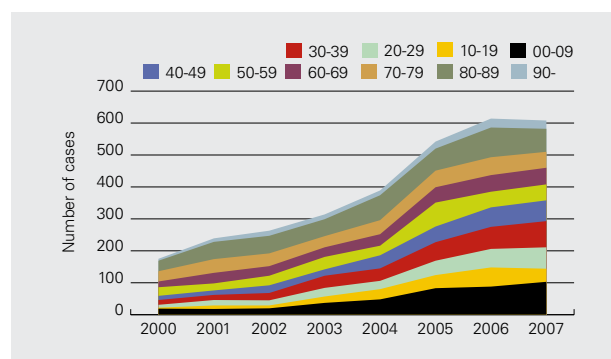


Figure 4.1.3. Age distribution of notified domestic cases of MRSA, Sweden 2000-2007.

In 2007, 58% of all domestic cases were identified in targeted screening and 41% due to clinical symptoms, Figure 4.1.4. Even if aggregated data on the total number of clinical cultures are not currently available, it is reasonable to assume that the number of cultures have increased as culturing of even boils and minor blisters is widely encouraged in primary care. Thus, wider indications for culturing in combination with spread of PVL (Panton-Valentine leucocidin)-positive MRSA in the community probably explains the increase of clinical isolates during the last years. Two thirds of the imported MRSA cases were found in targeted screening programmes and one third had clinical symptoms.

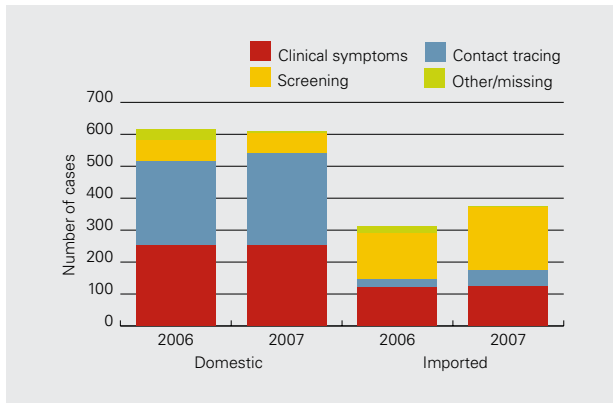


Figure 4.1.4. The culture indications for domestic and imported MRSA cases in Sweden 2006-2007.

Categorization according to place of acquisition of MRSA (not where the diagnosis was made) is based on epidemiological information. In 2007 the form used by physicians for the clinical notification of MRSA was slightly simplified in an attempt to improve data quality.

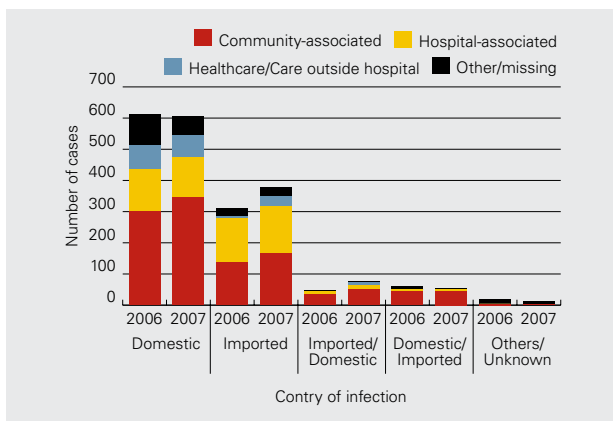


Figure 4.1.5. Source of MRSA acquisition by country of infection, Sweden 2006-2007.

Community associated infections dominated among domestic cases in 2007 and comprised 57% of all cases. This is an increase from the previous year and shows that MRSA in Sweden today is acquired primarily in the community. This was also the case for the imported MRSA cases where community associated infections predominated during 2007, representing 44% (165/376) of all cases. In 10% of all cases several countries are mentioned (2-5 countries) and community acquired MRSA is cited for 73% of these cases.

Hospital associated MRSA was relatively more common in imported cases, 152/376 (40%) than among domestic cases 127/608 (21%). Similar proportions were seen in 2006, 46% and 22%, respectively. Since there has been a debate about the risk of acquiring resistant bacteria such as MRSA while going abroad for elective surgery and “lipo-tourism”, we actively asked the CDCDCs for such information during the review. However, only a few cases were probably infected in connection to “medical tourism”.

Typing of MRSA

DNA-based methods have been used for typing of all MRSA isolates since 2000. During 2000-2005 pulsed field gel electrophoresis (PFGE) was the standard method. It was replaced by *spa*-typing in 2006 and is now the primary typing method. *spa*-typing is based on sequencing of the polymorphic X-region of the *Staphylococcus aureus* species-specific protein A gene, *spa*, and the Ridom StaphType® software is used for the analysis.

The ten most common *spa*-types were t032 (n=105), t008 (n=102), t044 (n=87), t002 (n=69), t037 (n=29), t015 (n=25), t437 (n=21), t690 (n=19), t024 (n=16), and t019 (n=15). The five most common types comprised more than one third, and the ten most common types comprised 46% of all cases. Isolates with *spa*-types t032, t037 and t015 were always negative for the PVL-toxin, whereas isolates with *spa*-types t044 and t019 were always positive. Among isolates of the other common *spa*-types both PVL-positive and -negative ones were found.

Among the PVL-positive isolates, those of *spa*-type t008 (PFGE pattern SE03-5) were the most rapidly increasing. Based on PFGE, they have been shown to have the same PFGE pattern as USA 300. This is an MRSA strain described as the dominating community-acquired strain in the US and it is now increasingly reported from many European countries also. During the last couple of years, PVL-positive MRSA represent more than 30% of all MRSA cases.

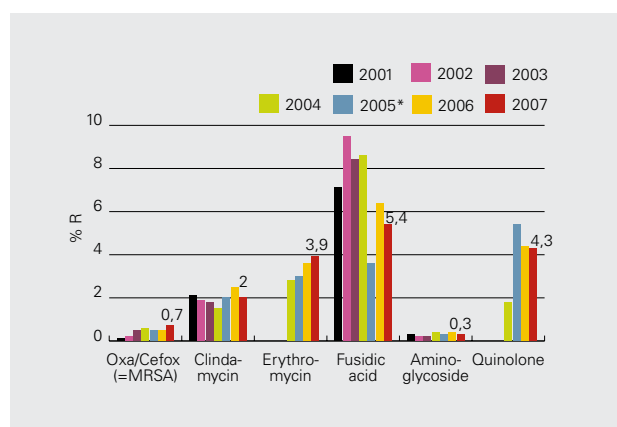
All MRSA isolates were investigated with regard to their resistance to antibiotics other than betalactam antibiotics, Table 4.1.2. Resistance to erythromycin and to ciprofloxacin were most frequently found during the whole investigation period although the frequencies were slightly lower (<40%) from 2004 and onwards. Macrolide resistance was nearly always of the MLSB type, indicated by simultaneous resistance to clindamycin (inducibly or constitutively expressed). Resistance to fusidic acid, which was typical for t044 isolates (PFGE pattern DK E97-1 and its variants) but also found in other types, became less frequent (<20%) from 2004 and onwards. Aminoglycoside resistance (gentamicin tested) was found in 15-20% of the isolates through the years. Resistance to mupirocin and rifampicin were found in less than 10% of the isolates.

Annual Resistance Surveillance and Quality Control (RSQC) programme

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

Table 4.1.2. Numbers and rates of resistance (%) to indicated antibiotics among MRSA strains 2000-2007.

Year/Antibiotic	Erythromycin	Clindamycin	Fusidic acid	Gentamicin	Ciprofloxacin	Mupirocin	Rifampicin
2000	179 (55.9)	nt	74 (23.1)	76 (23.8)	187 (58.4)	8 (2.5)	42 (13.1)
2001	208 (50.5)	nt	89 (21.6)	87 (21.1)	252 (61.2)	30 (7.3)	44 (10.7)
2002	220 (50.3)	nt	128 (29.3)	80 (18.3)	280 (64.1)	48 (11)	27 (6.2)
2003	220 (40.4)	nt	156 (28.7)	91 (16.7)	278 (51.1)	47 (8.6)	25 (4.6)
2004	229 (33.3)	nt	135 (19.7)	97 (14.1)	270 (39.3)	24 (3.5)	24 (3.5)
2005	374 (39.2)	326 (34.1)	155 (16.2)	183 (19.2)	318 (33.3)	21 (2.2)	34 (3.6)
2006	371 (37.1)	308 (30.8)	162 (16.2)	140 (14.0)	322 (32.2)	20 (2.0)	40 (4.0)
2007	433 (39.6)	343 (31.4)	159 (14.6)	207 (19.0)	401 (36.7)	20 (1.8)	47 (4.3)

Figure 4.1.6. Resistance rates for *Staphylococcus aureus* 2001–2007 (data from the annual RSQC programme, approximately 3000 isolates per year).

*In 2005 resistance rates were recorded in *S. aureus* isolated from wounds and secretions from elderly people (> 65 years).

Resistance rates are increasing for macrolides (erythromycin used as test compound), but stable at around 2% for clindamycin. This indicates an increased prevalence of *mef* genes but not of *erm* genes in the clinical isolates. The proportion of isolates resistant to fusidic acid is slowly falling, possibly indicating the end of the epidemic of fusidic acid resistant *S. aureus* which caused bullous impetigo and apparently peaked in 2002-2004. The frequency of MRSA in wound infections (cefoxitin used as test compound) increased in 2007 but is still below 1%.

Data on invasive isolates reported to EARSS

In 2007, only 0.5% of the invasive *S. aureus* isolates were MRSA (identified by the cefoxitin screen disk test and confirmed by the detection of the *mecA* gene). This level is lower than previous years, suggesting that infection control measures to prevent MRSA from spreading in the hospital environment have been successful.

Table 4.1.3. *Staphylococcus aureus* susceptibility results (number of strains and percentage) using the disk diffusion method and confirmation of the *mecA* gene according to SRGA in Sweden. Data reported from SMI to EARSS.

Year	S	I	R
2001	1618 (99.1%)	0	14 (0.9%)
2002	1830 (99.4%)	0	12 (0.6%)
2003	1839 (99.1%)	0	16 (0.9%)
2004	1891 (99.3%)	0	14 (0.7%)
2005	1756 (99%)	0	18 (1.0%)
2006	1849 (99.1%)	0	16 (0.9%)
2007	2162 (99.5%)	0	11 (0.5%)

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Streptococcus pneumoniae

Background

S. pneumoniae with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (henceforth designated PNSP) became notifiable under the Communicable Disease Act in 1996 after reports of increasing resistance in southern Sweden. In addition invasive infections with *S. pneumoniae*, regardless of resistance, became notifiable 2004.

Notifications under the Communicable Disease Act

In 2007 there were 672 notifications of PNSP in Sweden an increase with 6.5% compared to 2006, Figure 4.1.7. Sixtyseven percent of the cases were reported to be infected domestically and 10% in a foreign country. In the remaining 152 cases no country of infection was given.

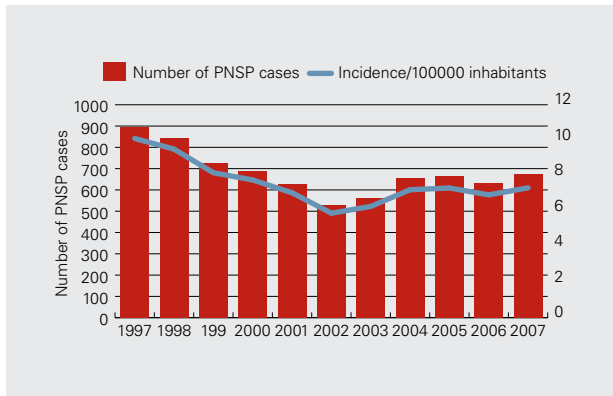


Figure 4.1.7. Number of PNSP cases and annual incidence of *S. pneumoniae* with reduced susceptibility to penicillin, (MIC > 0.5 mg/L) in Sweden 1997-2007.

The 2007 annual PNSP incidence in Sweden was 7.3/100 000 similar to that of 2006. After a fall from 10.1 to 5.9 per 100 000 populations from 1997 to 2002, the annual incidence has again started to rise. Previous analysis has indicated that the declining incidence from 1997 to 2002 was related to a concurrent decrease in nasopharyngeal culturing propensity. There is no sex difference in the patterns of reported cases. The majority of PNSP cases, irrespective of the year observed, are found in the age group 0-4 years, Figure 4.1.8.

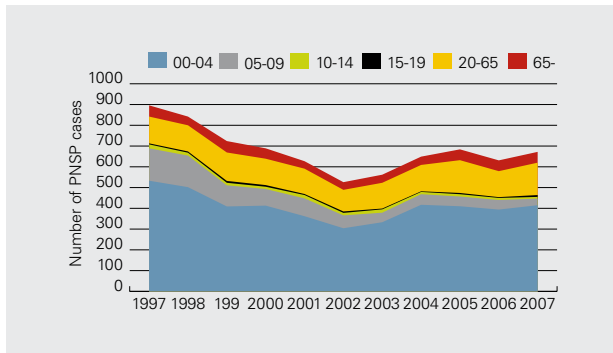


Figure 4.1.8. Age distribution of all cases reported with PNSP in Sweden 1997-2007.

PNSP notifications were received from all 21 counties with Stockholm (287 cases) and Skåne (195 cases) accounting for 72% of the total. The other counties reported 2-38 cases each. Case finding intensity varies between different counties in Sweden, due to regional differences in general culturing propensity, as well as presence of targeted screening programmes in some counties. This makes comparison of regional incidence rates difficult.

The majority, 83% of all notifications of PNSP, result from nasopharyngeal cultures. 27 cases in 2007 were reported to have invasive PNSP infections, 25 cases in blood and two in cerebrospinal fluid. The serotype was reported in seven of these cases, four cases had serotype 9, two had serotype 14 and one had serotype 23. The most commonly found serotypes among all PNSP were, in decreasing order: 19F, 14, 9V, 6B, 23F and 19A.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pneumococci have been included in the surveys by Swedish laboratories since 1994. These isolates were mainly derived from nasopharyngeal cultures. Approximately 3000 consecutive isolates per year from all the clinical laboratories have been tested for susceptibility to penicillin (by means of oxacillin 1 µg screen disk), erythromycin, tetracycline, and trimethoprim-sulfamethoxazol, using the disk diffusion method. The national summary of the results is shown in Figure 4.1.9. The steadily increasing trend seems to be broken in 2007 for all four tested antibiotics.

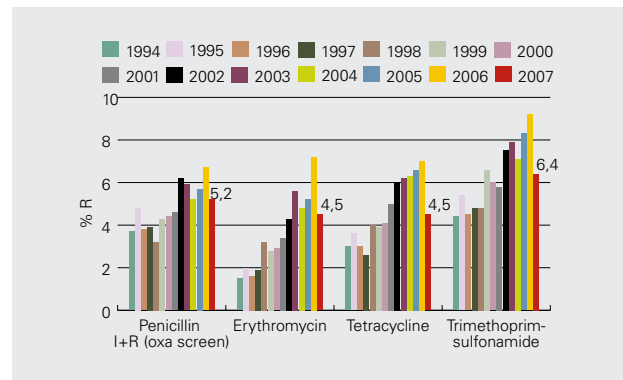


Figure 4.1.9. Resistance rates for *Streptococcus pneumoniae* 1994-2007 (data from the annual RSQC programme, approximately 3000 isolates per year).

Data on invasive isolates reported to EARSS

The Swedish data on susceptibility to penicillin and erythromycin for 2001-2007 are given in Table 4.1.4. Levels of resistance are lower in invasive isolates than in the nasopharyngeal isolates from the RSQC programme. In addition, the trend of increasing resistance in nasopharyngeal isolates is not mirrored in invasive isolates, neither for penicillin nor for erythromycin.

Table 4.1.4. Invasive isolates of *Streptococcus pneumoniae* reported to EARSS.

Penicillin * (I+R = PNSP)				
Year	S%	I%	R%	Total
2001	97.2	2.3	0.5	788
2002	97.5	2.4	0.1	783
2003	95.0	5.0	0	920
2004	96.8	2.8	0.4	955
2005	96.4	3.1	0.5	1017
2006	97.9	2.1	0	936
2007	97.1	2.9	0.1	1029
Erythromycin				
Year	S%	I%	R%	Total
2001	95.4	0.2	4.4	653
2002	94.7	0.1	5.2	700
2003	94.9	0.1	5.0	736
2004	94.7	0.1	5.2	869
2005	94.3	0.3	5.4	924
2006	94.8	0.4	4.8	813
2007	94.9	0.1	5.2	926

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

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Enterococcus faecium* and *Enterococcus faecalis

Background

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

Notifications under the Communicable Disease Act

There were 53 notified cases of VRE during 2007, the highest number since notification became mandatory. From 2000 to 2006 the numbers of reported cases of VRE were 20, 18, 19, 47, 21, 35 and 24 respectively. The increase in 2007 was due to an outbreak at a hospital in Stockholm County which involved intensive infection control efforts including screening and contact tracing, see below.

Notifications of VRE were received from 8 out of 21 Swedish counties with Stockholm accounting for 77% of the total (40 cases). The average age for all cases was 60 years. 39 of the notified VRE cases in 2007 were acquired domestically, whilst 12 were reported to have been acquired abroad. No information about country of infection was provided in two cases. In 45 of the 53 VRE cases the source of acquisition was healthcare related. In the remaining cases the source of acquisition was unknown.

In 2007, 52 cases of *Enterococcus faecium* were notified, 12 of which carried the *vanA*-gene, 38 the *vanB*-gene. The gene was

not specified in one isolate. *Enterococcus faecalis* was notified in two cases, one in a double infection with *Enterococcus faecium* with *vanA* present and one with no information given.

Overall the majority of VRE reported under the Communicable Disease Act 2000–2007 have been *Enterococcus faecium* carrying the *vanB*-gene whereas *Enterococcus faecium* with *vanA*, *Enterococcus faecalis* with *vanA* and *Enterococcus faecalis* with *vanB* have only been found as sporadic cases.

Nosocomial transmission of vancomycin resistant *Enterococcus faecium* in Stockholm hospitals during 2007

We know that only few patients have been diagnosed with vancomycin resistant *Enterococcus faecium* infection since it became notifiable in 2000, in Stockholm 0–13 patients yearly. During 2007, however, there was an increase to 40 patients, the majority being detected during the last four months.

During the late summer months two patients were diagnosed with VRE in clinical samples at the university hospital and a few weeks later VRE was detected in a third patient who had a screening faeces sample taken after being hospitalized abroad. All three had the same strain according to the PFGE pattern. Extensive contact tracing was undertaken with sampling of every patient both on admission and discharge from the affected ward. In total 35 patients with identical *vanB* strain of VRE were found. Eight patients had symptomatic infection and 27 were asymptomatic carriers in faecal samples.

In a regional hospital two additional minor outbreaks have been detected. Contact tracing and epidemiological typing showed that one outbreak was caused by *vanA* positive VRE and another by a *vanB* positive VRE different from the strain prevalent at the university hospital. It is evident that VRE has been spread at two hospitals in Stockholm, however, the overall prevalence of VRE in the population of Stockholm is still unknown.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Enterococcus faecalis was not included in the RSQC programme on antibiotic resistance for 2007.

Data on invasive isolates reported to EARSS

Since 2001, *Enterococcus faecalis* and *Enterococcus faecium* have been included in the EARSS network (Appendix 5). The main focus has been on vancomycin resistance, but also on high-level resistance to aminoglycoside antibiotics.

In 2003 the first four (2.2%) vancomycin-resistant invasive isolates of *Enterococcus faecium* were reported, and in 2004 three isolates were found, representing 1.2%, Tables 4.1.5 and 4.1.6. Molecular typing of these vancomycin-resistant isolates indicated that only two were related, both from the same hospital. In 2006 only two resistant blood isolates were found, and none in 2007.

High-level aminoglycoside resistance (HLAGR) was almost equally prevalent in *Enterococcus faecalis* (15.8%) and *Enterococcus faecium* (14.8%) in 2007. From 2006 and onwards all laboratories who report HLAGR use gentamicin (GEN) as test disk for detection.

Table 4.1.5. Resistance in invasive isolates of *Enterococcus faecalis* reported to EARSS 2001-2007.

Year	Vancomycin-R (%)	HLAGR (%)	Total number (number tested for HLAGR by GEN)
2001	0	12.7	395 (212)
2002	0	17	430 (235)
2003	0	17.5	593 (440)
2004	0	15.4	592 (533)
2005	0	18.7	567 (492)
2006	0.4	19.9	579 (563)
2007	0	16.1	651 (632)

Table 4.1.6. Resistance in invasive isolates of *Enterococcus faecium* reported to EARSS 2001-2007.

Year	Vancomycin-R (%)	HLAGR (%)	Total number (number tested for HLAGR by GEN)
2001	0	9.1	169 (99)
2002	0	6.3	181 (96)
2003	2.2	11.2	231 (170)
2004	1.2	7	260 (227)
2005	0	4.3	253 (211)
2006	0.3	14	286 (286)
2007	0	14.4	279 (263)

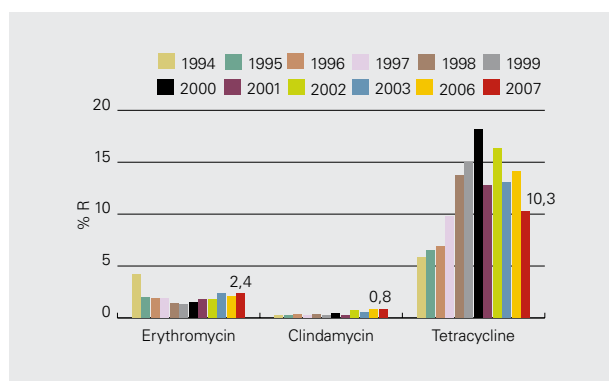
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Streptococcus pyogenes

Annual Resistance Surveillance and Quality Control (RSQC) programme

Streptococcus pyogenes was included in the RSQC programme in 2007. Approximately 3 200 clinical isolates (>=100 consecutive isolates from each of the clinical microbiology laboratories) have been tested for resistance to erythromycin, clindamycin and tetracycline using the disk diffusion method. Laboratories were advised to interpret D-zones caused by interaction between erythromycin and clindamycin as clindamycin-R, thereby giving a presumptive identification of the resistance mechanisms. The national overview of these data is given in Figure 4.1.10.

The average low level of erythromycin resistance has remained stable at 2 – 2.5%. Resistance to clindamycin has increased from almost nil (0.2% in 1994-2001) to an average of 0.8% in 2006-2007. The difference in resistance rates between erythromycin and clindamycin indicates that the main mechanism of macrolide resistance in *Streptococcus pyogenes* is efflux-mediated (*mef* genes), which does not affect clindamycin. Resistance to tetracycline is still above 10% but has shown a decreasing trend since 2000.

**Figure 4.1.10. Resistance rates (resistant isolates in percent of all *Streptococcus pyogenes* isolates) for three groups of antibiotics 1994-2007.**

Surveillance on invasive isolates additional to EARSS data

Out of a total of 9585 positive blood cultures in 2007, 119 (1.2%) were *Streptococcus pyogenes* (GAS). Two of the isolates (2%) were resistant to erythromycin and clindamycin, and nine (8%) were resistant to tetracycline. These figures were similar to the ones obtained in the RSQC programme, and the decline in tetracycline resistance was parallel in both sets of data (from 11% to 8% in blood isolates and from 14 to 10% in respiratory tract isolates).

Streptococcus agalactiae

Surveillance on invasive isolates additional to EARSS data

Out of a total of 9585 positive blood cultures in 2007, 137 (1.4%) were *Streptococcus agalactiae* (GBS). Twelve of the isolates, 8.8%, were resistant to erythromycin and clindamycin. This was a considerable increase since 2006, from 4.4% to 8.8%. A majority of the isolates were retrieved from adults, but 16 (11.7%) were isolated from children less than one year old.

Haemophilus influenzae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Haemophilus influenzae was not included in the RSQC programme in 2007 but will be re-entered in 2008.

Surveillance on invasive isolates additional to EARSS data

Out of a total of 9585 positive blood cultures in 2007, 51 (0.5%) were *Haemophilus influenzae*. Only three isolates were beta-lactamase-producing and ampicillin-resistant and one isolate was resistant to trimethoprim-sulfamethoxazole. No chromosomally mediated beta-lactam resistance was detected in this small material.

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Clostridium difficile

The emergence of a moxifloxacin-resistant *C. difficile*-strain with high morbidity and mortality (PCR ribotype 027) in North America and parts of Europe has led to increased typing activity of isolates sent to SMI in 2007. A project to monitor moxifloxacin-resistant *C. difficile* was initiated during 2007 and will continue in 2008. All Swedish laboratories are encouraged to participate in this project.

None of the 46 yet characterised moxifloxacin-resistant strains belonged to PCR ribotype 027 although three moxifloxacin-sensitive so-called “historical 027 isolates” collected during 1997-2001 have been identified. These isolates are however not identical to the new moxifloxacin-resistant epidemic strain that has spread throughout North America and parts of Europe.

Karin Tegmark Wisell, Tomas Åkerlund

Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBL)

Background

Increasing numbers of isolates at Swedish clinical laboratories and increasing numbers of reported outbreaks, both nationally and internationally, with bacteria producing beta-lactamases with an extended spectrum (ESBL) resulted in ESBL-producing *Enterobacteriaceae* becoming notifiable under the Communicable disease act from February 1st 2007. This was also in accordance with a governmental bill which urged notifications of health-care associated infections. Notification of ESBL is required only from laboratories. As a result, information on ESBL is restricted to data on age, gender and cultured material whilst information on the indications for sampling or place of acquisition is missing.

Notifications under the Communicable Disease Act

A total of 2099 cases were notified during the period February-December. Notifications came from all 21 counties of Sweden, corresponding to an average national incidence of 23 per 100,000 inhabitants, see Figure 4.1.11. Stockholm, Västra Götaland, Skåne och Uppsala reported 67% of all cases.

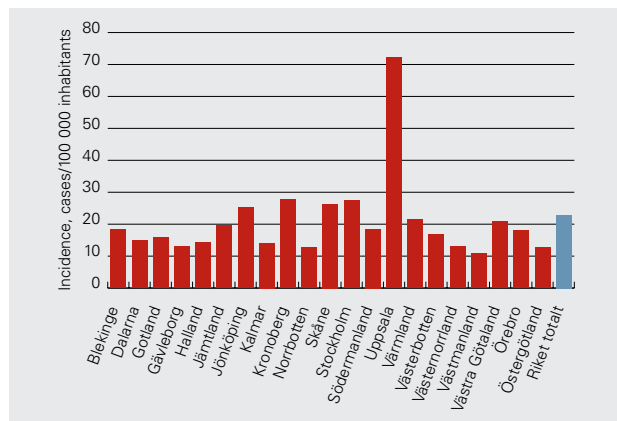


Figure 4.1.11. The incidence of ESBL in Swedish counties.

The high incidence in Uppsala county was a result of an extensive infection control and screening programme launched to control a large ESBL outbreak that occurred in 2005 and still ongoing.

The most commonly reported species were *Escherichia coli*, accounting in 77% of all cases, followed by *Klebsiella pneumoniae* with 12%. Information about species was missing for 7% of the cases. In 55 cases the patient carried several species belonging to *Enterobacteriaceae*, 51 of the patients carried two species, three patients carried three species and one patient was reported having four different species with ESBL activity. Bacteria were cultured from urine in 70% of all cases. The second most common source for ESBL-producing *Enterobacteriaceae* was screening samples from faeces (13%). 101 invasive ESBL infections have been notified in 100 patients with a positive blood culture and in one case from cerebrospinal fluid.

The age/sex distribution varied with the species, Figure 4.1.12. In ESBL-producing *E. coli* 69% were derived from women having an average age of 55 years, six years less than the average age in men. The *K. pneumoniae* ESBL cases were almost equally distributed between sexes, but with a higher mean ages, 68 years for women and 67 years for men.

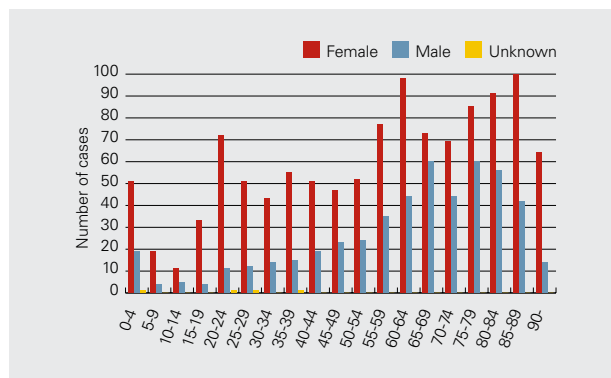


Figure 4.1.12 a. Age- and gender distribution of *E. coli* cases.

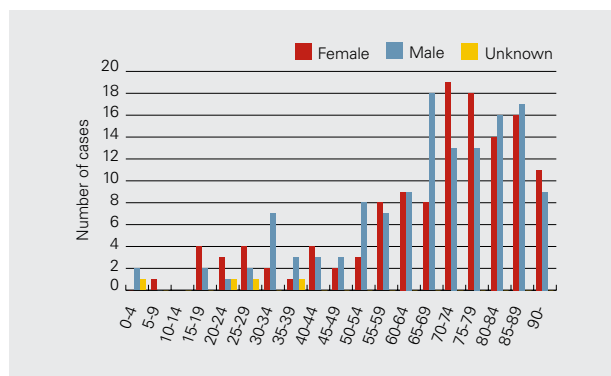


Figure 4.1.12 b. Age- and gender distribution of *K. pneumoniae* cases.

The first eleven months of mandatory notification show that ESBL-producing bacteria are a nation-wide endemic problem in Sweden. Concomitant resistance to several other antibiotics in many isolates (data not shown) limits the options for treatment.

Escherichia coli

Annual Resistance Surveillance and Quality Control (RSQC) programme

Escherichia coli, mainly derived from urinary tract infections, has been included in the RSQC program several times since 1996 and every year since 2001. Resistance to commonly prescribed oral antibiotics for treatment of UTI were tested each year. The resistance rates to ampicillin have increased yearly, from 17 up to 27%, Figure 4.1.13. The same trend is seen for trimethoprim with an increase from 10 to 17.5%. Quinolone resistance, detected by the screening disk nalidixic acid since 2002, has also shown an increase during this period and reached 12% in 2007.

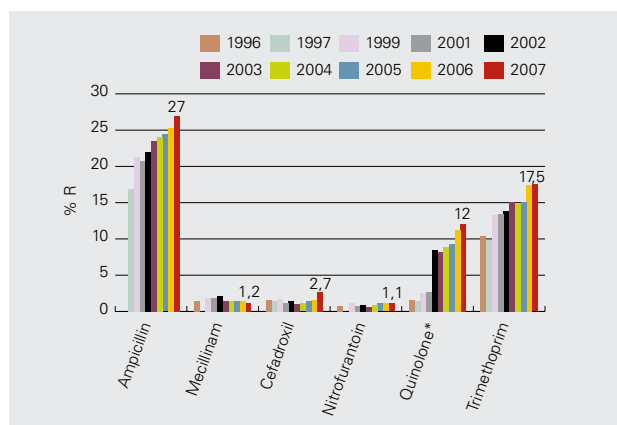


Figure 4.1.13. Resistance rates (resistant isolates in percent of all *Escherichia coli* isolates) for six antibiotics 1996-2007.

*Between 1996-2001 fluoroquinolone resistance was detected with Norfloxacin, from 2002 with Nalidixic acid.

In 2007 the RSQC programme was extended to last for three months, February – April, and included not only urine isolates but *E. coli* from all types of samples. Apart from the regular UTI antibiotics, the isolates should also be tested against cefotaxime, ceftazidime, and a carbapenem. From the results in Figure 4.1.13 it can be seen that cefadroxil resistance has almost doubled in recent years and has now reached 2.7% (>30 000 isolates tested). Resistance rates to cefotaxime, ceftazidime, and carbapenem were 2.4%, 2.2% and 0%, respectively. Isolates with verified ESBL-activity were collected and analysed further (n=240). Preliminary data on the resistance mechanisms involved show that the majority of resistance to these extended spectrum beta-lactam antibiotics was caused by ESBLs of the CTX-M type and that many of these strains were multi-resistant.

Data on invasive isolates reported to EARSS

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

Results for blood isolates collected in 2001-2007 are presented in Table 4.1.7. Ampicillin resistance, caused by production of plasmid-mediated beta-lactamase (most often

of TEM-type) was higher in blood isolates than in the urine isolates tested in the RSQC programme, 33% VS. 27%. However, the data for blood isolates was incomplete since one third of participating laboratories did not include ampicillin in susceptibility testing of invasive isolates. Ampicillin resistance rates in Sweden are still much lower than in most other European countries where ampicillin resistance often exceeds 50%. The level of resistance to third generation cephalosporins in blood isolates increased to 2.2% in 2007. In the majority of the cefotaxime-resistant isolates (1.6%) resistance was attributed to the presence of ESBLs of CTX-M type. Aminoglycoside resistance in *E. coli* has shown an increasing trend over the last couple of years and reached 2.3% in 2007. Reduced susceptibility and resistance to fluoroquinolones (I+R) has varied between 5.5% and 11% since 2001 but reached 13.3% in 2007. This rate of resistance in blood isolates is also reflected in urine isolates from the RSQC programme, as can be seen in Figure 4.1.13.

Table 4.1.7. *Escherichia coli* from blood cultures in Sweden 2001-2007, reported to EARSS.

Year	Ampicillin-R (%) *	Cefotaxime-R (%; ESBL / other mechanism)	Aminoglycoside-R (%) **	Fluoroquinolone-I/R (%) ***	Total number of isolates
2001	26.5	0.5	1	5.5	2627
2002	24.9	0.5	0.6	7.1	3062
2003	28.5	0.4	1	8.3	3300
2004	23	0.5 / 0.6	1.5	11.1	3336
2005	26	0.9 / 0.4	1.5	8.9	3212
2006	28.1	1.3 / 0.1	1.7	8.7	3514
2007	32.9	1.6 / 0.6	2.3	13.3	3745

*Only 55-60% of isolates were tested against ampicillin; **gentamicin or tobramycin, *** ciprofloxacin

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Klebsiella pneumoniae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Klebsiella pneumoniae was re-entered in the RSQC programme 2005 as it is one of the most important nosocomial pathogens, and was also included in the EARSS programme from July 2005. As for *E. coli*, the RSQC 2007 programme for *K. pneumoniae* was extended over three months and covered all types of material, although isolates from urine samples dominated. Both oral and intravenous antibiotics were tested, Figure 4.1.14. Data for 2007 indicate a decrease in resistance to aminoglycosides (from an already low level), while resistance levels to all other antibiotics increase.

Isolates with verified ESBL-activity were collected and analysed further (n=50), and preliminary data show that the majority was ESBLs of the CTX-M type and that many of the strains were multi-resistant.

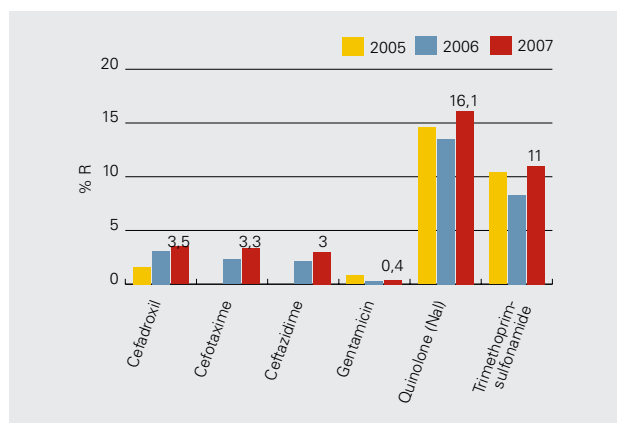


Figure 4.1.14. Resistance rates (resistant isolates in percent of all *Klebsiella pneumoniae* isolates) for four groups of antibiotics 2005-2007.

Data on invasive isolates reported to EARSS

From 1 July 2005, participants in the EARSS network have contributed with data on blood isolates of *Klebsiella pneumoniae*. A total of 281 isolates were reported from 20 laboratories in 2005, and 610 isolates in 2006. Results are shown in Table 4.1.8.

The majority of cephalosporin resistance was caused by ESBLs of CTX-M type as in *Escherichia coli* and levels of aminoglycoside and fluoroquinolone resistance were also the same.

Table 4.1.8. *Klebsiella pneumoniae* from blood cultures in Sweden 2005-2007, reported to EARSS.

Year	Cefotaxime-R (%; ESBL/ other mechanism)	Aminoglycoside-R (%) *	Fluoroquinolone-I/R (%) **	Total number of isolates
2005	0.7 / 0.7	1.4	9.8	281
2006	1.0 / 0.5	0.3	8.5	610
2007	1.1 / 0.3	1.1	10.8	649

*gentamicin or tobramycin, ** ciprofloxacin

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Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Data on *Pseudomonas aeruginosa* from the RSQC programme is available since 2003, Figure 4.1.15. All isolates were selected and tested in the same way, i.e. respiratory tract isolates were excluded, and tests were performed by disk diffusion. There were small fluctuations in resistance rates for all antibiotics, the most surprising being the decrease in quinolone resistance from 14 to 10.8%.

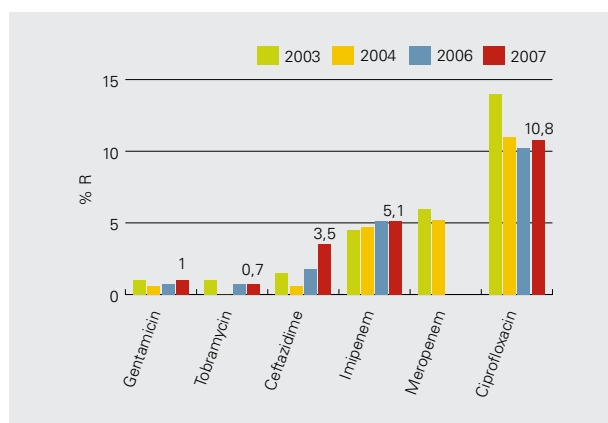


Figure 4.1.15. Resistance rates (resistant isolates in percent of all *Pseudomonas aeruginosa* isolates) for four groups of antibiotics 2003-2007.

Data on invasive isolates reported to EARSS

Pseudomonas aeruginosa was included in the EARSS network July 1st 2005. A total of 149 isolates from 20 Swedish laboratories were tested during the second half of 2005, and these data can be compared with complete data sets for 2006 and 2007, Table 4.1.9. The levels of resistance to beta-lactam antibiotics (ceftazidime and carbapenems) were in the range 3-6% for all three years. Data for 2007 showed good agreement with the data from the RSQC programme. The resistance levels for aminoglycosides and fluoroquinolones shown by the two data sets were also in good agreement.

Table 4.1.9. *Pseudomonas aeruginosa* from blood cultures in Sweden 2005-2007, reported to EARSS.

Year	Ceftazidime-R (%)	Carbapenem-R (%) *	Aminoglycoside-R (%) **	Fluoroquinolone-I/R (%) ***	Total number of isolates
2005 (half year)	4.7	Insufficient data	0	9.0	149
2006	2.6	4.4	0.5	10.4	296
2007	4.5	7.0	0	10.4	342

* imipenem, meropenem, ** gentamicin, tobramycin, *** ciprofloxacin

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Helicobacter pylori

Annual Resistance Surveillance

Helicobacter pylori derived from gastric biopsies have been monitored locally at a few laboratories. Frequencies of resistance to clarithromycin and metronidazole in clinical isolates from southwest of Sweden, representing a population of approximately 300 000, are presented in Table 4.1.10. In vitro resistance to metronidazole has previously been reported in approximately 40% but has not been tested since 2005.

Table 4.1.10. *Helicobacter pylori* University Hospital MAS, Malmö, Sweden 2001-2007.

Year	Clarithromycin R%	Metronidazole R%	Total number
2001	8.8	40.2	188
2002	9.0	44.1	124
2003	7.2	42.6	112
2004	11.6	41.0	151
2005*	11.2	nt	217
2006*	16.0	nt	257
2007*	9.8	nt	375

* Molecular biology technique from 2005

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Mats Walder

Salmonella and Shigella spp.

Annual Resistance Surveillance

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

Campylobacter spp

Annual Resistance Surveillance

Campylobacter spp. derived from patients with diarrhoea has been monitored locally at a few laboratories. Approximately 50% of *Campylobacter* strains are imported. Since resistance to fluoroquinolones is of major concern worldwide it is interesting to notice that the small decline in quinolone resistance among *Campylobacter* isolates noticed a few years ago has regained the former level of about 50%, Table 4.1.11. When screening for fluoroquinolone resistance using nalidixic acid disks was introduced in Sweden in 2001, it was expected to influence the resistance rates dramatically. The data for nalidixic acid and ciprofloxacin in parallel show, however, that the two disks are equally able to detect quinolone resistance in *Campylobacter*. It is noteworthy that macrolide resistance, tested by erythromycin, has increased since 2006 and reached 7% in 2007.

Table 4.1.11. *Campylobacter jejuni/coli* University Hospital MAS, Malmö, Sweden 2001-2007

Year	Nalidixic acid R%	Ciprofloxacin R%	Tetracycline R%	Erythromycin R%
2001	32	30	28	1
2002	29	28	30	0.5
2003	48	46	22	0
2004	50	47	29	2
2005	57	52	18	1
2006	50	44	21	4
2007	49	45	31	7

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Mats Walder

Neisseria gonorrhoeae

Notifications under the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable disease/infection and in 2007, 642 clinical cases of the infection were notified. Most of the cases were identified in the three largest counties of Sweden, which include Stockholm, Gothenburg and Malmö. Clinical isolates were characterised at the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Swedish Institute for Infectious Disease Control [SMI]), Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden and at the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden.

In 2007, isolates from 404 of the notified clinical cases were completely characterised at these laboratories, representing 63% of the notified cases. In total, 406 different *N. gonorrhoeae* strains were cultured from these cases (n=404). Susceptibility testing was performed by standardized methodology using Etest for MIC determination of ampicillin, cefixime, ceftriaxone, azithromycin, ciprofloxacin, and spectinomycin. The used SIR-breakpoints have been determined by The Swedish Reference Group for antibiotics (SRGA; <http://www.srga.org>). Production of β -lactamase was examined by using Nitrocefin discs. Results for 2007 are compared with those from 2001 to 2006 in Table 4.1.12.

Table 4.1.12. Antibiotic resistance rates (%) and β -lactamase production of Swedish *Neisseria gonorrhoeae* strains from 2001 to 2007.

	2001 (n=141)	2002 (n=120)	2003 (n=130)	2004 (n=149)	2005 (n=497)*	2006 (n=352)*	2007 (n=406)*
β -lactamase pos.	37	39	22	26	23	30	30
Penicillin G	38	48	-	-	-	-	-
Ampicillin	37	39	22	26	23	30	30
Cefuroxime	0	4	-	-	-	-	-
Cefixime	-	0	0	0**	0	0	0
Ceftriaxone***	-	0	0	0	0	0	0
Azithromycin	-	0	<1	0**	0	1	1
Tetracycline	56	54	-	-	-	-	-
Ciprofloxacin***	52	58	56	51	49	61	70
Spectinomycin	0	0	0	0	0	0	0

(- = not analysed)

* Data from the Swedish Reference Laboratory for Pathogenic Neisseria, Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden and the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. From 2001 to 2004, only data from the Swedish Reference Laboratory were reported.

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

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

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Magnus Unemo, Hans Fredlund

Neisseria meningitidis

Notifications under the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease. In 2007 49 clinical cases of the disease were reported. A total of 43 clinical isolates from blood or cerebrospinal fluid were analysed at the Swedish Reference Laboratory for pathogenic Neisseria, Department of Clinical Microbiology, Örebro University Hospital, Sweden. Susceptibility testing was performed by standardized methodology using Etest on Müller Hinton II agar medium with 5% defibrinated horse blood for determination of MIC for benzylpenicillin (pcG), phenoxymethylpenicillin (pcV), cefotaxime, ciprofloxacin, chloramphenicol and rifampicin. Production of beta-lactamase was examined by Nitrocefin discs.

None of the isolates produced beta-lactamase. Eleven isolates (26%) had reduced susceptibility to pcG (MIC>0.064 mg/L). The MIC for pcV is normally 5-10 times higher. All the isolates had cefotaxime – MIC \leq 0.008 and ciprofloxacin-MIC \leq 0.006. Chloramphenicol-MIC varied between 0.125 and 1.5 and rifampicin was not higher than 0.016 mg/L. The intervals for MIC within the SIR-system (as determined by RAF) are for pcG 0.25/1 (e.g. sensitive \leq 0.25 mg/L and resistant >1 mg/L), pcV 1/1, cefotaxime 0.12/0.12, ciprofloxacin 0.03/0.06, chloramphenicol 2/8 and rifampicin 1/1.

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Per Olcén

Mycobacterium tuberculosis

In 2007 a total number of 497 new cases of TB were diagnosed in Sweden i.e. about the same number as in 2006. However, the number of culture confirmed cases declined from 395 (79%) in 2006 to 365 (73%). *Mycobacterium tuberculosis* was identified in 360 cases, *Mycobacterium africanum* in one patient and *Mycobacterium bovis* in four patients. During 2007 the proportions of patients diagnosed with isoniazid resistant TB and MDR-TB (resistance against at least isoniazid and rifampicin) were the highest recorded since the present surveillance system started in 1991.

Resistance to at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) was reported in 49 patients (27 males and 22 females) which corresponds to 13.6% of the 361 patients with culture confirmed *Mycobacterium tuberculosis* or *africanum*. Four patients with *Mycobacterium bovis* isolates were not included as these strains are naturally resistant to pyrazinamid.

Resistant TB was reported in 6.3% of the Swedish born TB patients (5/77), 21% of Somalian patients (18/84) and in 13% of those born abroad (26/200). Three of the six Swedish born TB patients with resistant TB were children or young adults born in Sweden to foreign parents, one of them had MDR-TB.

Resistance to isoniazid was reported in 12.7% of the patients, followed by rifampicin in 4.2%, pyrazinamid in 3.0% and ethambutol in 1.9%, Table 4.1.13. MDR-TB was diagnosed in 4.2% (15/361) of all culture confirmed TB patients, 1.3% of those born in Sweden, 7% of those born in Somalia and 4% of those born abroad.

Six patients with resistant TB (three of them with MDR-TB) had a previous history of TB after 1949, which corresponds to 35% (17.6%) of the total 17 patients with a culture confirmed relapse or reinfection in 2007. One of these patients with initial resistance to isoniazid, rifampicin and amikacin developed resistance against ofloxacin during treatment i.e. was diagnosed with acquired XDR-TB.

By genetic typing with RFLP (restriction fragment length polymorphism) of all resistant strains of *Mycobacterium tuberculosis* 15 of the 49 patients with a resistant strain were identified to belong to 13 different clusters with two or more patients in each cluster. One patient with MDR-TB was infected with three different strains of *Mycobacterium tuberculosis*.

Genetic typing with RFLP indicate ongoing spread of resistant strains especially in the Stockholm area. Most cases

occur in the foreign born population from Africa. However, transmission have also been identified to the Swedish born population, especially in second generation immigrants. In addition, latent tuberculosis infection has been diagnosed in an unknown number of contacts of patients with isoniazid resistant tuberculosis as well as in a few contacts to patients with MDR-TB.

The proportion of patients with *Mycobacterium tuberculosis* resistant to isoniazid has gradually increased from an annual average of 5% in 1991-1998 to 9% in 2000-2006 and further to 12.7% in 2007. The proportion of MDR-TB increased in parallel from 1.1% to 1.3% and further to 4.2% in 2007. The observed high proportions of isoniazid resistance and also MDR-TB in Somalia TB patients demands greater awareness and action!

Table 4.1.13. Drug resistant tuberculosis in Sweden. Resistance among initial isolates of *Mycobacterium tuberculosis* of *africanum* to at least one of the four drugs: isoniazid, rifampicin, ethambutol or pyrazinamic.

Year of diagnosis	2000	2001	2002	2003	2004	2005	2006	2007
Culture confirmed <i>M. tuberculosis</i> or <i>M. africanum</i> (N=)	366 No. %	354 No. %	346 No. %	345 No. %	368 No. %	448 No. %	395 No. %	361 No. %
Any resistance Total (%)	45 12.3	38 10.7	36 10.4	32 9.28	43 11.7	52 11.6	43 10.9	49 13.6
Isoniazid	37 10.1	31 8.8	34 9.8	26 7.5	35 9.5	46 10.3	38 9.6	46 12.7
Rifampicin	5 1.4	6 1.7	4 1.2	10 2.9	6 1.6	5 1.1	6 1.5	15 4.2
Ethambutol	2 0.5	3 0.8	1 0.3	5 1.4	3 0.8	3 0.7	1 0.3	7 1.9
Pyrazinamid	11 3.0	6 1.7	4 1.2	7 2.0	12 3.3	6 1.3	6 1.5	11 3.0
Isoniazid + rifampicin (MDR)	5 1.4	4 1.1	4 1.2	8 2.3	5 1.4	4 0.9	3 0.8	15 4.2

Sven Hoffner, Victoria Romanus

4.2. Antifungal resistance

IN SWEDEN, infections caused by fungal pathogens are not notifiable according to the Communicable Disease Act. The Swedish Institute for Infectious Disease Control (SMI) maintains a programme for the periodic surveillance of invasive *Candida* infections. This programme includes surveillance of resistance to the antifungals most frequently used for systemic prophylaxis and treatment. Twenty-eight clinical microbiological laboratories (covering more than 98% of the population) participate in the programme by referring blood isolates and related clinical and microbiological data.

Candida species and other yeasts

Susceptibility testing of yeast isolates is routinely performed according to standardized methodology using the Etest on RPMI agar medium and the EUCAST broth microdilution method. The current MIC breakpoints within the SIR-system for antifungal drugs as determined by SRGA and recommended by the Nordic reference group for methods in medical mycology (NRMM) are 1/1 (sensitive ≤ 1 mg/L and resistant > 1 mg/L) for amphotericin B, 4/16 for flucytosine, 2/4 for fluconazole and 0.125/0.5 for itraconazole. Breakpoints for caspofungin and voriconazole have not yet been determined. Based on the national wildtype distributions, isolates with caspofungin MIC > 2 or voriconazole MIC > 1 are provisionally interpreted as having reduced susceptibility.

During 2007 typing and antifungal susceptibility testing analysis were completed for bloodstream isolates referred to SMI from all microbiologically confirmed episodes of candidemia in Sweden during one year (estimated coverage $> 98\%$), from September 2005 to August 2006. The annual incidence

of candidemia was 4.4 cases per 100.000 inhabitants. *Candida albicans* was isolated from the bloodstream in 244 cases (60.7%) out of 402 total candidemia episodes. Decreased susceptibility to fluconazole or itraconazole was detected in 3/244 (1.2%) of the *C. albicans* isolates, Table 4.2.1. None of the *C. albicans* isolates displayed reduced susceptibility to voriconazole or to the fungicidal drugs amphotericin B and caspofungin.

Candida non-albicans was isolated in 154/402 (38.3%) of the candidemia episodes and in 99 of these cases (64.3%) the isolates were resistant or showed some degree of decreased antifungal susceptibility to the antifungals listed above, underscoring the importance of rapid discrimination *albicans*/non-*albicans* and full species determination of isolates from normally sterile sites. *C. glabrata* and *C. krusei*, species that are inherently less susceptible or resistant to fluconazole and other azole compounds, were isolated in eighty-one (20.1%) and five (1.2%) episodes, respectively, Table 4.2.1. Rates of resistance or decreased susceptibility in *C. glabrata* isolates were 0% for caspofungin, 1.2% for amphotericin B, 98.8% for fluconazole, 100% for itraconazole, and 17.3% for voriconazole. In contrast to first-generation triazoles and imidazoles, voriconazole has a broader spectrum of activity against *Candida* species, including strains resistant to fluconazole. However, increasing recognition of clinical *C. glabrata* isolates with decreased susceptibility to voriconazole and the relatively frequent occurrence of cross-resistance between triazoles argue against the use of voriconazole in the treatment of infections caused by *Candida* spp. with innate decreased sensitivity to azole compounds. *Candida* species, as well as *Cryptococcus neoformans*, are generally susceptible to amphotericin B and

Table 4.2.1. Rates of antifungal resistance or reduced susceptibility among invasive yeast isolates. Data from SMI surveys 2003 and 2005-2006.

Species	No. of isolates (%)		% isolates with reduced susceptibility or resistant									
			Amphotericin B		Caspofungin		Fluconazole		Itraconazole		Voriconazole	
	2003	2006	2003	2006	2003	2006	2003	2006	2003	2006	2003	2006
<i>C. albicans</i>	143 (65.3)	244 (60.7)	0	0	-	0	1.4	0.8	2.8	0.4	0.7	0
<i>C. glabrata</i>	49 (22.4)	81 (20.1)	2.0	1.2	-	0	93.9	98.8	91.8	100	2.0	17.3
<i>C. parapsilosis</i>	14 (6.4)	36 (9.0)	7.1	2.8	-	0	14.3	5.6	7.1	2.8	0	0
<i>C. dubliniensis</i>	2 (0.9)	15 (3.7)	0	0	-	0	0	6.7	0	6.7	0	0
<i>C. krusei</i>	3 (1.4)	5 (1.2)	66.7	100	-	0	100	100	100	100	0	0
Other yeast	8 (3.7) ²	18 (4.5) ³	15.3	21.1	-	5.6	23.1	27.8	69.2	38.9	0	0
<i>C. non-albicans</i>	76 (34.7)	154 (38.3)	5.3	6.5	-	0.60	67.1	60.4	72.4	59.7	1.3	9.1

¹ As determined using current MIC breakpoints within the SIR-system for antifungal drugs recommended by SRGA and the Nordic reference group for methods in medical mycology, NRMM. Breakpoints are 1/1 (sensitive ≤ 1 mg/L and resistant > 1 mg/L) for amphotericin B, 2/4 for fluconazole and 0.125/0.5 for itraconazole. Isolates with caspofungin MIC > 2 or voriconazole MIC > 1 are provisionally interpreted as having reduced susceptibility.

² Including *C. lusitanae* (4 isolates), *C. tropicalis* (3 isolates) and *S. cerevisiae* (1 isolate).

³ Including *C. tropicalis* (8 isolates), *C. lusitanae* (8 isolates), *C. pelliculosa* (1 isolate), *G. capitatum* (1 isolate). Additional bloodstream isolates not assayed for antifungal susceptibility: *M. pachydermatis* (1 isolate), *T. mucilaginosa* (1 isolate) and *S. cerevisiae* (1 isolate).

development of resistance under therapy is extremely rare. Some non-albicans species such as *C. lusitaniae* can display reduced susceptibility. Ten isolates (6.5%) from non-albicans candidemia episodes, including all 5 cases caused by *C. krusei*, had MIC >1 mg/L for amphotericin B. Echinocandin antifungals are fungicidal against most *Candida* spp. but somewhat less potent against certain species, such as *C. parapsilosis* and *C. guilliermondii*. Caspofungin, the first echinocandin introduced in Sweden, is being used increasingly in the treatment of invasive candidiasis. In the present survey, a single isolate (*C. tropicalis*) consistently showed reduced susceptibility to

caspofungin with a MIC =8 mg/L. Overall, *Candida non-albicans* comprised 98% of clinical isolates displaying any level of resistance to antifungal drugs.

In conclusion, every fourth candidemia episode in Sweden (102/402, 25.4%) was caused by *Candida* spp. strains with decreased susceptibility or resistance, as assessed in vitro, to one or more of the compounds fluconazole, itraconazole, voriconazole, amphotericin B and caspofungin, representing >99% of the total antifungal used for systemic treatment in hospital care.

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Appendix 2: Abbreviations

ABU	Asymptomatic bacteriuria
AST	Antibiotic susceptibility testing
ATC	The Anatomical Therapeutic Chemical Classification system
CDCDC	County Department for Communicable Disease Control
DDD	Defined daily dose
DST	Drug susceptibility testing
EARSS	European Antimicrobial Resistance Surveillance System
ESBL	Extended spectrum beta-lactamase
ICU	Intensive care unit
MDR	Multidrug resistance
MIC	Minimal inhibitory concentration
MLSB	Macrolide – Lincosamide – Streptogramin B-type of resistance
MRB	Multiresistant bacteria
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
PFGE	Pulsed field gel electrophoresis
PNSP	Penicillin non-susceptible pneumococci, MIC \geq 0,5 mg/L
PVL	Panton-Valentine leukocidin
RSQC	Resistance Surveillance and Quality Control Programme
RTI	Respiratory tract infection
SRGA-M	The Swedish Reference Group of Antibiotics- subcommittee on Methodology
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
TB	Tuberculosis
UTI	Urinary tract infection
VRE	Vancomycin resistant enterococci

Appendix 3: Demographics and denominator data

Table App 2.1. Population of Sweden 2000-2007 (the numbers represents the population on December 31st the previous year)

	2000	2001	2002	2003	2004	2005	2006	2007
Population	8 861 265	8 882 831	8 909 322	8 940 744	8 975 669	9 011 391	9 047 803	9 113 297

Table App 2.2. Population by county and age group December 31st.

	0-6 years	7-19 years	20-59 years	60-79 years	80 years -	All ages
Stockholm	169 757	297 247	1 062 259	303 717	85 124	1 918 104
Uppsala	25 289	53 165	172 559	54 147	14 765	319 925
Södermanland	19 528	43 748	130 560	54 203	15 060	263 099
Östergötland	30 803	68 639	216 215	78 747	23 562	417 966
Jönköping	25 615	57 392	166 254	62 570	19 708	331 539
Kronoberg	13 251	29 403	91 210	34 950	10 821	179 635
Kalmar	15 379	38 121	114 744	50 415	15 117	233 776
Gotland	3 719	9 703	28 844	11 821	3 210	57 297
Blekinge	10 884	23 537	75 307	32 564	9 144	151 436
Skåne	91 103	187 158	620 885	220 498	64 856	1 184 500
Halland	23 110	49 717	144 352	55 776	15 904	288 859
Västra Götaland	117 490	249 499	812 050	276 588	82 697	1 538 324
Värmland	18 281	43 991	136 601	57 746	16 870	273 489
Örebro	19 969	45 037	139 812	53 861	16 351	275 030
Västmanland	17 991	40 824	126 015	49 879	13 780	248 489
Dalarna	18 649	45 765	135 859	58 070	17 368	275 711
Gävleborg	18 858	44 009	137 004	58 947	16 835	275 653
Västernorrland	17 286	38 322	120 525	53 044	14 801	243 978
Jämtland	8 827	20 325	63 555	26 062	8 251	127 020
Västerbotten	18 282	41 965	135 036	48 988	13 310	257 581
Norrbottn	17 172	40 509	128 048	53 440	12 717	251 886
Total country	701 243	1 468 076	4 757 694	1 696 033	490 251	9 113 297

Table App 2.3. Number of admissions and patient-days in medical care 1997-2006

	Admissions	Patient-days
1997	1 536 549	10 308 954
1998	1 534 480	10 166 192
1999	1 494 701	9 635 382
2000	1 446 371	8 908 831
2001	1 439 003	8 873 260
2002	1 421 954	8 670 503
2003	1 421 614	8 545 109
2004	1 433 826	8 424 038
2005	1 452 515	8 385 110
2006	1 472 407	8 582 835

Table App 2.4. Denominator data from the microbiological laboratories. NP = test not performed.
Screen MRB = Test performed specifically to identify bacteria with troublesome resistance such as MRSA, VRE, ESBL.

Laboratory	Number of analyses 2006						Number of positive cultures 2006				
	Blood (pair of bottles)	Cerebro-spinal fluid (CSF)	Nasopharynx	Throat	General culture	Screen MRB	Faeces SSYC	<i>Staphylococcus aureus</i>	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pyogenes</i>	<i>E coli</i>
Borås	12506	192	3581	4772	9968	1026	7252	3994	898	816	7097
Eskilstuna	7811	153	5863	4667	9318	1796	4145	3621	775	753	7412
Falun	12598	176	2651	1803	5428	2363	4681	3916	463	510	7032
Gävle	9186	155	1800	1130	7150	1050	3620	3289	289	339	6271
Göteborg	28963	1383	3691	4411	16614	30443	13574	11340	847	1085	16302
Halmstad	9547	119	2959	3144	8867	9074	6278	3181	498	686	6729
KS/HS Stockholm	59498	2862	37752	14534	75063	144090	24603	23345	5384	3426	39099
Jönköping	12680	202	3220	4300	12360	6690	7150	4690	610	1070	9470
Kalmar	8730	253	4022	3151	7171	10211	4643	4399	691	854	7975
Karlskrona	4385	66	1371	3152	5395	1760	3608	1950	245	406	4191
Karlstad	13195	237	1247	2785	12040	6779	4517	5734	287	652	7207
Kristianstad	7084	77	6186	5356	10561	8467	5328	3731	1049	1002	8077
Linköping	15169	940	5664	4148	18704	22036	8526	6549	839	792	9786
Lund	22795	1119	11950	8735	22402	13976	13826	13013	4005	3158	26257
Malmö	20405	350	5919	7627	19197	48923	12187	7883	1868	1526	15466
AlerisMedilab, Stockholm	NP	NP	10890	5190	8402	13529	8267	3826	1492	996	8422
St:Göran (Capio), Stockholm	6024	171	5813	4109	14748	28176	6414	4902	834	898	9796
Skövde	11053	155	2524	3070	10898	13275	5094	4025	503	505	9071
Sunderby, Luleå	7552	154	2728	3760	8161	1419	3736	2997	335	813	7985
Sundsvall	9055	133	2525	2006	5350	9124	4510	3471	610	546	7716
Uddevalla	16970	175	1825	4000	8500	4160	5300	4359	453	811	9374
Umeå	10442	622	2906	2843	10475	4920	4779	3506	520	652	8901
Uppsala	16952	654	4451	2772	13986	33174	5303	1356	749	445	7724
Visby	2961	22	2464	737	2824	0	1222	1217	349	176	2133
Västerås	9122	192	2674	2398	9086	4881	4768	3649	470	524	6993
Växjö	4624	717	2139	2125	5808	1819	3549	2514	366	439	4724
Örebro	13024	278	7779	1768	13151	3807	4996	5445	1169	589	7549
Östersund	5844	501	1977	1508	7129	6377	2095	2373	417	566	6103

Appendix 4: Surveillance of antibiotic consumption

Statistical sources and units of measurement

The ATC classification system and defined daily doses (DDD)

Since 1988, the Anatomical Therapeutic Chemical (ATC) classification system recommended by the WHO is used in Sweden for national drug statistics. To facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of the National Corporation of Swedish Pharmacies (Apoteket AB) are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway. The sales of drugs are presented as number of DDDs per 1000 inhabitants and day (DDD/1000/day), which give an estimate of the proportion of the population daily exposed to a particular drug. This figure is a rough estimate and should be interpreted with caution.

Swedish national statistics on drug utilisation

Since 1975, the National Corporation of Swedish Pharmacies regularly produces sales statistics on drugs, for the country as a whole and for individual counties. The sales are registered as number of DDDs, cash value and number of packages. Community care data include information on the sales of drugs dispensed on prescription by all Swedish pharmacies by the prescription survey, running since 1974. The statistical material was until 1995 built of samples of dispensed prescriptions. From 1996 all prescriptions dispensed by pharmacies are included. From 1999, ApoDos (individually packed doses of drugs often dispensed to elderly) is also included in the survey. Recorded data are trade name, quantity, patient fee, total cost,

sex and year of birth of the patient. Data can be expressed as DDD/1000/day or number of prescriptions/1000 inhabitants. Hospital care data include drugs delivered by all hospital pharmacies to the hospital departments. Data on drugs delivered to homes for the elderly are to some extent included in hospital care. The system also produces sales statistics for each hospital department and on national and county sales to hospitals. The sales are expressed as cash value, number of packages and number of defined daily doses.

The Swedish Prescribed Drug Register

Since July 2005, the Swedish National Board of Health and Welfare supplies an individually based register on all drugs prescribed and dispensed in community care. Among others this data gives information on the number of individuals treated with at least one course of antibiotics during a specific period of time, i.e. number of users per 1000 inhabitants and year (users/1000/year). It is also possible to follow the number of purchases per person.

Number of admissions and patient-days

Each of the 21 county councils in Sweden deliver once a year data to the National Patient Register kept by The National Board on Health and Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Data do not include patients in municipal care.

Since data for 2007 is not available until August denominator data from 2006 and sales data from 2007 are used in some figures in this report. The number of admissions and patient-days in Swedish medical care 1997-2006 is shown in Appendix 2, Table App 2.3. The Swedish Association of Local Authorities and Regions keeps a searchable database at the web, <http://www.skl.se/artikel.asp?A=3768&C=1801>.

Appendix 5: Antibiotic Susceptibility testing

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

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

mase detection in *Haemophilus influenzae*, *Neisseria gonorrhoeae* and others).

Phenotypic methods (disk diffusion or MIC) are performed on a basic medium for AST, ISA (IsoSensitest Agar) from Oxoid Ltd, UK. For this medium and the corresponding antibiotic paper disks, interpretive criteria for SIR-categorization are provided by the SRGA-M. The criteria are regularly updated and available through the web-site www.srga.org. Internal and external quality assurance and quality control of susceptibility testing is performed by each laboratory. Internal quality control includes using international QC strains regularly (every day, once a week) and analysing data in relation to national guidelines. Validation of susceptibility testing can also be done by histogram analysis of consecutive clinical isolates (see www.srga.org) External quality control is often done by participation in UK-NEQAS and/or other international programs, whereas quality assurance is one of the features of the Swedish ”100-strains or RSQC programme”.

Appendix 6: National surveillance of antibiotic resistance

Surveillance regulated in the Communicable Disease Act

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

Notification shall be done within 24 hours, in duplicate to the County Medical Officer for Communicable Disease Control and to the Swedish Institute for Infectious Disease Control (SMI). 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 different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with Penicillin G MIC ≥ 0.5 mg/L (PNSP) have been notifiable since 1996. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE) have been notifiable since 2000.

Since 1st February 2007 ESBL-producing *Enterobacteriaceae* were made notifiable by laboratory notifications.

All notifications are entered into the national computerized surveillance system, SMI-Net2. At the SMI, the clinical and laboratory notification for each case are merged and checked for errors. If data are missing, contact persons in the counties are asked to supplement the information. As an important complement to the notifications, the MRSA, VRA and PNSP strains are sent to SMI for epidemiological typing using pulsed-field gel electrophoresis (PFGE). Spa-typing replaced PFGE as the primary typing method for MRSA from 1st July 2006.

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 SMI. All resistant isolates are sent to SMI for epidemiological typing, using restriction fragment length polymorphism (RFLP).

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

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

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

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

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100-200 consecutive clinical isolates of a number of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. On one or several occasions *Escherichia coli*, *Enterococcus faecalis*/*E. faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* and *Enterobacter* have been part of these surveys. The number of antibiotics tested for each pathogen has varied between 4 and 6.

From 2002 a web-based software (ResNet) will receive the data from the laboratories and, following approval of registered data by one of two web administrators, instantly displayed it in the form of resistance frequencies on the geographical areas on maps of Sweden. Behind each resistance frequency the distribution of zone diameters or MICs together with the relevant demographic data are directly accessible. The software will accept both MIC and zone distributions of well-characterized data sets. The graphs presenting the data are designed to include all necessary information in order for the graphs to be used on their own (in presentations etc). A recently introduced feature enables each laboratory to view all its own data and also to link this information to a website of its own local health care system. The Resnet software also has the feature of displaying aggregated, quantitative data of invasive isolates which form the Swedish part of the EARSS network (see below).

EARSS

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

Participation in EARSS was initially intended for member states of the European Union, also including Norway and Iceland, but in year 2000 six countries in eastern Europe were included, and by 2003 28 countries provide susceptibility data regularly. Information about EARSS, as well as a database yielding information about the susceptibility results for each

country, year and pathogen, is available through a web-site (www.earss.rivm.nl).

Data collected by EARSS should be routinely generated quantitative data (MICs or inhibition zones), but the data presented are only in the format of susceptibility categories (SIR). External quality assurance exercises have so far been carried out by EARSS in cooperation with UK-NEQAS and the EARSS Advisory Board once every year. 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 form a solid base for surveillance of resistance and is constantly extended and improved.

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

Surveillance of invasive isolates additional to EARSS data

Data on invasive isolates on all positive blood cultures were obtained from eleven laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is 3.7 millions, thus representing more than 40% of the Swedish population. From these laboratories data for the pathogens specified by the EARSS network are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In the SWEDRES 2007 report data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* are presented.

Sentinel surveillance

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

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

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