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A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine

Smi
SMITTSKYDDSINSTITUTET
Swedish Institute for Communicable Disease Control

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Swedish Institute for Communicable Disease Control, SMI, is a government agency with the mission to monitor the epidemiology of communicable diseases among Swedish citizens and promote control and prevention of these diseases.

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Content

1. Preface

WELCOME to the tenth Swedish report combining results from the monitoring of antimicrobial resistance and antimicrobial usage in human and veterinary medicine: SWEDRES and SVARM, respectively. These two reports are printed jointly to increase the awareness of trends in incidence of antimicrobial use and antimicrobial resistance in the respective areas. The problem of antibiotic resistance is multisectorial but needs to be viewed upon as one where the dissemination of bacteria between humans, animals and the environment must be considered when preventive measures are discussed.

In humans ESBL-producing *Enterobacteriaceae* are by far the largest growing resistance problem with approximately 5000 new cases reported during 2010. Earlier studies have shown that hospital associated transmission and international travel are two modes of spread of these bacteria. Even more worrisome than the 5000 new ESBL-cases are the 18 identified cases of carbapenemase producing *Enterobacteriaceae* in Sweden, as of to date, caused by the genes NDM-1, KPC or VIM. This new threat of multiresistant and in many cases totally resistant bacteria have in countries like Greece and India caused large hospital and community associated outbreaks. The cases seen in Sweden are all but one directly linked to import from such high incidence countries. One can only hope that the carbapenemases will not have the same rapid dissemination as has been seen for CTX-M-type ESBLs. However the spread reported from the Indian subcontinent indicate that the NDM-1 gene and it´s genetic proximities indeed possess all the traits needed for successful spread.

MRSA continues to slowly increase. Among domestically acquired MRSA-cases the community acquired dominate, a trend noted since 2007. It is therefore apparent that healthcare related infection control measures will not be sufficient to stop the increase of MRSA. In order to stop community associated dissemination we need, in addition to the prudent use of antibiotics, to implement new and challenging strategies.

During 2010 the decrease in antibiotic sales continued albeit at a lower rate than was seen in 2009. Unexplained large differences between counties exist which need to be addressed. Furthermore the report shows that the differences are especially prominent among children and for the group of antibiotics prescribed for respiratory tract infections.

To encourage, strengthen and intensify the work with prudent antibiotic use, the Swedish government has in 2010 allocated stimulatory conditional funding to be received by county councils decreasing outpatient antibiotic use by increasing adherence to treatment guidelines.

As antibiotic resistant strains become more common the more important it will be to avoid selection of these strains by unnecessary antibiotic use. What we can and must do is to continue the important strive to keep the selective antibiotic pressure as low as possible and to promote infection control. Through comprehensive and well communicated resistance data, the national and local guidelines can continuously be updated to support the prescribing physicians in their important treatment decisions. The work with prudent antibiotic use must go on. If these measures will buy us valuable time only the future will tell. Our hope is that the information in SWEDRES and SVARM is translated into further investigations and actions in order to preserve our increasingly threatened, but still favourable, situation.

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2.1. Summary

Use of antibiotics

A marked decrease (5.5%) in sales of antibiotics occurred in 2009 as compared with 2008. This decrease continued in 2010, but was smaller (1.2%). In outpatient care a small decrease was seen in all age groups, except the group 5-14 years. The small decrease encompasses almost all antibiotic groups except the following substances which increased: nitrofurantoin (15.6%), pivmecillinam (0.7%) and trimethoprim with sulphonamides (3.5%). About half of the Swedish counties showed a small decrease, the rest did not. However, there are still large differences between counties. Prescriptions per 1000 inhabitants and year ranged from 419 in the county of Stockholm to 311 in the county of Jämtland.

Beta-lactamase sensitive penicillins together with tetracyclines are the most commonly used antibiotics in outpatient care. Penicillin V is by far the most commonly used antibiotic. The total sale of penicillin decreased with 0.2% in 2010. Doxycycline is the most frequently used tetracycline, a substance mainly used to treat respiratory tract infections. The total sale of tetracyclines decreased with 0.3% in 2010 as compared with 2009.

Treatment of lower urinary tract infections in women has been the subject of information campaigns for several years. The use of the two first line recommended substances, pivmecillinam and nitrofurantoin, has increased every year and represented 71% of the total sale of antibiotics commonly used to treat urinary tract infections in this group in 2010.

In recent years, antibiotic use in hospital care has shown a shift from an extensive use of cephalosporins to an increased use of narrow spectrum penicillins. This trend continued also in 2010. However, there are still large differences between counties in this respect. The regional differences are also evident regarding the use of newer classes of broad spectrum antibiotics such as carbapenems and piperacillin with tazobactam.

Use of antifungals

Despite the introduction of several new compounds to treat antifungal infections systemically in the past few years, the total amount of antifungals in hospital care has not increased dramatically. From 2006 until 2009 there was only a 10.8% increase from 50.2 to 55.6 DDD/10^6 inhabitants and day. However during 2010 there was an increase of 12% to 62.0 DDD/10^6 inhabitants and day. Looking at the broad-spectrum antimycotics the increase was even higher; 30%. A large part of this increase is due to a 60% increase in the use of amphotericin B. The reason for this trend is unknown. There has not been issued any new national guidelines that might explain the increased use. Most of the rise comes from two counties, Stockholm and Uppsala, both with large tertiary hospitals. Since the overall figures are low the increase might be due to the treatment of only a few patients, but as there have been reports from other countries of increased azole resistance in *Aspergillus fumigatus* we cannot currently rule out that the increase in amphotericin B is due to clinical failure with azole-therapy. It is of great importance to closely monitor the future development.

Antibiotic resistance

Swedish surveillance of antibiotic resistance is based on testing of clinical samples and samples taken according to local screening programmes. Some bacterial species with specific mechanisms of antibiotic resistance are notifiable under the Communicable Disease Act and therefore form an important part of the surveillance programme. The vast amount of data on antibiotic resistance in Sweden is however based on susceptibility testing of clinical samples in local clinical microbiology laboratories. Data is voluntarily reported to one or both of the systems RSQC, in which all laboratories take part, and EARS-Net, in which three fourths of the laboratories contribute with data on defined invasive isolates. For some bacterial species resistance data are produced and presented by laboratories with referral functions and/or with special interest in certain species (e.g. *Neisseria* spp.). In the present report the most recent data on antibiotic resistance is presented and analysed together with data from previous years.

Staphylococcus aureus: A total of 1580 cases of MRSA were notified in 2010, a 7% increase compared with 2009. Of all the reported cases 43% (n=687) had acquired MRSA in Sweden, and 38% (n=595) had acquired the infection abroad. The average country incidence was 16.8 cases/100 000 inhabitants, an increase compared with 15.8 in 2009. Community-acquired infections dominated among domestic cases (63%) but were less frequent among imported cases (36%). Hospital-acquired infections were comparatively more common in imported cases (40%) than among domestic cases (9%), indicating continued good compliance to basal hygiene principles in Sweden. Invasive isolates of MRSA were as few in 2010 (n=15) as in previous years 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 EARS-Net.

Epidemiological typing of all MRSA isolates by *spa*-typing showed that the five most commonly encountered *spa*-types in 2010 were t008, t002, t044, t019 and t223, comprising almost one third of all isolates. The prevalence of MRSA with PVL toxin was 36% and was present in all or a majority of isolates with the common *spa*-types t008, t044, and t019. Multiresistance among MRSA, defined as resistance to beta-lactam antibiotics and to three or more other categories of antibiotics, was rare. Most cases could be correlated to seven different *spa*-types, and the acquisition of such strains was often from abroad and associated with healthcare.

Staphylococcus aureus from skin and soft tissue infections (RSQC programme) were susceptible to tested antibiotics in > 95% of cases except for fusidic acid where the level of resistance was 6.2%.

Streptococcus pneumoniae: In 2010 there were 409 notifications of PNSP (*Streptococcus pneumoniae* with MIC of penicillin ≥ 0.5 mg/L) in Sweden, a decrease by 8% compared with 2009. PNSP have decreased in annual incidence rate per 100 000 inhabitants from 10 in 1997 to 4.3 in 2010. 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 23 cases the PNSP isolates came from an invasive site, i.e. blood. Multiresistance (resistance to penicillin and at least two more antibiotics) was common among PNSP. The most commonly found serotypes among all PNSP were, in decreasing order, types 19F, NT, 9V, 14, 19A, and 35B.

For five antibiotics tested on *Streptococcus pneumoniae* in the yearly RSQC programme 2010 the rates of resistance were either slowly increasing or stable compared with 2009, and low rates of quinolone-resistant isolates have been seen since 2005.

Rates of non-susceptibility to penicillins in *Streptococcus pneumoniae* (=PNSP) were lower among invasive isolates reported to EARS-Net than in the nasopharyngeal isolates from the RSQC programme, and in 2010 also resistance to macrolide antibiotics was lower.

Enterococcus faecalis and *Enterococcus faecium*: From 2000 to 2006 only low numbers (18-35 per year) of VRE-cases were reported in Sweden. In 2007 there was an increase to 53 notified cases, followed by 618 in 2008, 402 in 2009, and 214 in 2010. These high notification rates were attributable to the spread of a *vanB*-carrying *Enterococcus faecium* strain in three counties, Stockholm, Halland and Västmanland. Intensive infection control efforts, implementation of screening programmes, contact tracing, and also other measures undertaken have all contributed to the reduction in numbers of new cases in 2010. In 2010, however, yet another new strain of *Enterococcus faecium* with *vanB* was spread within the healthcare setting in the county of Västernorrland.

There were only two new cases of invasive vancomycin resistant *Enterococcus faecium* in 2010. One of them was reported from an "EARS-Net"-laboratory, resulting in 0.3% as reported to EARS-Net. Among invasive isolates of both *Enterococcus faecalis* and *Enterococcus faecium* high-level resistance to aminoglycosides (HLAR) was common with 15% and 22%, respectively.

Streptococcus pyogenes: Data on 118 invasive isolates of *S. pyogenes*, out of 12.296 consecutive blood isolates from 11 laboratories, was obtained in 2010. Two of these 118 isolates (1.7%) were resistant to erythromycin and clindamycin, indicating MLS_B type of resistance. Fifteen isolates (12.7%) were resistant to tetracycline. Both results were similar to what has been found during the last three years.

Streptococcus agalactiae: Data on 166 invasive isolates of *S. agalactiae*, out of 12.296 consecutive blood isolates from 11 laboratories, was obtained in 2010. Thirteen isolates (7.8%) were resistant to erythromycin and nine of those also to clindamycin, a figure similar to those from the previous years.

Haemophilus influenzae: Data on beta-lactamase-producing isolates of *H. influenzae* was obtained in the RSQC programme in 2010 and was compared with the same kind of data (recalculated to include only the beta-lactamase positive isolates) from the previous two years. Beta-lactamase production was found in approximately 15% of isolates, whereas close to 20% of isolates were resistant to trimethoprim-sulfamethoxazole. *Haemophilus influenzae* was rarely found among blood isolates, only 75 cases out of 12.296 consecutive blood isolates from 11 laboratories. Seven of those were ampicillin-resistant (9.3%) but only five produced beta-lactamase. Seventeen isolates (13.3%) were resistant to trimethoprim-sulfamethoxazole.

Enterobacteriaceae producing extended spectrum beta-lactamases (ESBL) were made notifiable by the laboratories from February 2007. A total of 4983 cases were notified during 2010, an increase with 33% compared with 2009. Reports came from all 21 counties of Sweden, corresponding to a national incidence of 53 cases per 100 000 inhabitants. The most commonly reported species was *Escherichia coli* with 81% of all cases, followed by *Klebsiella pneumoniae* with 8%. Most ESBLs were found in urine samples (65%). 204 new cases of invasive infections with ESBL-producing bacteria were noted in 2010. Isolates with ESBLs, most often of CTX-M-type, were often multiresistant, i.e. resistant to several other antibiotics, seriously limiting the options for treatment.

Escherichia coli, mainly derived from urinary tract infections, has been included in the national surveillance program (RSQC) since 1996, and invasive isolates have been reported to EARS-Net since 2001. Ampicillin resistance, caused by production of plasmid-mediated beta-lactamase (most often of TEM-type) was increasingly found in both blood isolates and urine isolates (34% and 28%) in 2009. The level of resistance to third generation cephalosporins among blood isolates has increased to 3.2%, and in the majority of these cases the resistance was caused by plasmid-mediated ESBLs of CTX-M type. This resistance was often accompanied by resistance to many other antibiotics, e.g. aminoglycosides and fluoroquinolones. Resistance to fluoroquinolones has increased every year and was almost the same in urine as in blood isolates (13 vs. 14%) in 2010.

Klebsiella pneumoniae has also been monitored in the RSQC programme and through EARS-Net since 2005. The rates of resistance to tested antibiotics were comparable between the two surveillance programmes. Approximately 2% of *Klebsiella pneumoniae* were cephalosporin resistant and ESBL-producing, thus no increase from 2009. Since 2007, when the first isolate of *K. pneumoniae* with a carbapenemase (KPC-2) was detected in Sweden, more attention has been put to this new threat of multiresistant bacteria. In total, we have encountered 18 cases of $ESBL_{CARBA}$ in Sweden to date, 9 isolates with KPC enzymes, 6 cases with VIM enzymes, and 3 cases with the newly detected carbapenemase NDM-1. All the cases were healthcare related.

Pseudomonas aeruginosa has been monitored in the RSQC programme and through EARS-Net since 2005. The levels of resistance to tested antibiotics were comparable between the two surveillance programmes, including carbapenems with approximately 7% resistance. Fluoroquinolone resistance was stable at approximately 10%.

The national surveillance program for *Clostridium difficile*, initiated by SMI in 2009, continued in 2010. The program included both a voluntary laboratory reporting system of all new cases and determination of resistance and epidemiological typing of collected isolates. On all *C. difficile* isolates collected during weeks 11 and 39, susceptibility tests and PCR ribotyping was performed. Resistance rates to moxifloxacin, erythromycin and clindamycin were 16-20%, and most of the resistant isolates were associated with PCR ribotypes 012, 017, 046 and 231/SE37. There was an overall positive correlation between the rate of moxifloxacin use and the proportion of moxifloxacin resistant isolates.

Helicobacter pylori derived from gastric biopsies have been monitored for clarithromycin resistance at the University Hospital MAS, Skåne. Following a steady increase since 1994, a peak of 16% in 2006, a temporary decline during three years, the level of resistance was back to 16% in 2010.

In *Campylobacter* spp. high levels of resistance were seen for fluoroquinolones (30-60%), tetracyclines (20-35%) and low but variable for erythromycin (1-7 %) during the last ten years.

In *Salmonella* spp. and *Shigella* spp. the levels of fluoroquinolone resistance are high although these species are not monitored as regularly as others. In 2010 there was special focus on a serovar of *Salmonella* referred to as monophasic Typhimurium, which in 2010 was the third most common serotype in Sweden. Susceptibility testing at SMI showed that almost 70% of the isolates were resistant to ampicillin, streptomycin, sulphonamides and tetracycline (ASSuT). A few isolates were also resistant to fluoroquinolones and to cefotaxime (ESBL-producing).

Neisseria gonorrhoeae: Gonorrhoea is a notifiable disease, and in 2010 842 cases of the disease were reported. Isolates from 618 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, representing more than 70% of the notified cases. In 2010 29% of these isolates were beta-lactamase producing and ampicillin resistant, and 56% were resistant to ciprofloxacin.

Mycobacterium tuberculosis: The total number of new cases of TB diagnosed in Sweden 2010 was 683, a 6% increase compared with 2009. The numbers of cases diagnosed with isoniazid resistant TB in 2010 were 57/523 (11%) and with MDR-TB 18/523 (3.4%).

Genetic typing with RFLP (restriction fragment length polymorphism) was completed on 56 of the 70 resistant strains of *Mycobacterium tuberculosis* or *M. africanum* and is ongoing on the remaining 16. Thirty-one of the 56 examined isolates belong to 24 different clusters with two or more patients in each cluster.

2.2. Sammanfattning

Antibiotikaförbrukning

Efter flera år av små förändringar i antibiotikaförbrukning skedde en kraftig minskning (5,5 procent) under 2009 jämfört med 2008. Under 2010 sågs en mer blygsam minskning på 1,2 procent. I öppenvård sågs en liten minskning i alla åldersgrupper, förutom i åldersgruppen 5-14 år. Minskningen ses i hälften av alla län och omfattar de flesta preparaten, förutom följande substanser där förbrukningen ökade: nitrofurantoin (15,6 procent), pivmecillinam (0,7 procent) och sulfonamider och trimetoprim-kombinationer (3,5 procent). En stor skillnad i antibiotikaförbrukning ses fortfarande inom landet. Förskrivningen varierar från 419 recept/1000 invånare och år i Stockholm till 311 recept/1000 invånare och år i Jämtland.

Tetracykliner tillsammans med betalaktamaskänsliga penicilliner, är de antibiotika som oftast förskrivs på recept och bland de sistnämnda förskrivs penicillin V mest. Under 2010 minskade användningen av penicillin V med 0,2 procent jämfört med 2009. Doxycyklin är den tetracyklin som förskrivs mest och en substans som används mestadels mot luftvägsinfektioner. Under 2010 ökade förskrivningen tetracykliner med 0,3 procent jämfört med 2009.

I flera år har behandling av nedre urinvägsinfektion hos kvinnor varit i fokus för informationsinsatser. De två rekommenderade förstahandspreparaten, pivmecillinam och nitrofurantoin, har successivt ökat och utgjorde under 2010 nästan 71 procent av förskrivningen av antibiotika som ofta används vid urinvägsinfektioner.

De senaste åren har antibiotikaförskrivningen i slutenvården skiftat från en hög användning av cefalosporiner till en ökad användning av smalspektrumpenicilliner. Denna trend fortsatte även under 2010. Stora regionala skillnader sågs dock mellan länen. De regionala skillnaderna ses också tydligt vad gäller användande av nya klasser av bredspektrumantibiotika, såsom karbapenemer och piperacillin med tazobaktam.

Förbrukning av antimykotika

Under de senaste fem åren har utbudet av läkemedel för systemiskt bruk mot svampinfektioner ökat, och man har sett en ökad användning av främst echinocandinerna, men också av de nyare azolerna. Från 2006 till 2009 ökade förbrukningen av antimykotika inom slutenvård med 10,8 procent från 50,2 till 55.6 DDD/10^6 invånare och dag. Under 2010 ökade användningen ytterligare med 12 procent till 62,0 DDD/10^6 invånare och dag. Det finns en tendens att smalspektrumantimykotika, dvs. flukonazol minskar och att bredspektrumantimykotika tar motsvarande marknadsandel. Denna utveckling ses än tydligare om man även inkluderar receptförsäljning av vorikonazol och posakonazol i sjukhusdata, eftersom dessa läkemedel så gott som alltid förskrivs av sjukhusspecialister.

Den totala mängden av antimykotika på sjukhus är fortsatt låg med 62 DDD/10^6 invånare och dag. Det är dock viktigt att noga följa både resistens och konsumtionsdata på både lokal och nationell nivå för att tidigt upptäcka förändringar i resistensmönster eller i artfördelning.

Antibiotikaresistens

Antibiotikaresistens hos vissa bakteriearter anmäls enligt smittskyddslagen (MRSA, VRE, PNSP och ESBL), men den frivilliga rapporteringen av resistensdata från de svenska kliniskt mikrobiologiska laboratorierna utgör basen för resistensövervakningen. Alla laboratorier deltar sålunda i den årliga insamlingen av data till ResNet (RSQC), och tre fjärdedelar av laboratorierna bidrar med data avseende invasiva isolat av sju bakteriearter som definierats av EARS-Net. För vissa mikroorganismer sammanställs data av laboratorier med referensfunktion och/eller specialkunskap (till exempel *Neisseria*-arter). I denna rapport presenteras aktuella svenska resistensdata från 2010 och kommenteras i förhållande till föregående års data.

Staphylococcus aureus: Totalt 1580 fall av MRSA anmäldes 2010, en ökning med 7 procent från 2009. Nästan hälften av fallen hade blivit smittade i Sverige (687 fall), och en dryg tredjedel (595 fall) hade blivit smittade utomlands. Incidensen av MRSA-fall 2010 var något högre än 2009 (16,8 jämfört med 15,8 fall per 100 000 invånare). Antalet invasiva isolat av MRSA var lika få 2010 (n=15) som föregående år, vilket medför att Sverige fortfarande är ett av få länder i Europa som ännu ej nått nivån 1 procent av alla invasiva *Staphylococcus aureus* (EARS-Net-data).

Epidemiologisk typning av MRSA görs med *spa*-typning. De fem vanligast förekommande *spa*-typerna var t008, t002, t044, t019 och t223. Förekomsten av MRSA med PVL-toxin var 36 procent och förekom hos alla eller hos majoriteten av de vanliga *spa*-typerna t008, t044 och t019, men dessutom hos ett flertal andra *spa*-typer. Multiresistens var sällsynt och förekom framför allt hos kända ”utländska” stammar som de med *spa*-typ t037. *Staphylococcus aureus* i sårinfektioner (data från ResNet) var i mer än 95 procent av fallen känsliga för antibiotika med undantag för fusidinsyra (6,2 procent resistens).

Streptococcus pneumoniae: Under 2010 noterades 409 fall med nedsatt känslighet för penicillin (isolat med MIC av penicillin ≥ 0,5 mg/L definierade som PNSP). Incidensen PNSP (antal fall per 100 000 invånare) har minskat från 10,1 1997 till 4,3 2010. Majoriteten av PNSP-fallen var i åldersgruppen 0-4 år. I 23 fall påvisades PNSP från blod. Multiresistens (resistens mot penicillin och minst två andra antibiotika) var vanlig hos PNSP. De vanligast förekommande serotyperna var 19F, NT, 9V, 14, 19A och 35B. Enligt data rapporterade i ResNet sågs en långsam ökning av resistens mot testade antibiotika. Frekvensen PNSP var lägre hos invasiva isolat (EARS-Net) än hos nasofarynx-isolat, och detta gällde även frekvensen makrolidresistens.

Enterococcus faecalis och *Enterococcus faecium*: Antalet anmälda fall av vankomycin-resistenta enterokocker (VRE) var lågt 2000-2006 (18-35 per år), men ökade från 2007 till 53 fall, och därefter rapporterades 618 fall 2008, 402 fall 2009 och 214 fall 2010. Det stora antalet fall kunde tillskrivas förekomst och spridning av en *vanB*-innehållande *Enterococcus faecium* som återfanns i Stockholms län, i Halland och i Västmanland. Genom epidemiologisk typning med PFGE framkom att den aktuella VRE-stammen sannolikt inte hade förekommit i Sverige före 2007. Under 2010 har antalet fall med den stammen minskat, däremot har Västernorrland drabbats av omfattande spridning inom sjukvården av en annan VRE-stam. Endast två invasiva VRE-isolat förekom 2010 varav ett rapporterades från ett "EARS-Net"-laboratorium (= 0,3 procent resistens). Höggradig aminoglykosidresistens (HLAR) var vanligare hos båda enterokock-arterna, 15 respektive 22 procent av isolaten.

Streptococcus pyogenes: Data för 118 invasiva isolat, erhållna från elva laboratorier under 2010, visade att 1,7 procent var resistenta mot makrolider och 12,7 procent var tetracyklinresistenta.

Streptococcus agalactiae: Data för 166 invasiva isolat, erhållna från elva laboratorier under 2010, visade att 7,8 procent var makrolid-resistenta, vilket var samma nivå som 2007-2009.

Haemophilus influenzae: Data från övervakningen i ResNet 2008-2010 visade att cirka 15 procent av isolaten var betalaktamas-producerande (och alltså ampicillin-resistenta) medan nästan 20 procent var trimetoprim-sulfa-resistenta. Utredning pågår om hur stor andel som utgörs av cefalosporinresistenta (ej betalaktamasproducerande) isolat. Tidigare år har nivåerna legat på 2-4 procent.

Haemophilus influenzae var ett sällsynt fynd bland invasiva isolat, och endast 75 fall fanns registrerade från de elva laboratorierna 2010. Fem av dessa var betalaktamas-producerande och sjutton var resistenta mot trimetoprim-sulfa.

Enterobacteriaceae som producerar betalaktamaser med utvidgat spektrum, så kallade ESBL, blev anmälningspliktiga i februari 2007. Totalt 4983 fall rapporterades under 2010. Samtliga landsting rapporterade, och den genomsnittliga incidensen i Sverige var 53 fall per 100 000 invånare. De flesta isolaten återfanns i urinprover och vanligast var *Escherichia coli* (81 procent) följt av *Klebsiella pneumoniae* (8 procent). ESBL av CTX-M-typ dominerade, men fynd av plasmidmedierat AmpC (=$ESBL_M$) utgjorde cirka 5 procent i en punktprevalensstudie från 2009. Multiresistens var ett vanligt fynd hos isolaten med ESBL.

Escherichia coli huvudsakligen från urinvägsinfektioner, har övervakats enligt det nationella programmet (ResNet) sedan 1996, och blodisolat har inkluderats i EARS-Net sedan 2001. Ampicillinresistens, oftast orsakad av plasmidmedierad betalaktamasproduktion av TEM-typ, återfanns i ungefär samma frekvens hos blodisolat och urinisolat 2010 (34 procent och 28 procent). Blodisolat med resistens mot 3:e generationens cefalosporiner hade ökat till 3,2 procent, och hos majoriteten av dessa var resistensen orsakad av plasmidmedierade ESBL av CTX-M-typ. De cefalosporin-resistenta stammarna var ofta resistenta mot andra antibiotikagrupper som aminoglykosider och kinoloner. Kinolonresistens utgjorde 2010 13-14 procent.

Andra Gram-negativa bakterier som övervakats nationellt och/eller internationellt är *Klebsiella pneumoniae* och *Pseudomonas aeruginosa*. Resistensnivåerna hos respektive patogen var desamma oberoende av övervakningsprogram och typ av prov. Hos *K. pneumoniae* var cirka 2 procent resistenta mot cefalosporiner genom ESBL-produktion. Under 2007 identifierades det första isolatet med karbapenemas av KPC-typ i Sverige, och sedan dess har ytterligare åtta fall med KPC-enzym identifierats, 6 fall med VIM-enzym (ett metallo-betalaktamas), samt tre fall med det nyligen upptäckta enzymet NDM (New Dehli Metallo-betalactamase). I samtliga dessa fall fanns en bakomliggande historia med sjukvård utomlands. Hos *P. aeruginosa* var karbapenemresistensen lika vanlig hos invasiva isolat som hos övriga isolat (cirka 7 procent), och kinolonresistensen var stabil på cirka 10 procent.

Salmonella av en serotyp som kallas monofasisk Typhimurium är nu den tredje vanligaste i Sverige. En studie visade att cirka 70 procent av isolaten hade resistensprofilen ASSuT (resistens mot ampicillin, streptomycin, sulfonamid och tetracyklin). Ett litet antal isolat var även resistenta mot cefotaxim (ESBL-producerande) och kinoloner.

Helicobacter pylori har övervakats regelbundet vid ett laboratorium. Resistens mot klaritromycin har ökat stadigt under flera år, minskat något från 2007 men var åter uppe på nivån 16 procent 2010.

Hos *Campylobacter* spp. har kinolonresistensen under de senaste tio åren varit 30-60 procent, tetracyklinresistensen 20-35 procent, och erytromycinresistensen 1-7 procent.

Neisseria gonorrhoeae: Gonorré är en anmälningspliktig sjukdom och 2010 rapporterades 842 kliniska fall. Isolat från 618 av dessa har undersökts vid det svenska referenslaboratoriet i Örebro eller vid laboratoriet för klinisk bakteriologi, Karolinska Universitetssjukhuset Huddinge, Stockholm. 2010 var 29 procent av isolaten beta-laktamasproducerande och därmed ampicillinresistenta, och 56 procent var resistenta mot ciprofloxacin.

Mycobacterium tuberculosis: Antalet anmälda nya fall av tuberkulos var 683 under 2010, en ökning med 6 procent från 2009. *M. tuberculosis* med resistens mot isoniazid var 11 procent (57/523) och resistens mot minst två antibiotika (MDR-TB) rapporterades hos 3,4 procent. Epidemiologisk typning med RFLP av de resistenta TB-isolaten visade att de tillhörde 24 olika kluster med två eller fler patienter i varje.

3. Use of antimicrobials

3.1. Use of antibiotics

Interpretation of data

Antibacterials for systemic use are indexed as J01 in the Anatomical Therapeutic Chemical classification system. Unfortunately, the J01 group also includes the antiseptic substance methenamine. This is not an antibiotic and has no influence on antibiotic resistance. Throughout this report, methenamine is consequently excluded wherever antibiotics are referred to or presented.

Comparison of use of antibiotics between counties and to elderly people over time is complicated by the fact that there are differences in how medicines are distributed to residents in nursing homes. In Sweden, most people living in nursing homes still get their medicines by prescription, and data on this consumption is included in outpatient care data. However, there are also nursing homes where medicines are bought by the institution and then dispensed to the residents. Such consumption is included in hospital care data. Since routines differ between counties and over time, the appraisal of antibiotic use to elderly people is not entirely reliable.

Wherever sales of antibiotics to a certain group of people is displayed (children 0-6 years, women 18-79 years, inhabitants in a county), the denominator is of course the number of individuals in the same group.

In this report the term outpatient care includes primary care, open specialist surgeries and parts of nursing homes. Hospital care includes sales to hospitals and parts of nursing homes. Since national data on sales of antibiotics to hospitals in Sweden is aggregated with sales to some nursing homes, this is not suitable for evaluation of antibiotic use in hospital care. Therefore, data on sales exclusively to hospitals has been provided by pharmacists in local Strama groups in all counties.

Treatment recommendations are adopted locally by County Drug and Therapeutics Committees, and therefore the prescribed daily doses for certain indications can vary between counties. This should be kept in mind, as it affects the result of the statistics.

Total sales of antibiotics

The total use of antibiotics in Sweden was 1.2% lower in 2010 than in 2009, Table 3.1.1.

Outpatient care

Sales of antibiotics in outpatient care decreased with 0.4% in 2010 measured as prescriptions/1000 inhabitants. This should be seen in the light of the notable change between 2008 and 2009, when the sales of antibiotics decreased with 7.4%, the greatest decrease since 1995 calculated as a percentage. As discussed in SWEDRES 2009 the great reduction in 2009 may have several explanations. One major reason suggested is the increased awareness of infection control issues and hand hygiene evoked by the outbreak of the pandemic influenza 2009. A great proportion of the Swedish population was also vaccinated against the pandemic influenza in 2009 which may have affected the infection-pattern during the year.

The small decrease in 2010 encompasses all age groups except the age group 5-14 years. In this age group the prescription increased with 1%. The greatest decrease in 2010 was among the elderly aged 65-99 years.

The amount of antibiotics prescribed to the youngest children, 0-4 years, has changed significantly over the last two decades. After a 40% decrease between 1992 and 1997 antibiotic sales have continued to decline, albeit at a slower pace. Between 2008 and 2009 there was a sudden drop of antibiotic use in this age group. In 2010 the antibiotic sales decreased marginally, Figure 3.1.1.

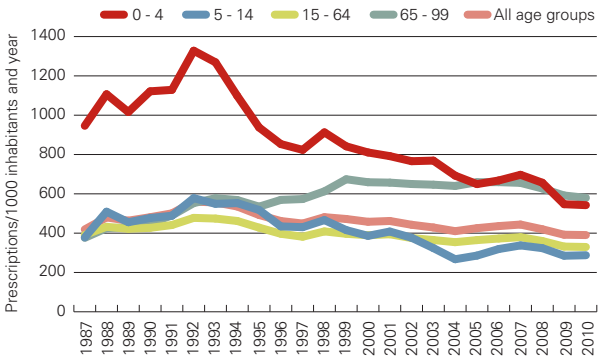

FIGURE 3.1.1. The sales of antibacterial drugs for systemic use in outpatient care 1987-2010, different age groups, prescriptions/1000 inhabitants and year.

TABLE 3.1.1. Sales of antibiotics in outpatient and hospital care 2000-2009, DDD/1000 inhabitants and day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Out-patient care	13.7	13.8	13.3	13.0	12.8	13.1	13.5	13.9	13.7	12.9	12.8
Percent change from previous year		1%	-4%	-2%	-2%	3%	3%	3%	-1%	-6%	-1%
Hospital care	1.30	1.30	1.30	1.30	1.40	1.43	1.50	1.55	1.52	1.49	1.52
Percent change from previous year		0%	0%	0%	8%	2%	5%	4%	-2%	-2%	2%
Total sales	15.2	15.3	14.8	14.6	14.3	14.8	15.2	15.6	15.4	14.5	14.3
Percent change from previous year		0%	-3%	-1%	-2%	3%	3%	3%	-2%	-6%	-1%

Seasonal variations in antibiotic use have been less pronounced during the last years and this trend continued in 2010. This could be regarded as an indicator of good quality in prescribing, Figure 3.1.2.

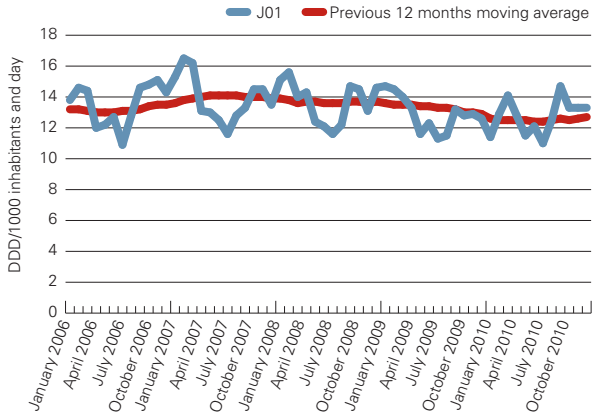

FIGURE 3.1.2. Antibiotics in outpatient care 2006-2010, DDD/ 1000 inhabitants and day. Monthly sales and 12 months moving average.

The decrease in sales encompasses almost all antibiotic groups except nitrofurantoin, pivmecillinam and trimethoprim with sulphonamides. Trimethoprim (J01EA) and cephalosporins (J01DB-DE) are the two antibiotic groups with the greatest decrease expressed in percentage. Beta-lactamase sensitive penicillins (J01CE) together with tetracyclines (J01AA) are the most commonly used antibiotics in outpatient care 2010, Figure 3.1.3.

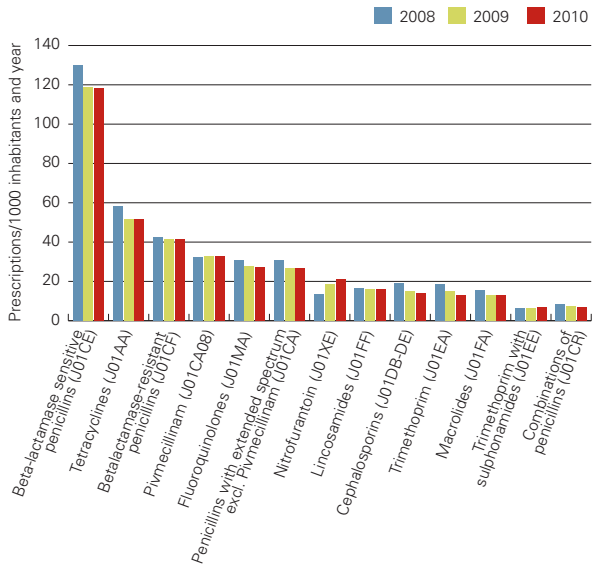

FIGURE 3.1.3. Antibiotics in outpatient care 2008-2010, prescriptions/ 1000 inhabitants and year.

Tetracyclines

Doxycycline is the most frequently used tetracycline measured as prescriptions/1000 inhabitants and year and stands for 76% of the sales of tetracyclines in 2010. This substance is mainly used to treat respiratory tract infections, which can be one explanation to the great seasonal variation. In Figure 3.1.4 the seasonal variation in use of tetracyclines during the period 2006-2010 is shown. There has been a decline during the last years which may be an effect of the new treatment guidelines for lower respiratory tract infections launched by Strama and The Swedish Medicinal Products Agency in April 2008. Campaigns and information activities have been arranged since then in order to communicate the main messages. Treatment with tetracyclines may give rise to photo sensibility which can be a contributing reason why the use decreases during summer. Antibiotic use for the indication acute bronchitis has also been debated in media and may have influenced the antibiotic prescribing pattern.

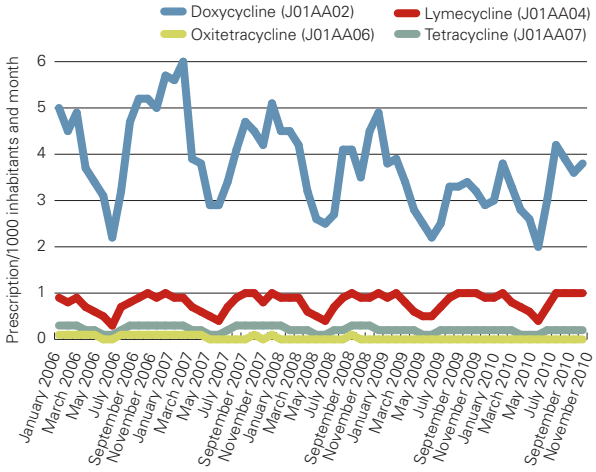

FIGURE 3.1.4. Seasonal variation of tetracyclines, outpatient care 2006-2010, prescriptions /1000 inhabitants and month.

Antibiotics commonly used to treat respiratory tract infections, urinary tract infections and skin and soft tissue infections

Antibiotics commonly used to treat respiratory tract infections are the most commonly prescribed antibiotics. Among these substances we also find the greatest difference within the country in terms of number of prescriptions/1000 inhabitants and year: from 245 in Stockholm County to 145 in Jämtland County, Figure 3.1.5.

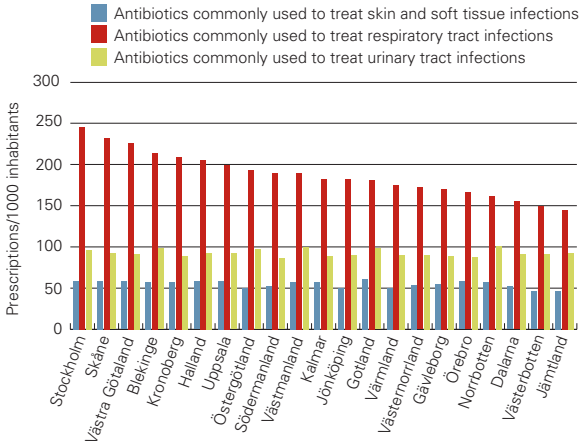

FIGURE 3.1.5. Antibiotics commonly used to treat respiratory tract infections (J01AA02, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infection (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01) and skin and soft tissue infections (J01FF01 and J01CF05) in outpatient care 2010, per county. Both sexes, all ages, prescriptions/1000 inhabitants, age and gender standardized.

The same difference in prescribing pattern seen in Figure 3.1.5 is also seen between municipalities, both in big city counties and in sparsely-populated counties, Figures 3.1.6 and 3.1.7. Within Stockholm County the number of prescriptions of antibiotics commonly used to treat respiratory tract infections, varies from 290 in Upplands Väsby to 195 in Salem measured as prescriptions/1000 inhabitants and year, Figure 3.1.6. In Jämtland county prescriptions of antibiotics commonly used to treat respiratory tract infections vary from 211 in Ragunda to 130 in Krokom measured as prescriptions/1000 inhabitants and year, Figure 3.1.7.

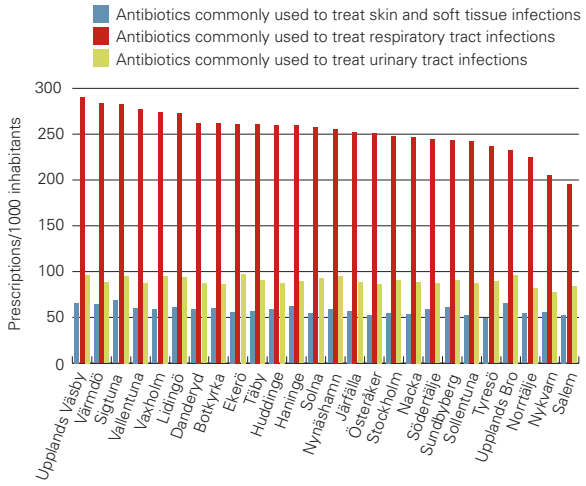

FIGURE 3.1.6. Antibiotics commonly used to treat respiratory tract infections (J01AA02, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infection (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01) and skin and soft tissue infections (J01FF01 and J01CF05) in outpatient care 2010, per municipalities in Stockholm County. Both sexes, all ages, prescriptions/1000 inhabitants, age and gender standardized.

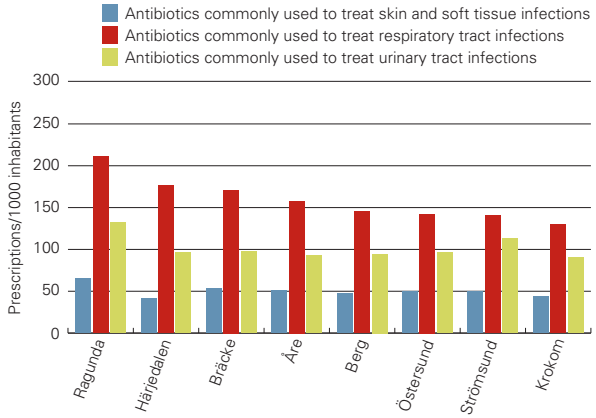

FIGURE 3.1.7. Antibiotics commonly used to treat respiratory tract infections (J01AA02, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infection (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01) and skin and soft tissue infections (J01FF01 and J01CF05) in outpatient care 2010, per municipalities in Jämtland County. Both sexes, all ages, prescriptions/1000 inhabitants, age and gender standardized.

Recommendations for the treatment of lower urinary tract infections in women over 18 years, launched by Strama and the Swedish Medical Products agency in 2007, recommend pivmecillinam and nitrofurantoin over trimethoprim, and prescribers are also encouraged to minimize the use of fluoroquinolones. The two first-line drugs account for 71% of antibiotics commonly prescribed to treat this condition in 2010. Pivmecillinam is more commonly used than nitrofurantoin and stands for 61% of all prescriptions of the first-line drugs. In all, the number of nitrofurantoin prescriptions to women increased by 16.5% in 2010, while the number of DDDs decreased by 0.4%. This can partly be explained by the introduction of a new package adapted to the recommendations mentioned above. Taken together, after three years with a decreasing sale of antibiotics commonly used to treat urinary tract infections in women, the sales increased with 1% in 2010, Figure 3.1.8.

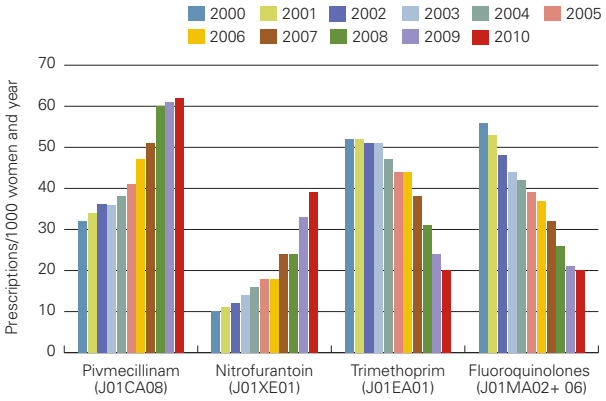

FIGURE 3.1.8. Antibiotics commonly used to treat lower urinary tract infections in women, 2000-2010, prescriptions/ 1000 women and year.

County data

The share of people treated with at least one course of any kind of antibiotic (users per 1000 inhabitants) was the same in 2010 as in 2009, Table 3.1.2. However, the share of people treated with antibiotics varies within Sweden, from 251 users per 1000 inhabitants in Stockholm County to 185 users per 1000 inhabitants in Västerbotten County, Figure 3.1.9. A comparison of data, standardized for age and gender, reveals the highest use in big cities and their surroundings.

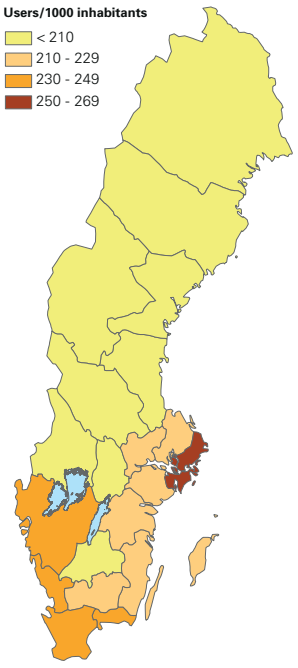

FIGURE 3.1.9. Share of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2010 (users/1000 inhabitants).

Antibiotic consumption in children

The share of children treated with at least one course of any kind of antibiotic ranges from 341 users per 1000 children in Skåne County to 181 users per 1000 children in Jämtland County, Figure 3.1.10. Taken together in Sweden the share of children treated with antibiotics was 301 users per 1000 children, which is 10% higher than in 2009, Table 3.1.2.

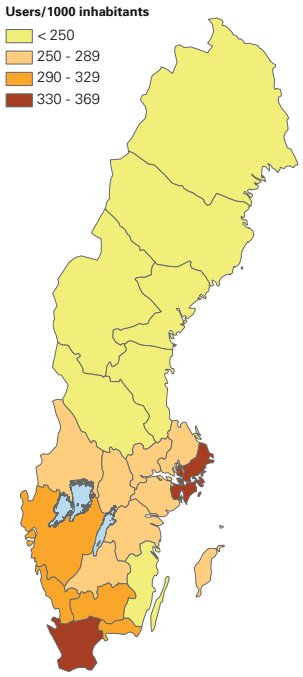

FIGURE 3.1.10. Share of children aged 0 to 6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2010 (users/1000 children).

As seen in Table 3.1.2 the number of prescriptions of antibiotics to children aged 0-6 years decreased with 1.4% in 2010. Most of this is due to a decrease (20%) in the number of prescriptions of amoxicillin-clavulanate (J01CR).

Different kinds of penicillins are still the most commonly prescribed antibiotics in outpatient care. Amoxicillin-clavulanate, amoxicillin and penicillin V represent 76% of all antibiotics to children aged 0-6 years in outpatient care 2010.

Consumption of antibiotics among children varies greatly within the country. The number of prescriptions ranges from 608 prescriptions per 1000 children in Skåne County to 260 prescriptions per 1000 children in Jämtland County, Figure 3.1.11. Jämtland is also the county with the greatest decrease (11%) in antibiotic prescribing in 2010.

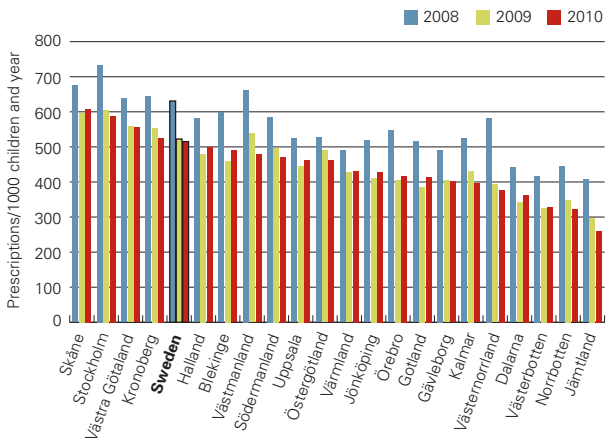

FIGURE 3.1.11. Antibiotics in outpatient care to children aged 0-6 years, per county and Sweden 2008-2010. Prescriptions/1000 children and year.

Antibiotic use in children has been in focus of Strama's information activities the last years. The great reduction in sales of antibiotics between 2008 and 2009 may have several explanations; one being improved hand hygiene. This topic was the subject of many campaigns arranged by several actors during 2009. One study has shown that using alcohol-based hand disinfection in preschools reduces absence from Swedish day care centers with 12%.

Antibiotics in dentistry

Dentists account for approximately 7% of all antibiotic prescribing in outpatient care. The prescribing of antibiotics by dentists decreased with 6% in 2010. Penicillin V is the most commonly prescribed antibiotic and represents 75% of all antibiotics prescribed by dentists.

The Swedish Government sets national target for antibiotic use in outpatient care

In December 2010 the Swedish Government announced a 500 million SEK commitment to improving patient safety in health care during 2011 out of which 100 million SEK will be allocated to the work with improving rational use of antibiotics.

The 100 million SEK to be shared between the 21 county councils in Sweden are conditional. To receive funding they are firstly required to form a Strama group with a clear mandate and funding to coordinate local activities. Secondly, prescribers must increase the adherence to treatment recommendations aiming at no more than 250 prescriptions per 1000 inhabitants and year by 2014, a national target set by the Swedish government. The funding will be allocated yearly in relation to potential step-wise fulfillment of the mentioned criteria. The goal must not be applied to a single care unit but at the county level. Swedish Institute of Communicable Disease Control is appointed to evaluate the county councils work in this matter.

In 2010 the average use of antibiotics in outpatient care in Sweden was 390 prescriptions per 1000 inhabitants. To reach the national target the antibiotic use in Sweden must decrease with 36% in four years. There are great regional differences within the country. Prescriptions per 1000 inhabitants range from 419 in Stockholm County to 311 in Jämtland County. The use of antibiotics decreased in eleven of the Swedish counties in 2010, Figure 3.1.12.

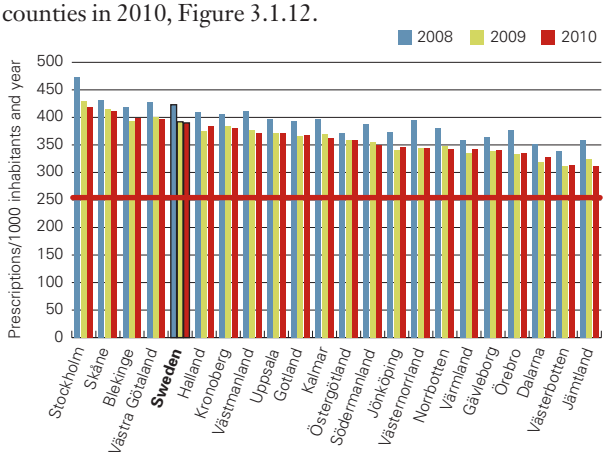

FIGURE 3.1.12. Sales of antibiotics in outpatient care 2008-2010, prescriptions/1000 inhabitants and year. The red line indicates Strama´s goal at 250 prescriptions/1000 inhabitants and year in outpaitent care.

TABLE 3.1.2. Antibiotics in outpatient care, classes of antibiotics and age groups. DDD/1000 inhabitants and day, prescriptions/1000 inhabitants and year and users/1000 inhabitants and year, 2006-2010.

Age group (years)	DDD/1000 and day					Prescriptions/1000 and year					Users/1000 and year				
	2006	2007	2008	2009	2010	2006	2007	2008	2009	2010	2006	2007	2008	2009	2010
Tetracyclines (J01AA)															
0-6	0.00	0.00	0.00	0.00	0.00	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
7-19	3.12	3.23	3.26	3.31	3.40	32.7	33.9	32.0	31.6	32.5	20.4	21.5	19.6	19.2	20.1
20-59	3.56	3.68	3.50	3.26	3.32	66.3	68.3	61.3	53.7	53.9	51.8	53.4	47.6	41.7	42.0
60-79	4.11	4.29	4.05	3.64	3.60	96.3	99.3	90.1	78.3	77.0	71.6	74.4	67.2	60.1	59.4
80 -	2.89	2.93	2.78	2.43	2.32	76.4	77.8	71.7	62.2	58.6	60.1	62.0	56.8	49.7	46.8
All age groups	3.33	3.44	3.29	3.08	3.11	62.6	64.3	58.3	51.7	51.6	46.9	48.6	43.7	38.8	38.9
Penicillins with extended spectrum (J01CA) excl. pivmecillinam															
0-6	1.59	1.74	1.71	1.52	1.62	86.9	95.2	90.8	72.7	73.3	64.6	70.5	66.7	56.3	57.6
7-19	0.45	0.46	0.43	0.39	0.43	14.1	14.5	13.6	11.8	12.4	12.4	12.8	11.5	10.1	10.6
20-59	0.72	0.77	0.75	0.66	0.66	18.4	19.4	18.7	16.5	16.4	16.0	16.7	15.1	14.2	14.1
60-79	1.59	1.62	1.63	1.52	1.49	41.4	42.0	41.3	37.9	.36.9	32.3	32.9	29.9	30.1	29.4
80 -	1.81	1.79	1.83	1.76	1.74	47.3	46.8	46.5	44.0	42.1	38.3	38.0	32.9	35.4	34.1
All age groups	0.98	1.02	1.02	0.93	0.94	29.6	31.0	30.5	26.9	26.9	23.4	24.5	22.5	21.1	21.2
Pivmecillinam (J01CA08)															
0-6	0.01	0.01	0.01	0.01	0.02	0.5	0.5	0.7	0.8	1.1	0.4	0.5	0.6	0.7	1.0
7-19	0.17	0.19	0.24	0.24	0.24	10.7	12.4	15.5	16.1	15.9	9.6	11.0	13.6	13.9	13.9
20-59	0.34	0.36	0.43	0.44	0.44	20.1	22.2	26.9	27.3	27.7	17.3	19.0	22.5	23.0	23.4
60-79	0.71	0.74	0.84	0.85	0.84	40.3	43.0	49.5	49.9	49.8	31.2	33.1	37.3	38.1	38.1
80 -	1.84	1.84	1.95	1.92	1.90	106.7	109.3	116.6	115.8	115.0	80.1	81.8	85.1	83.9	83.1
All age groups	0.43	0.46	0.53	0.54	0.53	25.5	27.6	32.2	32.8	33.0	20.7	22.3	25.6	25.9	26.2
Beta-lactamase sensitive penicillins (J01CE)															
0-6	3.59	4.03	4.14	3.56	3.71	327.3	350.7	343.7	287.4	290.6	230.8	244.3	235.9	210.7	219.3
7-19	3.38	3.68	3.64	3.46	3.52	135.0	142.5	135.0	123.3	124.6	113.1	117.3	110.2	100.7	102.3
20-59	4.28	4.49	4.42	4.00	3.96	107.9	112.8	108.4	97.7	96.6	91.6	95.2	90.9	83.8	83.4
60-79	4.46	4.57	4.51	4.25	4.09	107.0	109.0	106.1	99.6	95.8	88.0	89.4	87.0	84.5	82.1
80 -	3.33	3.36	3.51	3.38	3.29	84.2	84.2	85.7	81.7	79.5	71.4	72.2	72.4	69.9	68.2
All age groups	4.09	4.30	4.26	3.96	3.93	128.1	134.3	130.0	118.6	118.4	104.0	108.1	103.7	96.0	96.3
Beta-lactamase resistant penicillins (J01CF)															
0-6	0.35	0.33	0.33	0.31	0.30	35.6	32.9	32.8	30.8	29.4	26.7	25.2	24.8	24.2	23.5
7-19	0.70	0.69	0.80	0.79	0.77	33.6	31.9	31.9	31.2	31.0	27.5	26.4	26.2	25.4	25.6
20-59	0.95	0.96	1.14	1.13	1.11	33.5	33.3	33.2	32.6	31.9	26.9	26.7	26.5	26.2	26.9
60-79	2.04	2.04	2.37	2.29	2.26	57.4	56.3	56.9	55.0	54.7	37.7	37.1	37.3	37.1	37.5
80 -	4.44	4.40	5.01	4.92	4.92	123.4	122.6	122.1	119.4	113.2	68.7	67.9	66.8	65.5	66.8
All age groups	1.25	1.25	1.46	1.45	1.43	42.9	42.2	42.3	41.7	41.3	31.2	30.7	30.5	30.1	30.6
Combinations of penicillins (J01CR)															
0-6	0.73	0.75	0.67	0.52	0.39	51.2	52.7	46.4	33.7	25.3	34.4	35.2	30.9	24.0	18.0
7-19	0.22	0.21	0.20	0.18	0.17	6.4	6.4	6.0	5.4	4.9	5.1	4.9	4.5	4.1	3.8
20-59	0.18	0.20	0.21	0.20	0.21	3.9	4.4	4.6	4.3	4.5	3.5	3.9	4.0	3.7	3.9
60-79	0.22	0.25	0.27	0.28	0.30	4.5	5.1	5.5	5.7	6.1	3.6	4.1	4.4	4.06	4.8
80 -	0.15	0.17	0.20	0.22	0.24	3.0	3.4	4.1	4.3	4.8	2.3	2.7	3.2	3.4	3.9
All age groups	0.24	0.26	0.26	0.24	0.24	8.0	8.5	8.3	7.2	6.7	6.1	6.5	6.3	5.5	5.2
Cephalosporins (J01DB-DE)															
0-6	0.52	0.52	0.46	0.36	0.34	49.0	49.7	43.6	34.1	33.2	37.6	38.0	33.9	28.1	27.7
7-19	0.30	0.29	0.27	0.21	0.20	20.6	20.2	18.4	14.9	13.8	17.4	17.2	15.7	12.6	11.6
20-59	0.29	0.28	0.25	0.20	0.18	16.8	16.2	14.5	11.4	10.3	14.2	13.7	12.2	9.8	8.8
60-79	0.46	0.40	0.36	0.29	0.26	22.6	20.2	17.7	13.8	12.7	17.1	15.5	13.5	10.7	9.8
80 -	0.73	0.65	0.54	0.41	0.38	40.5	35.4	29.4	22.7	21.6	30.9	27.4	22.9	17.9	16.6
All age groups	0.37	0.35	0.31	0.25	0.23	22.5	21.5	19.0	15.2	14.1	17.9	17.2	15.3	12.3	11.4

Age group (years)	DDD/1000 and day					Prescriptions/1000 and year					Users/1000 and year				
	2006	2007	2008	2009	2010	2006	2007	2008	2009	2010	2006	2007	2008	2009	2010
Trimethoprim (J01EA)															
0-6	0.12	0.12	0.10	0.09	0.09	16.0	15.4	14.0	12.6	12.2	11.1	10.6	9.8	9.7	9.6
7-19	0.21	0.18	0.15	0.11	0.10	12.4	10.9	8.9	7.0	5.9	10.8	9.5	7.8	6.0	5.1
20-59	0.33	0.29	0.24	0.18	0.16	17.4	14.6	11.8	8.7	7.2	14.7	12.4	9.9	7.2	6.0
60-79	0.84	0.76	0.64	0.52	0.47	40.7	35.2	29.2	23.1	20.4	29.7	25.6	21.0	16.7	14.7
80 -	2.19	1.91	1.58	1.30	1.23	120.1	104.5	84.7	69.6	63.3	73.3	61.6	49.1	38.6	34.5
All age groups	0.49	0.43	0.39	0.29	0.26	26.3	22.8	18.8	14.9	13.1	19.8	16.9	13.8	10.7	9.3
Trimethoprim with sulphonamides (J01EE)															
0-6	0.16	0.16	0.14	0.13	0.12	18.1	18.8	16.7	14.8	13.7	13.2	13.5	12.0	10.7	10.1
7-19	0.10	0.10	0.11	0.11	0.10	4.0	4.1	4.2	4.3	4.0	2.7	2.6	2.7	2.6	2.4
20-59	0.13	0.14	0.14	0.15	0.16	2.9	3.0	3.1	3.3	3.4	1.9	1.9	2.0	2.1	2.2
60-79	0.36	0.39	0.44	0.47	0.48	8.8	9.2	10.1	10.4	10.8	5.8	6.1	6.8	7.1	7.4
80 -	0.36	0.39	0.43	0.43	0.46	11.7	12.2	13.1	12.5	13.1	8.8	9.1	9.9	9.7	10.1
All age groups	0.19	0.20	0.21	0.22	0.23	6.3	6.4	6.5	6.6	6.8	4.0	4.1	4.3	4.2	4.3
Macrolides (J01FA)															
0-6	0.80	0.85	0.68	0.51	0.53	37.3	38.1	29.9	22.4	23.1	29.6	30.4	23.3	18.1	18.8
7-19	0.76	0.74	0.54	0.31	0.33	22.1	21.7	15.4	12.7	13.8	17.9	17.2	11.8	9.7	10.7
20-59	0.54	0.55	0.49	0.28	0.28	16.3	16.5	14.3	12.1	11.9	13.0	13.2	11.3	9.6	9.6
60-79	0.50	0.50	0.47	0.32	0.30	14.5	14.6	13.0	11.3	10.7	11.0	11.0	9.6	8.4	8.0
80 -	0.34	0.32	0.30	0.23	0.21	9.3	8.7	8.4	7.4	6.9	7.2	6.8	6.4	5.5	5.2
All age groups	0.58	0.59	0.50	0.31	0.31	18.2	18.4	15.3	12.8	12.8	14.4	14.4	11.7	9.9	10.0
Lincosamides (J01FF)															
0-6	0.02	0.03	0.02	0.02	0.02	5.0	5.3	5.0	5.2	5.0	3.6	3.9	3.7	3.8	3.9
7-19	0.11	0.12	0.12	0.12	0.12	7.8	8.3	8.4	8.2	8.1	6.2	6.7	6.9	6.6	6.5
20-59	0.28	0.29	0.30	0.29	0.29	14.3	15.6	15.6	15.0	14.9	11.1	12.2	12.2	12.0	12.0
60-79	0.55	0.55	0.57	0.57	0.55	23.7	24.4	24.6	23.8	23.6	15.3	15.9	16.3	16.4	16.2
80 -	0.75	0.74	0.76	0.72	0.73	32.6	32.8	33.2	31.0	31.7	18.1	18.6	19.2	18.8	19.2
All age groups	0.31	0.32	0.33	0.32	0.32	15.4	16.3	16.4	15.9	15.9	10.9	11.7	11.9	11.7	11.7
Fluoroquinolones (J01MA)															
0-6	0.01	0.01	0.01	0.01	0.01	0.8	0.8	0.7	0.7	0.8	0.4	0.4	0.4	0.4	0.5
7-19	0.12	0.13	0.12	0.12	0.12	5.5	5.5	4.8	4.3	4.3	4.7	4.4	3.9	3.5	3.5
20-59	0.80	0.76	0.69	0.63	0.61	30.2	27.8	23.8	20.9	20.2	22.0	20.3	17.3	15.4	14.9
60-79	2.05	1.93	1.75	1.67	1.62	80.2	73.7	63.9	58.6	56.8	52.7	48.7	42.7	40.2	39.3
80 -	3.00	2.74	2.41	2.25	2.26	136.8	119.7	98.5	88.2	87.3	92.5	81.5	68.1	61.4	60.9
All age groups	0.98	0.93	0.84	0.80	0.78	39.0	35.7	30.6	27.8	27.1	27.0	24.9	21.5	19.6	19.2
Nitrofurantoin (J01XE)															
0-6	0.07	0.07	0.06	0.06	0.06	6.3	6.3	6.2	6.9	7.2	4.2	4.2	4.2	4.9	5.1
7-19	0.12	0.14	0.13	0.15	0.14	5.2	6.7	6.6	9.2	10.6	4.4	5.8	5.8	7.9	9.0
20-59	0.20	0.24	0.23	0.26	0.25	8.5	11.0	10.6	14.7	17.2	7.0	9.1	8.8	12.2	14.2
60-79	0.36	0.46	0.47	0.53	0.53	14.6	19.4	20.6	28.1	32.5	10.7	14.3	15.2	20.8	24.1
80 -	0.78	0.97	0.95	1.05	1.06	37.2	46.7	47.7	61.7	70.6	24.0	30.3	31.2	40.3	45.6
All age groups	0.24	0.30	0.29	0.32	0.32	10.5	16.5	13.6	18.5	21.3	8.0	10.3	10.4	14.1	16.3
All agents (J01 excl. methenamine)															
0-6	7.98	8.62	8.34	7.11	7.21	634.7	666.8	630.8	522.4	515.0	333.5	348.5	330.3	298.0	301.4
7-19	9.79	10.18	10.02	9.52	9.65	311.1	319.8	301.8	280.8	282.5	204.5	208.1	195.8	182.1	184.1
20-59	12.63	13.04	12.82	11.70	11.64	357.6	366.1	348.0	318.9	318.1	223.9	228.7	217.8	204.1	203.8
60-79	18.34	18.58	18.46	17.26	16.86	554.5	553.7	531.0	497.7	489.6	288.8	289.6	279.0	269.6	265.8
80 -	22.74	22.33	22.37	21.13	20.85	833.3	807.9	765.1	723.5	710.9	379.4	372.5	356.2	340.1	336.0
All age groups	13.51	13.87	13.70	12.76	12.68	436.1	443.8	423.1	391.9	390.3	249.8	254.1	242.5	228.0	227.8

Before the Swedish Government decided the target for antibiotic use in outpatient care, the same goal was proposed by Strama (see SWEDRES 2009). Of great importance when promoting a reduced use of antibiotics is to ensure that this does not bring about increased morbidity. Also it is important to emphasize that all patients benefiting from antibiotics should be treated according to current guidelines.

As mentioned in SWEDRES 2009 Strama also proposed two qualitative goals for antibiotic prescribing in outpatient care:
1. 80% of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years should be penicillin V (J01CE02). The numerator is penicillin V (J01CE02) and the denominator is amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulanate (J01CR02), cephalosporins (J01DB-DE) and macrolides (J01FA). This quality indicator is also used by The National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions in their annual benchmarking of medical treatments and procedures.

In 2010 the proportion of penicillin V of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years was 65% on a country level and the proportion of penicillin V increased in the majority of all counties. Värmland County had the greatest proportion, 79%, and Stockholm County the lowest, 59%, Figure 3.1.13.

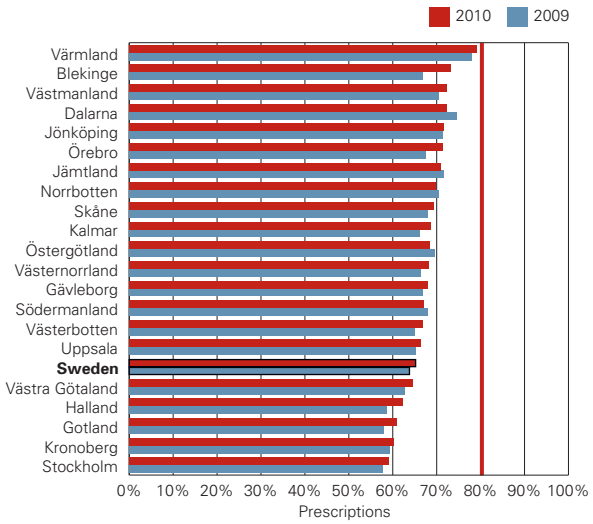

FIGURE 3.1.13. Proportion penicillin V of antibiotics commonly used to treat respiratory tract infections* in children 0-6 years, per county. The red line indicates Strama´s goal at minimum 80% penicillin V. *Amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulate (J01CR02), macrolides (J01FA) and cephalosporins (J01DB-DE).

2. The proportion of fluoroquinolones should not exceed 10% of antibiotics commonly prescribed to treat urinary tract infections in women 18-79 years. The numerator is ciprofloxacin (J01MA02) and norfloxacin (J01MA06) and the denominator is pivmecillinam (J01CA08), trimethoprim (J01EA01), ciprofloxacin (J01MA02), norfloxacin (J01MA06) and nitrofurantoin (J01XE01).

In Sweden the average proportion of fluoroquinolones prescribed to women aged 18-79 was 15 % in 2010. Kronoberg was the county with the highest proportion (19%) and Dalarna was the county with lowest proportion (13%), Figure 3.1.14.

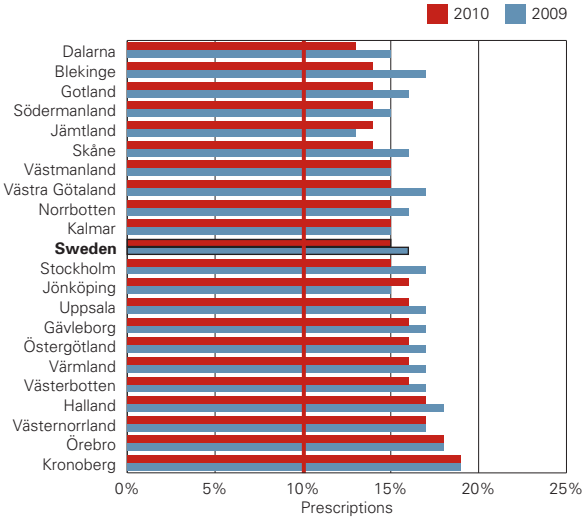

FIGURE 3.1.14. Proportion of fluoroquinolones of commonly used antibiotics in treatment of urinary tract infections* in women 18-79 years, per county. The red line indicates Strama´s goal of maximum 10 % fluoroquinolones. * Fluoroquinolones (J01MA02+06), pivmecillinam (J01CA08), nitrofurantoin (J01XE01), trimethoprim (J01EA01).

More information about Strama's prescribing goals is available in SWEDRES 2009 and at Stramas webpage (www.strama.se).

Jenny Hellman, Christer Norman

Hospital care

As reported in earlier issues of Swedres, a change toward less broad spectrum and more narrow spectrum antibiotics is desirable and has been promoted for a long time. The communication of this issue has been intensified the last years in accordance with the action plan to prevent ESBL resistance in enteric bacteria. Penicillin V (J01CE02) is recommended by The Swedish Society of Infectious Diseases as first hand choice in community-acquired pneumonia and the use of cephalosporins should be reduced. The Swedish Reference Group for Antibiotics has also published a list of "substitutional" antibiotics to be used instead of cefuroxime which has been extensively used for a variety of indications. Stramas point prevalence surveys, performed in 2003, 2004, 2006, 2008 and 2010 confirm that the use of cephalosporins for treatment of uncomplicated community-acquired pneumonia has decreased considerably.

The decrease in the use of cephalosporins continues in 2010, although at a slower rate than recent years, Figure 3.1.15. From 2007 to 2010 the sales of second generation cephalosporins, of which more than 90% was cefuroxime, decreased by 76%. Sales of third generation cephalosporins, mainly cefotaxime and ceftazidime, increased by more than 100% during the same period measured as DDD/1000 inhabitants and day. The decrease in DDD is partly explained by a shift from cefuroxime to cefotaxime since the prescribed daily dose, PDD, in Sweden of cefuroxime and cefotaxime do not correspond to the WHO definition of DDD. Cefuroxime has often a higher PDD and cefotaxime a lower PDD as compared with WHO's DDD, considering this the actual decrease is not that large.

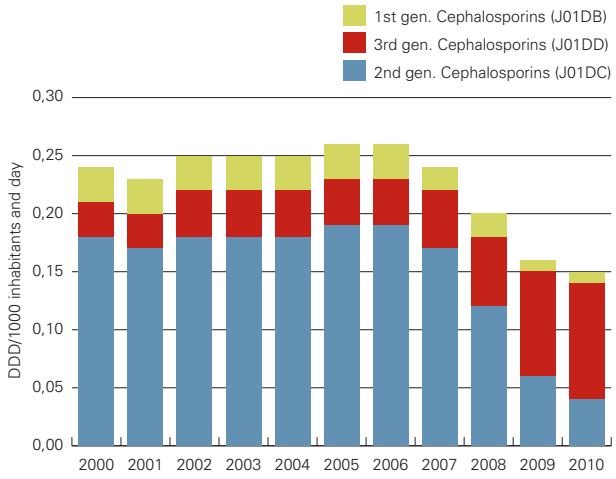

FIGURE 3.1.15. Cephalosporins in hospital care, DDD/1000 inhabitants and day, 2000-2010.

As mentioned initially in this chapter, the analysis and interpretation of data regarding antibiotics to inpatients is complicated by the fact that these numbers reflect not only hospitals but also other types of caregivers, mainly nursing homes. This brings about several problems in the comparison of data regarding substances as well as between geographical regions and trends over time. The magnitude of the error of course varies between substances; certain antibiotics used in advanced medical care tend to be falsely low whereas antibiotics commonly used to treat lower urinary tract infections are falsely high. Figure 3.1.16 shows the proportion of inpatient antibiotics actually used in hospitals in Swedish counties. On the national level, the proportion of inpatient antibiotics actually used in hospitals is about 75%, and has been so for the last five years.

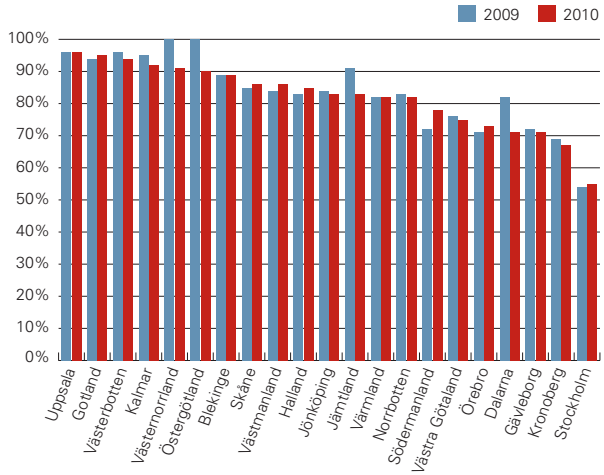

FIGURE 3.1.16. Proportion of inpatient antibiotics actually used in hospitals, DDD/1000 inhabitants and day, 2009 and 2010.

Sales data exclusively to hospitals provided by local Strama groups in all counties

Despite the fact that several counties did initiate stock-piling of certain antibiotics to meet increased needs due to severe outbreaks of influenza in 2009, the antibiotics sales to Swedish hospitals was at the same level 2010 as in 2009.

Due to the recent rapid decrease (38% between 2007 and 2010) in use of cephalosporins, the betalactamase-resistant penicillins (J01CF) are now the largest group of antibiotics in inpatient care, Figure 3.1.17. This substance is largely used as prophylaxis before surgery and the use of this substance increased with 3% in 2010. After several years of decreasing use of fluoroquinolones (J01MA) in accordance with recommendations, the use in 2010 stayed at the same level as 2009. Piperacillin with tazobactam still represents a small proportion (5%) of antibiotic use in hospitals, but it is increasing rapidly. In 2010 piperacillin with tazobactam was the antibiotic that had the greatest increase (16%) measured as DDD/1000 inhabitants and day.

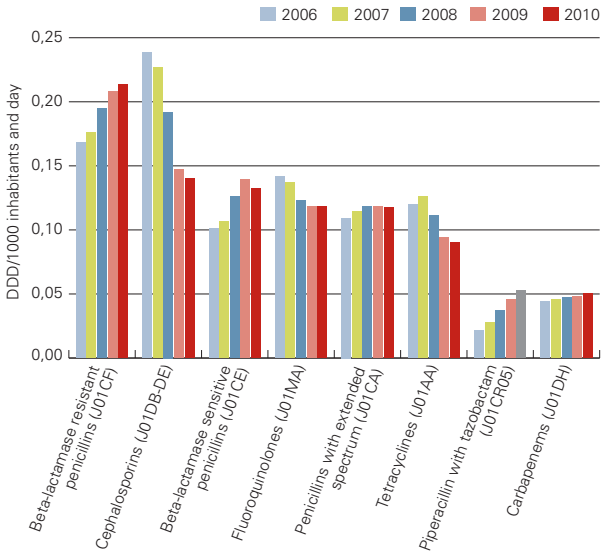

FIGURE 3.1.17. Use of some antibiotic groups in Swedish hospitals 2008-2010, DDD/1000 inhabitants and day.

The choice of denominator is crucial when comparing data on antibiotics to inpatients. In the following sections, sales data is related to the number of patient-days and admissions to hospitals in somatic care.

Sales of all kinds of penicillins have increased every year since 2006, but in 2010 betalactamase sensitive penicillins decreased with 5%. The group penicillins with enzyme inhibitors (J01CR), has more than doubled over these five years. Around 80% of this group constitutes of piperacillin with tazobactam, the rest is amoxicillin with clavulanate, Table 3.1.3 and 4.

Taken together, the amount of antibiotics used per 100 patient-days and 100 admissions in hospital remains quite stable since 2006 – the former increased by 7% and the latter decreased by 3% during these years, Table 3.1.3 and 4. The major changes in antibiotic use in hospital care seem to lie in the shifts between substances.

TABLE 3.1.3. DDD/100 patient-days in somatic medical care in Swedish hospitals 2006-2010.

	2006	2007	2008	2009	2010*
Tetracyclines (J01AA)	5.49	5.75	5.48	4.71	4.57
Penicillins with extended spectrum (J01CA)	5.01	5.21	5.84	5.93	5.96
Betalactamase sensitive penicillins (J01CE)	4.62	4.85	6.21	7.01	6.71
Betalactamase resistant penicillins (J01CF)	7.70	8.04	9.61	10.44	10.82
Combinations of penicillins (J01CR)	1.28	1.57	2.28	2.83	3.32
Cephalosporins (J01DB-DE)	10.92	10.35	9.48	7.40	7.11
Carbapenems (J01DH)	2.02	2.08	2.33	2.42	2.55
Trimethoprim (J01EA)	1.29	1.22	1.19	1.01	0.86
Trimethoprim with sulphonamides (J01EE)	1.47	1.60	1.88	2.03	2.09
Macrolides (J01FA)	1.02	1.01	0.98	0.99	0.88
Lincosamides (J01FF)	1.48	1.53	1.70	1.67	1.68
Aminoglycosides (J01GB)	0.72	0.74	0.88	1.02	1.06
Fluoroquinolones (J01MA)	6.48	6.25	6.08	5.94	6.01
Glycopeptides (J01XA)	0.65	0.64	0.70	0.76	0.70
Imidazole derivatives (J01XD)	1.60	1.52	1.54	1.36	1.27
Methenamine (J01XX05)	0.90	0.86	0.79	0.66	0.59
Linezolid (J01XX08)	0.05	0.05	0.06	0.06	0.08
All agens (J01)	53.17	53.77	57.57	56.77	56.94

*Denominator data from 2009.

TABLE 3.1.4. DDD/100 admissions in somatic medical care in Swedish hospitals 2006-2010.

	2006	2007	2008	2009	2010*
Tetracyclines (J01AA)	28.77	29.91	26.46	22.30	21.64
Penicillins with extended spectrum (J01CA)	26.22	27.13	28.18	28.09	28.19
Betalactamase sensitive penicillins (J01CE)	24.20	25.21	29.99	33.17	31.76
Betalactamase resistant penicillins (J01CF)	40.31	41.82	46.41	49.43	51.22
Combinations of penicillins (J01CR)	6.71	8.18	10.99	13.42	15.69
Cephalosporins (J01DB-DE)	57.17	53.86	45.76	35.01	33.66
Carbapenems (J01DH)	10.60	10.83	11.27	11.46	12.09
Trimethoprim (J01EA)	6.74	6.33	5.76	4.78	4.09
Trimethoprim with sulphonamides (J01EE)	7.71	8.34	9.08	9.59	9.88
Macrolides (J01FA)	5.36	5.26	4.73	4.69	4.18
Lincosamides (J01FF)	7,.77	7.96	8.20	7.90	7.94
Aminoglycosides (J01GB)	3.77	3.84	4.24	4.81	5.03
Fluoroquinolones (J01MA)	33.91	32.52	29.37	28.10	28.44
Glycopeptides (J01XA)	3.39	3.35	3.40	3.62	3.33
Imidazole derivatives (J01XD)	8.37	7.93	7.44	6.42	6.00
Methenamine (J01XX05)	4.73	4.46	3.80	3.13	2.81
Linezolid (J01XX08)	0.27	0.27	0.30	0.27	0.36
All agens (J01)	278.38	279.76	278.02	268.70	269.50

*Denominator data from 2009.

The proportion of broad and narrow spectrum antibiotics used in hospitals varies greatly between counties, as seen in Figures 3.1.18 and 3.1.19. Only 6% of systemic antibacterials in hospitals in Uppsala County are penicillins V or G, whereas in Värmland County these substances represent 20%. Less variation is seen in sales of one of the most common broad spectrum substances, the fluoroquinolones, which constitute between 8 and 14% of all antibiotics to hospitals in the counties. After several years of decreasing use, the cephalosporins make up only 4% of antibiotics in Södermanland County. In Stockholm, Östergötland and Gävleborg Counties the proportion is four times higher.

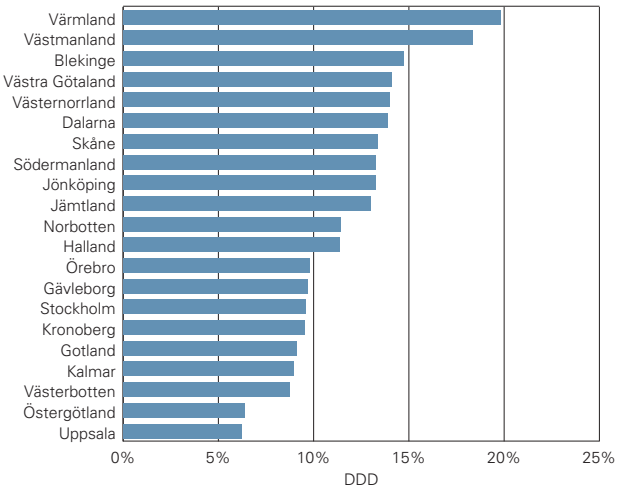

FIGURE 3.1.18. Percentage of narrow spectrum penicillins (penicillin V and G, J01CE) of all antibiotics in Swedish hospitals 2010, per county.

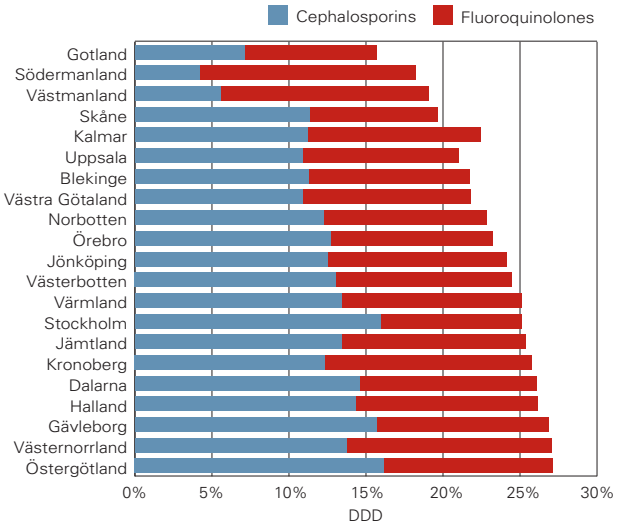

FIGURE 3.1.19. Percentage of broad spectrum antibiotics (cephalosporins, J01DB-DE, and fluoroquinolones, J01MA) of all antibiotics in Swedish hospitals 2010, per county.

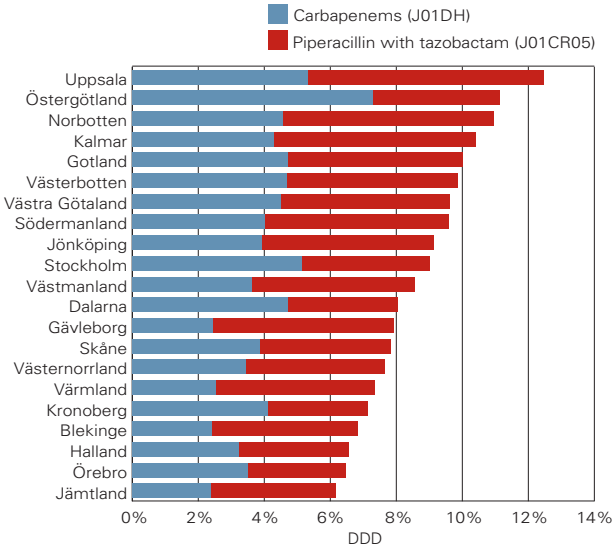

FIGURE 3.1.20. Percentage of carbapenems (J01DH) and piperacillin with tazobactam (J01CR05) of all antibiotics in Swedish hospitals 2010, per county.

As seen in Figure 3.1.20 newer broad spectrum antibiotics as carbapenems and piperacillin with tazobactam, represent a small but steadily growing proportion of the total use of antibiotics in hospitals. There are also great geographical differences; from just a few percent in some counties to over ten percent in others. The Swedish Point Prevalence Surveys indicate that the increase in piperacillin with tazobactam includes several diagnosis groups. The proportion of carbapenems of all antibiotics in hospitals varies threefold, from 2% in Jämtland County to 8% in Östergötland County. Concerning piperacillin with tazobactam, proportion vary from 3% in several counties to 7% in Uppsala and Norrbotten Counties.

Jenny Hellman

Adverse reactions related to antibiotic use.

Spontaneously reported drug-related adverse reactions are continuously entered into SWEDIS, a national database administered by the Swedish Medical Products Agency. The reports originate from health care professionals. The antibiotic related adverse reactions in the last five years, 2006-2010, were analysed for various groups of agents. The following organ system groups received most reports related to the use of systemic antibiotic drugs (J01): skin- and subcutaneous tissue disorders (n=577), hepato-biliary disorders (n=215), gastrointestinal disorders (n=240), general disorders (n=141), musculoskeletal disorders (n=78), blood disorders (n=123), and neurological reactions (n=115). The majority of the reports (61%) concern female patients. The 10 antibiotic substances most commonly associated with adverse reactions, in the last 5 years unadjusted for consumption and regardless of the cause of the report are presented in Table 3.1.5.

TABLE 3.1.5. Most reported antibiotic agents to the Swedish Medical Products Agency 2006–2010

Antibiotic	Total number of ADR reports 2006 to 2010	Number of 'serious' reports	Number of fatal cases (causal relationship possible)
Ciprofloxacin	153	100	4
Flucloxacillin	118	74	4
Nitrofurantoin	111	59	2
Fenoxymethylpenicillin	97	47	0
Clindamycin	85	42	1
Sulphamethoxaxol + trimethoprim	80	53	2
Doxycyline	78	28	2
Trimethoprim	55	27	0
Amoxicillin	51	23	0
Cefuroxime	48	21	1

We have previously reported that amended treatment recommendations resulted in changed prescription patterns for uncomplicated urinary tract infections. There was a decreased consumption of fluoroquinolones which is reflected in a decrease in reported adverse events. For nitrofurantoin which was increasingly prescribed a weak trend of a 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 regarding these trends, Table 3.1.6.

TABLE 3.1.6. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2006 – 2010

	2006	2007	2008	2009	2010	2006-2010
Fluoroquinolones (J01MA)						
Total no of reports	45	55	35	34	28	197
Number of reactions						
Musculoskeletal	11	15	9	9	5	49
tendinitis	6	7	2	3	3	21
tendon rupture	3	2	5	3	2	15
Skin- and subcutaneous tissue	4	13	4	8	11	40
Psychiatric disorders	8	4	2	1	5	20
Nitrofurantoin (J01XE01)						
Total no of reports	20	22	24	21	24	111
Number of reactions						
Respiratory system	12	3	7	9	6	37
dyspnoea	4	0	1	2	3	10
interstitial pneumonia	2	2	2	3	2	11
pulmonary fibrosis	2	0	0	0	0	2
Skin- and subcutaneous tissue	7	8	7	6	9	37
General disorders	8	7	6	7	9	37
fever	4	3	4	4	3	18

Charlotta Edlund, Ulf Persson

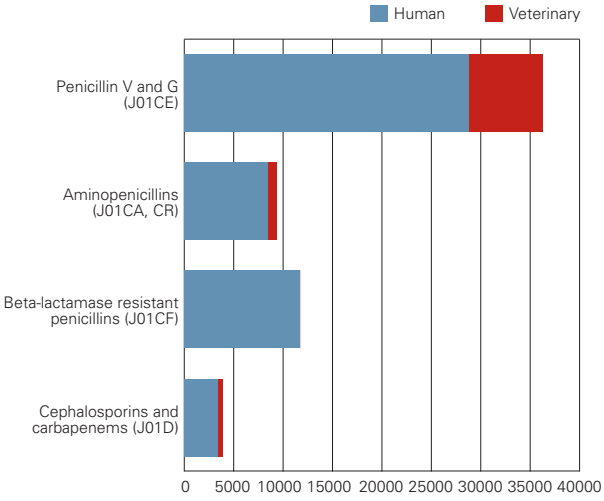

FIGURE 3.1.21. Amount of beta-lactam antibiotics in human and veterinary medicine, kg substance 2010. Please note the difference in indexation of the x-axis between Figures 3.1.21. and 3.1.22.

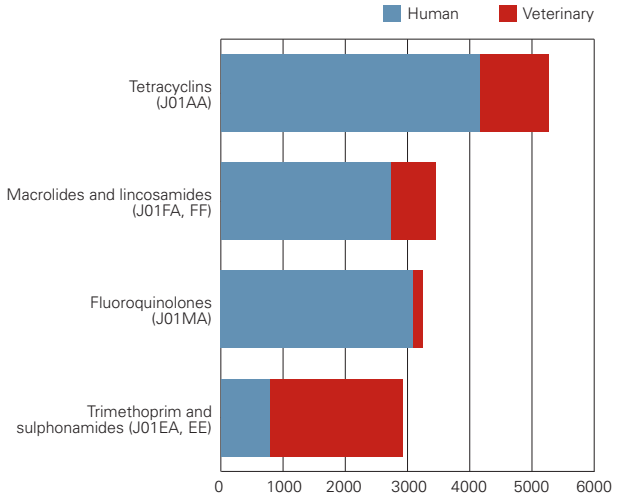

FIGURE 3.1.22. Amount of fluoroquinolones, macrolides, lincosamides, trimethoprim and sulphonamides, and tetracyclins in human and veterinary medicine, kg substance 2010. Please note the difference in indexation of the x-axis between Figures 3.1.21 and 3.1.22.

Antibiotic use in human and veterinary medicine

Increasing efforts are made to share experiences and coordinate initiatives regarding antibiotic policies between the human and veterinary medical sectors. This brief comparison of antibiotics prescribed in the two sectors is an attempt in that direction. Data collection and analysis have been done in collaboration between SMI (Swedish Institute for Communicable Disease Control) and the Strama-group for the veterinary medicine and the food industry, Strama VL. For more data on use of antibacterials in animals, please see SVARM 2010.

Figures reflecting total sales of antibiotics for systemic use in humans were retrieved as defined daily doses and recalculated as kilograms. Data on sales of antibiotics to animals are those presented in SVARM 2010. Sales for aquacultures are not included, nor are sales of medicines authorized for humans but sold for use in animals. The antibiotics included in the comparison are substances that are used in both disciplines and were sold in a quantity exceeding 1000 kg during 2010.

In total, 63.7 tons of antibiotics for systemic use (products indexed as ATC J01, excluding methenamine) were sold to humans. This is less than in 2009 and is consistent with the decrease in number of DDD:s. The corresponding figure for antibiotics for veterinary use (indexed QJ01) is 13.6 tons. Penicillins represent most of the weight in both categories; approximately 80 percent of human antibiotics and 60 percent of animal antibiotics.

Figure 3.1.21 displays the sales of beta-lactam antibiotics. These substances are by far the most used antibiotics in both human and veterinary medicine and also represent the largest amounts measured as kilograms. From an environmental and resistance most of them are relatively harmless. However, the increasingly alarming global situation regarding carbapenem-resistance in Enterobacteriaceae must be kept in mind.

The substances in Figure 3.1.22 are sold in much smaller quantities (n.b. the difference in indexation of the x-axis between the figures), but their impact on the emergence of antibiotic resistance and the environment is more pronounced due to their chemical and pharmacological properties.

Ulrica Dohnhammar, Christina Greko

3.2. Use of antifungals

Hospital care

Despite the arrival of several new compounds to treat antifungal infections systemically in the past few years, the total amount of antifungals in hospital care has not increased dramatically. From 2006 until 2009 there was only a 10.8% increase from 50.2 to 55.6 DDD/10^6 inhabitants and day. In the single year of 2010 though there was an increase of 10% to 62.0 DDD/10^6 inhabitants and day. Looking at the broad-spectrum antimycotics the increase is even higher; 30% in the last year. A large part of this increase is due to a 60% increase in the use of amphotericin B. The reason for this trend is unknown. There has not been issued any new national guidelines that might explain the increased use. Most of the rise comes from two counties, Stockholm and Uppsala, both with

large tertiary hospitals. Since the overall figures are low the increase might be due to the treatment of only a few patients, but as there has been reports from other countries of increased azole resistance in *Aspergillus fumigatus* we can´t currently rule out that the increase in amphotericin B is due to clinical failure with azoletherapy. It is of great importance to closely monitor the future development.

Fluconazole which is a narrow spectrum antimycotic with effect towards candida species (excluding among others *C. krusei* and some strains of *C. glabrata*) stands for approximately 72% of all consumption. It is a fungiostatic drug that is indicated for treatment of invasive candidosis in non neutropenic patients and for cryptococcosis. It is also used as prophylaxis against candida infection and as treatment for local infections such as thrush.

The new azoles; voriconazole which is regarded as treatment of choice for proven or probable aspergillosis, and posaconazole, increasingly used as prophylaxis against invasive fungal infection in certain high risk neutropenic patients, both have excellent bioavailability after oral administration. Both drugs have good effect against the most common candida species with the possible exception of *C. glabrata*, which is an emerging pathogen in Sweden as well as in other parts of the world. This is a possible result of the widespread use of fluconazol, both as prophylaxis and as treatment.

The use of voriconazole is still low in absolute numbers (2.36 DDD/10^6 inhabitants and day), and has been constant for the last few years. The total use in outpatient settings is three times higher and the absolute majority of voriconazole therapy is initiated and monitored by hospital physicians, so it is probably more correct to confer those data to hospital use rather than primary health care use.

Voriconazole is the only broad-spectrum antifungal drug that can be given orally and is therefore often used when the initial intravenous therapy is switched to oral, even in those cases when therapy was started with an echinocandin or amphotericin B. It is also used as secondary prophylaxis against aspergillus infections.

Posaconazole can also be given orally, as a suspension, but in Sweden it is only licensed as second line therapy for invasive fungal infection and as prophylaxis, so it is mainly used as prophylaxis in hematologic units. The total use increased by 10% in 2010.

Since 2005 there has been a small but steady increase in the use of the echinocandins. This is a new group of antimycotics with a fungicidal effect. The first drug in this group, caspofungin has been available in Sweden since 2002, and has now been joined by two more compounds anidulafungin and micafungin. (The latter has not been used much in Sweden due to preclinical reports of an increased incidence of liver tumors in rats.) The echinocandins have a more potent effect against candida species and are also effective against *Aspergillus fumigatus*. Therefore those agents are increasingly used as first line therapy for patient with febrile neutropenia when antibiotics alone have not been successful and when there is a suspicion of infection with yeasts or mold. Both indications and side effects differ a little between the different agents but the antifungal spectrum is similar. As a class the echinocandins have increased in use by 28% during 2010.

Amfotericin B has for a long time been considered the golden standard for treatment of invasive fungal infection due to its broad spectrum and well documented effect against most yeasts and molds. However the tolerability is a problem. Side effects are common with nephrotoxicity and electrolyte imbalance as the most severe. Therefore amfotericin B is now mostly used in its liposomal form, which improves tolerability. The use has remained at the same level from 2005-2009 but increased substantially by 60% during 2010.

During the last years there have been many reports of a shift in the distribution of candida species, with an increase in non albicans, especially *C. glabrata*, whose sensitivity to the azoles is debated. Two European centers have also reported the emergence of voriconazole resistance in *Aspergillus fumigatus* during azoletherapy. An increased awareness and monitoring of developing resistance to antifungal drugs is warranted.

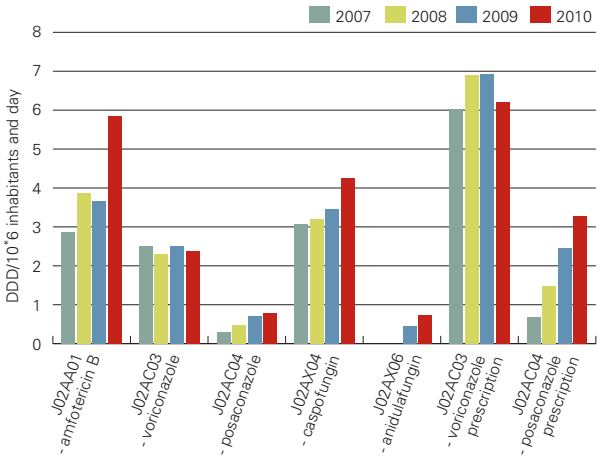

FIGURE 3.2.1. Use of broadspectrum antifungals in hospital care, 2007-2010, DDD/10^6 inhabitants and day.

Outpatient care

77% of all systemically administrated antifungal drugs are sold on prescription measured as DDD/1000 inhabitants and day. The majority of those prescriptions took place in primary health care. The most commonly prescribed drug is fluconazole, mainly for mucocutaneal infections.

There are many different topical applications containing imidazoles, with or without steroids, mainly used for dermatophyteinfections of the skin or vaginal yeasts infections. Some of those are sold on prescription and others are available as OTC drugs for self medication.

Jesper Ericsson

4. Antimicrobial resistance

SWEDISH SURVEILLANCE of antimicrobial resistance is normally based on testing of clinical samples and samples taken according to local screening programmes and outbreak investigations. Each part of the Swedish surveillance programme is based on data collected from all of the clinical microbiology laboratories. In these laboratories testing of clinical isolates for antibiotic susceptibility is routinely performed using the standardized disk diffusion method. During 2010, several laboratories have already shifted to the newly standardized disk diffusion methodology as proposed by EUCAST (Appendix 4). Commercially available tests for MIC determination are also used, and in recent years there has also been an increase in the use of automated methods for susceptibility testing and categorization.

Notifications according to the Communicable Disease Act form the first part of the national surveillance programme. The first finding of a methicillin resistant *Staphylococcus aureus* (MRSA), a pneumococcus with decreased susceptibility to penicillin G (PNSP, MIC ≥ 0,5 mg/L), a vancomycin-resistant *Enterococcus faecalis* or *Enterococcus faecium* (VRE) or an *Enterobacteriaceae* producing extended-spectrum betalactamases (ESBL) are notifiable according to the Communicable Disease Act, regardless of whether it was judged to be a clinical infection or colonisation without infection. MRSA, PNSP and VRE require notifications by laboratories as well as by the diagnosing clinicians, whereas ESBL require laboratory notification only. The definition of an ESBL was altered in 2010 to encompass not only classical ESBLs which are inhibited by clavulanic acid (=$ESBL_A$) but also plasmid-mediated AmpC-betalactamases (=$ESBL_M$) and metallo-betalactamases / carbapenemases (= $ESBL_{CARBA}$).

The annual resistance surveillance and quality control (RSQC) programme, initiated in 1994, form the second part of the national surveillance (Appendix 5). Well-characterized data on resistance in many bacterial species are now available from several years both at regional and national level. Because of the shift in disk diffusion methodology introduced in 2010 (Appendix 4) the sampling period was moved from spring to autumn this year in order to allow for the new methodology to be implemented in as many laboratories as possible.

Under the heading **Data on invasive isolates reported to ECDC/EARS-Net,** results from the Swedish part of the European Antimicrobial Resistance Surveillance Network are presented. Twenty of twenty-eight Swedish laboratories, covering approximately 75% of the population, regularly report susceptibility data on invasive isolates of seven defined bacterial species to ECDC/EARS-Net via the Swedish coordinator at SMI.

Eleven of these laboratories also deliver data on invasive isolates from all positive blood cultures (Appendix 5). For bacterial species other than those reported to ECDC/EARS-Net, data on resistance is presented under the heading **Surveillance of invasive isolates in addition to EARS-Net.**

One of the cornerstones in the battle against antibacterial resistance in Sweden has been the early identification of cases via screening programmes and contact-tracing around cases with notifiable resistance markers. The annual numbers of samples specifically registered in the laboratories to be analysed for screening for (multi-)resistant bacteria, MRB, is shown in Figure 4.1. Even though the screening programmes and criteria for registering analyses under this heading may vary between laboratories, they are fairly constant within each laboratory over time. In 2010 all 28 laboratories provided data on MRB- screening.

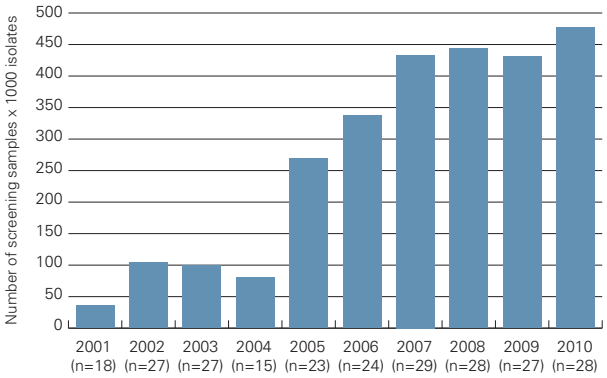

FIGURE 4.1. Annual number of recorded screening samples for multi-resistant bacteria 2001-2010. n refers to the number of participating laboratories

Staphylococcus aureus including MRSA

Notifications of MRSA according to the Communicable Disease Act

MRSA has been mandatory notifiable since the year 2000. Infection control programmes have been developed and implemented locally under supervision of the County Medical Officers (CMO) 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. In 2010 national action plans addressing the control of MRSA in the community setting, and in particular in the child-care setting, were published by Strama and the National Board of Health and Welfare.

The following presentation is based on data collected in the national web-based notification system SmiNet. During the last five years an active effort has been made to improve the quality of data and to collect missing data. The notifications have been reviewed and complemented with available relevant epidemiologic information from investigations around each case in collaboration with the CMOs.

In 2010 a total of 1580 cases of MRSA were notified, an increase by 100 cases (7%) compared with 2009, Figure 4.2.

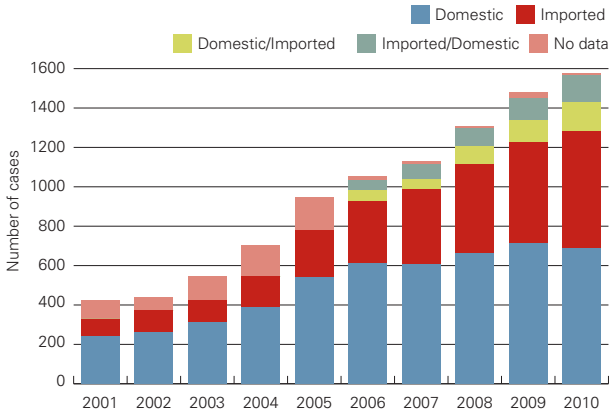

FIGURE 4.2. Number of MRSA cases annually notified in Sweden 2001-2010 by country of infection. "Domestic/Imported" and "Imported/Domestic" indicate several mentioned countries of infection with the most likely mentioned first.

In 2010, four of the Swedish counties, Kalmar, Skåne, Jämtland and Stockholm, had a higher incidence than the average national incidence of 16.8 cases/100 000 inhabitants, Table 4.1.

During 2010, 43% (n=687) of all reported MRSA cases were domestically acquired and 38% (n=595) were acquired abroad. China (46 cases), Iraq (44 cases), Serbia and Montenegro (38 cases), Philippines (38 cases) and India (34 cases) made up the five most common countries for imported MRSA infection. In 18% of the cases Sweden and at least one more country were mentioned as possible countries for acquisition of MRSA. When these reported secondary countries also were considered, the most common countries were still the same, but in a different order (China 63 cases, Iraq 60 cases, Philippines 43 cases, India 43 cases and Serbia and Montenegro with 42 cases. The country for acquisition was reported as "unknown" in 15 cases.

TABLE 4.1. MRSA notifications according to the Communicable Disease Act 2001-2010 by county

	2001		2002		2003		2004		2005		2006		2007		2008		2009		2010	
County	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *
Stockholm	166	9,0	205	11.1	228	12.3	277	14.8	315	17.1	356	18.9	351	18,0	342	17.3	375	18.6	412	20,0
Uppsala	17	5.7	10	3.3	12	4,0	26	8.6	28	9.2	24	7.9	33	10.2	40	12.2	33	9.9	41	12.2
Södermanland	1	0.4	4	1.5	2	0.8	8	3.1	11	3.8	9	3.4	26	9.8	20	7.5	23	8.5	30	11.1
Östergötland	7	1.7	7	1.7	14	3.4	14	3.4	101	24.3	48	11.5	49	11.6	43	10.2	45	10.5	47	10.9
Jönköping	6	1.5	5	1.5	24	7.3	14	4.3	40	12.1	44	13,0	17	5.1	20	6.0	66	19.6	54	16,0
Kronoberg	0	0,0	4	2.3	5	2.8	17	9.5	11	6.1	14	7.8	13	7.2	19	10.4	26	14.2	23	12.5
Kalmar	5	0.9	5	2.1	6	2.6	16	6.8	23	9.7	26	11.1	36	15.4	29	12.4	42	18.0	72	30.8
Gotland	10	17.5	3	5.3	2	3.5	1	1.7	10	17.3	4	6.9	8	14,0	6	10.5	6	10.5	5	8.7
Blekinge	1	0.7	3	2,0	2	1.3	3	2,0	9	5.9	4	2.7	16	10.5	10	6.6	11	7.2	8	5.2
Skåne	76	6.7	68	5.9	104	9.1	128	11.3	162	13.9	179	15.5	166	13.8	273	22.5	284	23.1	313	25.2
Halland	26	9.4	13	4.7	13	4.6	9	3.2	21	7.4	23	8.1	18	6.2	16	5.5	45	15.2	40	13.4
Västra Götaland	56	3.7	48	3.2	63	4.2	118	7.8	125	8.1	177	11.6	178	11.5	245	15.7	258	16.4	264	16.7
Värmland	7	2.6	6	2.2	11	4,0	18	6.6	9	3.2	13	4.8	32	11.7	22	8.0	33	12.1	28	10.2
Örebro	7	2.6	16	5.9	8	2.9	11	4,0	16	5.8	35	12.8	25	9.1	46	16.6	45	16.1	40	14.3
Västmanland	8	3.1	6	2.3	11	4.2	12	4.6	35	13.4	48	18.4	54	21.7	23	9.2	46	18.3	32	12.7
Dalarna	5	1.8	1	0.4	2	0.7	3	1.1	6	2.1	11	4,0	15	5.4	23	8.3	28	10.1	27	9.7
Gävleborg	1	0.4	12	4.3	5	1.8	5	1.8	24	8.6	17	6.1	12	4.4	26	9.4	12	4.3	26	9.4
Västernorrland	12	4.9	7	2.9	10	4.1	5	2,0	4	1.6	9	3.7	22	9,0	35	14.4	43	17.7	30	12.4
Jämtland	0	0,0	2	1.6	5	3.9	1	0.8	8	6.2	4	3.1	24	18.9	31	24.4	18	14.2	28	22.1
Västerbotten	17	6.7	10	3.9	13	5.1	16	6.2	10	3.8	7	2.7	23	8.9	22	8.5	28	10.8	39	15,0
Norrbotten	5	2,0	7	2.8	9	3.6	7	2.8	8	3.1	5	2,0	10	4.4	16	6.4	13	5.2	21	8.4
Total	429	4.8	442	4.9	549	6.1	709	7.8	975	10.8	1057	11.7	1128	12.3	1307	14.1	1480	15.8	1580	16.8

* = Incidence (cases/100 000 inhabitants)

Among the domestic MRSA cases 2006-2010, the incidence was highest in the age group 80 years and older, Figure 4.3. In this age group there has been a decreasing trend since 2006, but in 2010 the incidence increased again. In the age group 0-6 years the incidence was generally 11-14, except for 2009 when it was 17. In all other age groups the incidence of domestic MRSA has remained at a low and stable level around 5.

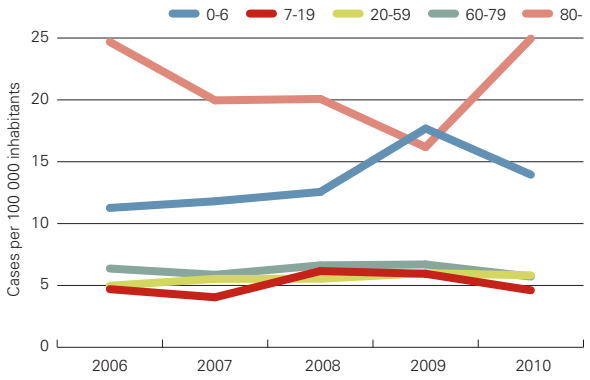

FIGURE 4.3. Age group adjusted incidence of notified domestic MRSA cases in Sweden 2006-2010.

In 2010, 43% of the domestic cases were identified through contact tracing, 10% in targeted screening, and 47% during investigations of clinical symptoms, Figure 4.4. For imported cases the corresponding figures were 9%, 56% and 34%, respectively. Invasive MRSA infection was reported in 15 cases 2010. 13 of those were newly notified cases 2010 and two occurred in patients previously known to carry MRSA.

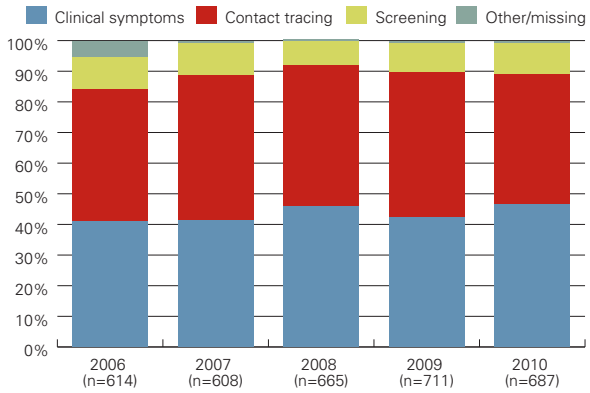

FIGURE 4.4. The reasons for detection of domestic MRSA cases in Sweden 2006-2010. n refers to the number of reported cases each year.

Epidemiological classification of the acquisition of MRSA was based on information in the clinical notifications and from subsequent investigations by the CMOs, Figures 4.5.a and b.

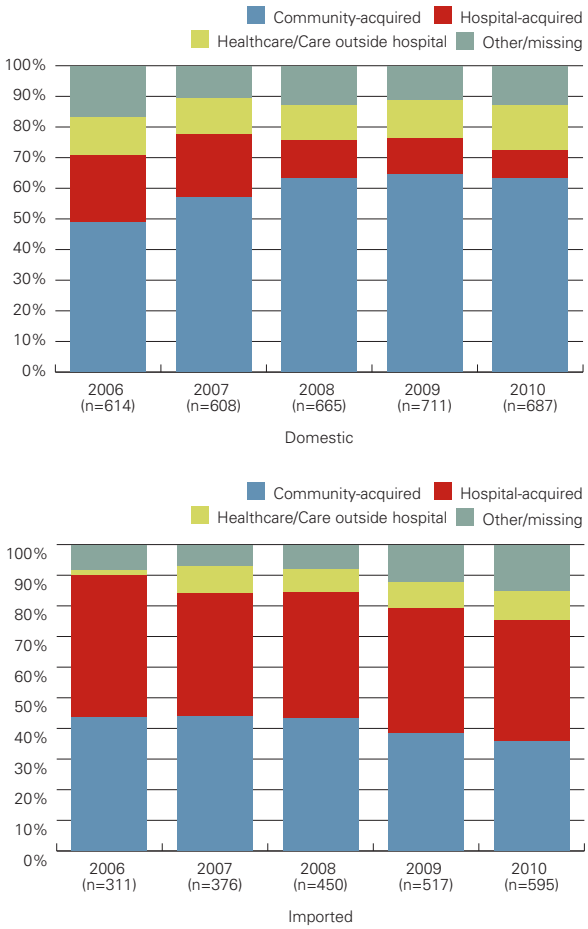

FIGURE 4.5. A AND B. Epidemiological classification of the acquisition of domestic (a. top) and imported (b. bottom) MRSA, Sweden 2006-2010. n refers to the number of notified cases each year.

Community-acquired infections dominated among domestic cases 2010 and comprised 63% (n=434) of all domestic cases. There has been a continuous increase of the proportion of community acquired cases since 2007, and in Sweden today MRSA is acquired primarily in the community. Among the imported cases the proportion of community acquired infections was 36% (n=213). Community acquisition was reported in 75% of the cases for which it was uncertain whether MRSA was acquired domestically or imported (n=283, not presented graphically).

Hospital acquired MRSA was comparatively more common in imported cases, 40% (n=237), than among domestic cases, 9% (n=64). The number of domestic cases with hospital acquired MRSA decreased from 88 to 64 compared with 2009 and the number of domestic hospital acquired cases has been halved as compared with 2006 and 2007, when 135 and 127 cases were reported, respectively.

The number and the proportion of domestic cases with MRSA acquired in healthcare/care outside the hospital increased to 102 (15%) in 2010 compared with 88 (12%) in 2009.

During 2010 only minor outbreaks in different counties were reported from the Swedish healthcare system and from long-term care facilities.

Epidemiological typing of MRSA

DNA-based methods have been used for epidemiological typing of MRSA in Sweden since 2000. Pulsed-field gel electrophoresis (PFGE) was the first method used. In 2006 this method was replaced by *spa*-typing, which is now the primary typing method. An advantage of *spa*-typing, compared with PFGE, is that it is a sequence based method with an internationally well recognised nomenclature, the Ridom nomenclature (http://spaserver.ridom.de/), that is easy to use and communicate.

In 2010, 268 *spa*-types were identified. Ten of them were seen among 42% of the notified MRSA cases. Nine of these ten *spa*-types were the same as in 2009 (Table 4.2). The most noteworthy change was the decrease in prevalence of *spa*-type t015. According to earlier PFGE-typing results, isolates with this *spa*-type always had PFGE-pattern SE97-3 (Berlin IV-like) and belonged to MLST sequence type 45. t015 is a common *spa*-type also among methicillin-sensitive *Staphylococcus aureus* (MSSA). *S. aureus* with *spa*-type t015 have been found both in healthcare settings and in the community. PVL-genes have not been detected in t015 isolates.

TABLE 4.2. Ten most common *spa* types in 2007-2010 listed in decreasing order per year. Numbers of notified cases are shown in brackets for 2009 and 2010.

2007	2008	2009	2010
t032	t002	t008 (157)	t008 (150)
t008	t008	t044 (108)	t002 (100)
t044	t044	t002 (106)	t044 (98)
t002	t019	t019 (59)	t019 (65)
t037	t032	t015 (58)	t223 (53)
t015	t127	t437 (53)	t437 (52)
t437	t437	t127 (44)	t127 (51)
t690	t024	t223 (46)	t032 (35)
t024	t015	t032 (38)	t015 (32)
t019	t037	t037 (27)	t021 (26)

Also all isolates with *spa*-type t032 or t223 were PVL-negative, whereas isolates with *spa*-type t044 were always positive. Among isolates with the other most common *spa*-types both PVL-positive and –negative ones were found.

In total, 539 (36%) of all tested isolates from 2010 were PVL-positive. This proportion has been unchanged during the last couple of years, when PVL-positive isolates have represented more than 30% of all MRSA cases. Among the PVL-positive isolates, those with *spa*-type t008 were most frequently encountered in 2010. Some of these isolates have been typed by PFGE and identified as SE03-5 (Swedish nomenclature) which corresponds to the PFGE type USA300 (CDC nomenclature).

Since 2006 there has been focus on the zoonotic potential of MRSA and especially the occurrence of the livestock associated MRSA belonging to MLST clonal complex (CC) 398. However, only few isolates with *spa*-types common among CC398 MRSA were seen in human samples in Sweden 2006-2010 - t011 (n=7), t108 (n=2), t034 (n=11), and t571 (n=2). None of these isolates were PVL-positive. Two of the t011 cases were reported in 2010. They had both, either directly or indirectly, had contact with horses or other domestic animals. Six of the t034 cases were reported in 2010, but none of them had any obvious connections to animals. In addition, twelve cases with PVL-positive t034 MRSA were identified during these years. However, they all seemed to be unrelated to the livestock associated MRSA that have been causing problems in the Netherlands, Denmark and other European countries.

Antibiotic resistance in MRSA

All MRSA isolates were investigated with regard to resistance to antibiotics other than betalactam antibiotics, Table 4.3. Out of 1227 isolates tested (MRSA from all counties except Skåne and Örebro), 515 (42%) had no other resistance marker than the *mecA* gene defining them as MRSA. Among the other strains, concomitant resistance to erythromycin and clindamycin was still most frequently seen. These resistance markers were found in strains of many different *spa*-types, indicating that macrolide resistance is a widespread phenomenon. Resistance to ciprofloxacin was the second most common resistance marker, followed by resistance to gentamicin and other aminoglycosides, resistance to fusidic acid, and to a much lesser degree resistance to rifampicin or to mupirocin. The general trend described in previous SWEDRES reports was still valid.

The decreased proportion of multiresistant MRSA probably reflected the transition from hospital- or healthcare-associated strains to community associated strains. When defining multiresistance as resistance to at least three different categories of antibiotics apart from the betalactam antibiotics, there were only 93 strains meeting these criteria. The antibiotic categories were fluoroquinolones (ciprofloxacin tested), macrolides (counting erythromycin and clindamycin as one category), fusidic acid, aminoglycosides (gentamicin tested), and rifampicin. Seven different *spa*-types were frequently found to be multiresistant and are described in Table 4.3.

TABLE 4.3. Characteristics of the seven most frequent *spa*-types among multiresistant MRSA 2010.

Spa type	No of strains	Acquisition	Route of transmission	Antibiogram[a]	CC/ST[b]
t003	13	Sweden	Healthcare/ Community	CDEG	CC5 /ST5 Europe
t037	18	Sweden/ abroad	Healthcare	CDEFGR CDEG	CC8 /ST239, worldwide
t041	6	Abroad	Healthcare/ Community	CDEG	CC5 /ST228, Germany, Italy
t067	13	Sweden/ abroad	Healthcare	GEGM	ST125, Europe, Spain
t149	3	Abroad	Healthcare/ Community	CDEG	CC5 /ST5, S America
t189	4	Sweden/ abroad	Healthcare/ Community	CDEG	ST188, worldwide (also as MSSA)
t324	6	Sweden/ abroad	Community	DEGM	ST72, Asia

[a] C = ciprofloxacin, D = clindamycin, E = erythromycin, F = fusidic acid, G = gentamicin, R = rifampicin.

[b] Information retrieved from Ridom SpaServer (www.spaserver.ridom.de).

Annual Resistance Surveillance and Quality Control (RSQC) programme

Staphylococcus aureus from skin and soft tissue infections has been included in the annual RSQC programme since 2001 (Appendix 5). Twenty-eight laboratories normally provide data on 100 consecutive isolates using the disk diffusion method for cefoxitin (from 2004 used as screening disk for detection of MRSA), clindamycin, fusidic acid, and an aminoglycoside (gentamicin or tobramycin). Erythromycin (group representative for macrolide antibiotics) and a fluoroquinolone (ciprofloxacin or norfloxacin) have also been tested since 2004. From 2006 laboratories were asked to provide data on 200 isolates each to increase the statistical power of the trend analyses. In 2010, because of methodological changes (Appendix 4), only 20 laboratories provided data, but still more than 4500 isolates were included in the analysis. The average resistance rates, as retrieved from ResNet, are shown in Figure 4.6.

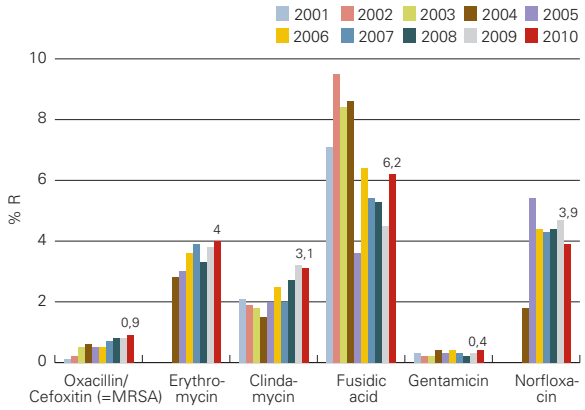

FIGURE 4.6. Resistance rates for *Staphylococcus aureus* from skin and soft tissue infections 2001–2010 (data from the annual RSQC programme, 3000-5000 isolates per year). In 2005 resistance rates were recorded in S.aureus isolated from skin and soft tissue infections from elderly (> 65 years) people only.

The frequency of MRSA in skin and soft tissue infections (SSTI) (cefoxitin used as test compound) has increased slowly but the level in 2010 still remained below 1%. The resistance rate for erythromycin (4%) was slightly higher than that for clindamycin (3.1%) but similar to the levels in 2009. The simultaneous increase in clindamycin and erythromycin resistance indicated a shift towards an increased prevalence of *erm* genes (constitutively or inducibly expressed) among the clinical isolates. The level of fusidic acid resistance was higher than in 2009 and reached above 6%. Almost no resistance to aminoglycosides was seen in bacteria from SSTI. Fluoroquinolone resistance was stable around 4%.

Data on invasive isolates reported to ECDC/EARS-Net

In 2010, 0.7% of the invasive *S. aureus* isolates were MRSA (identified by the cefoxitin screen disk test and confirmed by detection of the *mecA* gene), Table 4.4. This low level has remained during the eleven years of mandatory reporting, indicating that infection control measures to prevent MRSA from spreading in the hospital environment have been successful.

TABLE 4.4. *Staphylococcus aureus* susceptibility results (number of strains and percentage) in blood isolates by the disk diffusion method and by confirmation of the *mecA gene*. Data from Sweden 2001-2010 reported to ECDC/EARS-Net.

Year	S	R
2001	1618 (99.1%)	14 (0.9%)
2002	1830 (99.4%)	12 (0.6%)
2003	1839 (99.1%)	16 (0.9%)
2004	1891 (99.3%)	14 (0.7%)
2005	1756 (99%)	18 (1.0%)
2006	1849 (99.1%)	16 (0.9%)
2007	2162 (99.5%)	11 (0.5%)
2008	2408 (99.3%)	16 (0.7%)
2009	2621 (99.1%)	18 (0.9%)
2010	2651 (99.3%)	19 (0.7%)

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Streptococcus pneumoniae

Background

S. pneumoniae with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (PNSP) became notifiable according to the Communicable Disease Act in 1996. In addition invasive infections with *S. pneumoniae*, regardless of resistance, became notifiable in 2004. Pneumococci have been part of the annual RSQC programme since 1994.

Notifications according to the Communicable Disease Act

In 2010 there were 409 PNSP cases notified in Sweden, a decrease by 8% compared with 2009, Figure 4.7. Forty-nine percent of the cases had been infected domestically and 12% of the cases in a foreign country. In the remaining 160 cases no country for acquisition was given.

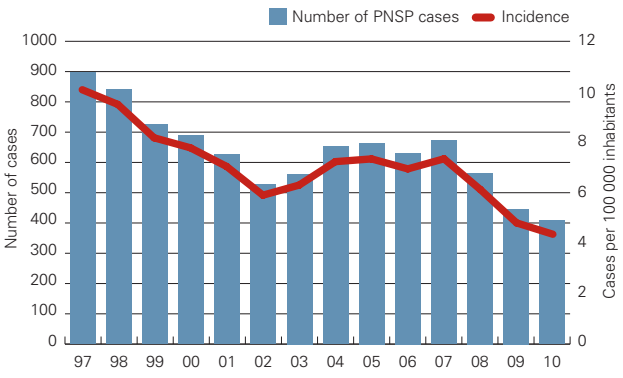

FIGURE 4.7. Number of cases of *S. pneumoniae* with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (left) and cases per 100 000 inhabitants (right), Sweden 1997-2010.

The incidence of PNSP in Sweden 2010 was 4.3 cases per 100 000 inhabitants. Previous analyses have indicated that the declining incidence was related to a concurrent decrease in nasopharyngeal culturing propensity. The majority of PNSP

cases, independent of year observed, were found in the age group 0-4 years, Figure 4.8. Since 2007, the decrease in the number of reported cases was found primarily in this age-group. There was no difference in the proportion of the reported cases with regard to sex.

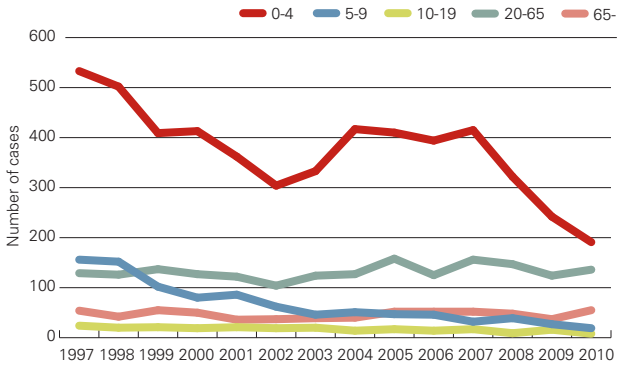

FIGURE 4.8 Age-group distribution among all cases reported with PNSP in Sweden 1997-2010.

PNSP were reported from 20 of 21 Swedish counties, with Stockholm (171 cases) and Skåne (108 cases) accounting for 68% of all notifications (but only 35% of the Swedish population). In these two counties, the notifications have decreased by 20% in Skåne and increased with 19% in Stockholm, compared with 2009. The remaining counties reported 2-30 cases each, but from Halland no cases were reported in 2010. Due to regional differences in general culturing propensity, case finding intensity as well as presence of targeted screening programmes, a comparison of regional incidences is not meaningful.

The majority, 79% of all notifications of PNSP, were found in cultures from the nasopharynx. In 45% of all cases the detection of PNSP was due to clinical infection, and in 18% due to targeted screening including contact tracing. In the remaining cases another reason for sampling was stated (2%) or the information was missing (35%).

Serotype distribution

In 2010, 23 cases of invasive PNSP infections were reported, all from blood. For 18 of these cases the serotypes were reported, and nine had serotype 14, seven serotype 9, one serotype 6 and one serotype 19A. The serotype distribution among cases with invasive PNSP isolates 2006-2010 show that serotypes 9V and 14 dominate, Figure 4.9.

The serotype distribution among all PNSP 2010 changed somewhat compared with 2009. The most commonly found serotypes among all PNSP during 2010 were, in decreasing order, type 19F (23%), followed by non-typeable (NT) (12%), 9V (11%), 14 (10%), 19A (10%), and 35B (7%). In 2010 approximately 60% of PNSP were multiresistant.

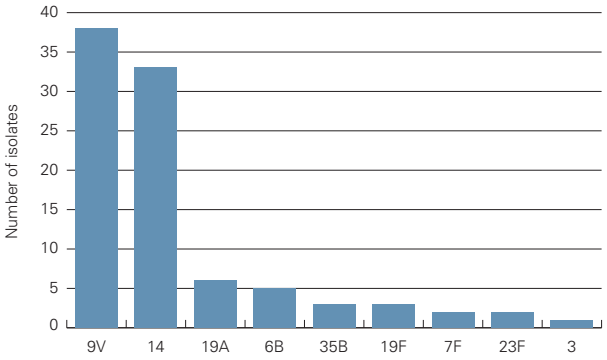

FIGURE 4.9. Serotype distribution among invasive isolates of PNSP (MIC ≥0,5mg/L) 2006-2010.

Annual Resistance Surveillance and Quality Control (RSQC) programme

The isolates collected during the RSQC surveys are mainly derived from nasopharyngeal cultures. Usually 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, clindamycin (since 2004), tetracycline, trimethoprim-sulfamethoxazole, and norfloxacin (since 2005, used as indicator for fluoroquinolone resistance) using the disk diffusion method. In 2010, because of methodological changes (Appendix 4), only 20 laboratories provided data, and approximately 1600 isolates were included in the analysis. The national summary of the results, as retrieved from ResNet, are shown in Figure 4.10. Previously, there has been a steady increase in rates of resistance for all tested antibiotics except norfloxacin every year. The data for 2010 indicated a continued increase in penicillin non-susceptibility and in quinolone resistance, although from a lower level. However, no increase, or even reduced resistance rates, were seen for macrolides (erythromycin tested), clindamycin, tetracycline and trimethoprim-sulfamethoxazole.

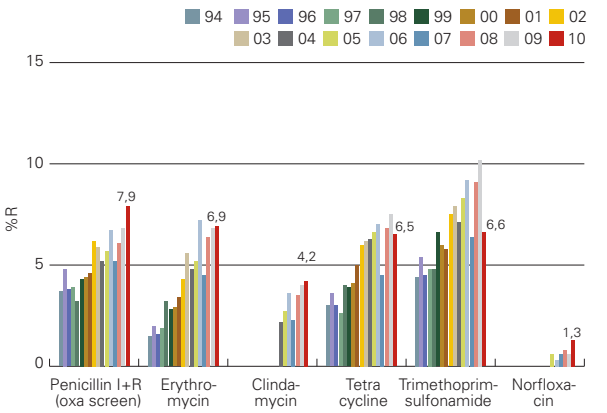

FIGURE 4.10. Resistance rates for *Streptococcus pneumoniae* 1994-2010 (data from the annual RSQC programme, approximately 3000 isolates per year).

Data on invasive isolates reported to ECDC/EARS-Net

The Swedish data on susceptibility to penicillin and erythromycin among invasive isolates for 2001-2010 are given in Table 4.5. Levels of resistance were lower among invasive isolates than in the nasopharyngeal isolates from the RSQC programme. One explanation, although not proven, could be that asymptomatic carriers diagnosed during contact tracing are included in the RSQC pogramme. Also, there has been no increased resistance among invasive isolates, neither for penicillin nor erythromycin, contrary to the nasopharyngeal isolates.

TABLE 4.5. Invasive isolates of *Streptococcus pneumoniae* (number of strains and percentage). Data from Sweden 2001-2010 reported to ECDC/EARS-Net.

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
2008	98.0	1.6	0.4	1213
2009	97.2	2.8	0	1098
2010	97.4	3.6	0	1013
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
2008	94.4	0.4	5.2	1123
2009	96.8	0.1	3.1	1098
2010	96.1	0.1	3.8	947

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

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Enterococcus faecalis and *Enterococcus faecium*

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 immunocompromised and intensive care patients. Like MRSA, VRE were made notifiable according to the Swedish Communicable Disease Act in the year 2000 and since 2004 contact tracing is mandatory.

From 2000 to 2006 only low numbers (18-35 per year) of VRE-cases were reported in Sweden. In 2007, 53 cases were notified, and during the autumn 2007 reports came from Stockholm County about an increase in the number of VRE-cases. An increased occurrence of VRE was also reported from Västmanland, Halland and Uppsala counties during 2008-2009. Since August 2007 until the end of 2009 altogether 1057 cases of VRE had been reported. Of these, 95% were domestic healthcare-related cases and almost all cases (90%) had an *Enterococcus faecium* with *vanB*. Epidemiological typing of these *Enterococcus faecium vanB* showed that all examined isolates from Västmanland and Halland, as well as the majority of isolates from Stockholm county, had closely related PFGE patterns, suggesting spread of the same strain. The recognition of the outbreak in 2007-2008 lead to intensive contact tracing, screening activities and to other infection control measures.

Notifications of VRE according to the Communicable Disease Act

During 2010 a total of 214 cases were reported, a decrease by 47% compared with 2009. VRE cases were reported from 16 of the 21 Swedish counties. Half of the 214 cases were still reported from the three counties with previously reported outbreaks, Stockholm (n=55), Västmanland (n=41) and Halland (n=13). The corresponding incidence figures had decreased in Stockholm from 8.8 to 2.7, in Halland from 19.9 to 4.3 and in Västmanland from 53 to 16.2. An additional 45 cases were reported from the remaining 12 counties. The average national incidence of VRE was 2.3. In Figure 4.11 the epidemic curve of the outbreak strain prevailing in 2007-2009 is shown. The number of cases has decreased significantly in 2010, although isolates with the typical PFGE pattern of this strain are still detected.

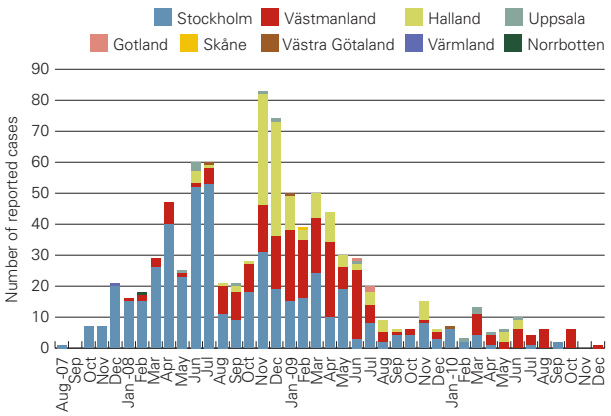

FIGURE 4.11. Epidemic curve for spread of domestic *Enterococcus faecium* with *vanB* with PFGE-pattern SE-EfmB-0701.

The highest number of VRE cases (n=60) and the highest incidence, 24.7, was reported from Västernorrland county. This was explained by outbreaks in two regional hospitals. The strain isolated from most of the cases was a new *Enterococcus faecium vanB* strain, i.e. not related to the previously reported outbreak strain. The counties of Uppsala and Norrbotten also

had incidence figures above the national average, with 3.0 and 2.8 cases per 100 000 inhabitants, respectively.

Of all cases, 83% (n=177), were reported as domestic, and almost all of these (n=162) were healthcare related. For the remaining 15 domestic cases the route of transmission was not known. In 33 cases VRE had been acquired abroad, and 21 different countries were stated. In four cases the country of acquisition was unknown. Twenty-nine of the 33 imported cases were healthcare related. The domestic VRE cases were detected due to contact tracing in 138 cases (78%), 11% in screening and 9% due to clinical symptoms. For 2% another reason for detection was stated. 28 of the imported cases were found in screening, four cases due to clinical symptoms and one case in contact tracing.

In 2010, 207 cases had *Enterococcus faecium*. Of these 135 carried the *vanB* gene and 63 *vanA* . Information was missing for nine cases. *Enterococcus faecalis* was reported in six cases, three with *vanA* gene and one with *vanB*. For the two remaining cases the resistance gene was not reported. One case was reported with both *Enterococcus faecalis* and *Enterococcus faecium*. The species and resistance genotype distribution per county for domestic and healthcare related cases in 2010 are presented in Table 4.6.

TABLE 4.6. Species and resistance genotype for VRE in domestic, healthcare-related cases 2010.

County	Total number of cases	Efm [a], *vanB*	Efm, *vanA*	Efs [b], *vanB*	Efs, *vanA*
Västernorrland	59	59	-	-	-
Västmanland	41	35	6	-	-
Stockholm	36	19	13	-	-
Halland	13	7	6	-	-
Norrbotten	5	-	5	-	-
Uppsala	4	4	-	-	-
Västra Götaland	2	1	1	-	-
Östergötland	1	1	-	-	-
Skåne	1	1	-	-	-

[a] Efm = *Enterococcus faecium*, [b] Efs = *Enterococcus faecalis*

Distribution between genders was even and the median age for women was 79 years and for men 72 years. According to the first laboratory notifications for each case the majority of isolates were from faeces (60%), rectum 13%, "other" 6%, and urine in 3% of the cases. Invasive VRE infections, all from blood, were reported in two cases only. The findings of VRE in faeces or rectum in more than 70% indicated that most of the cases were detected by screening.

Epidemiological typing of VRE

For enterococci PFGE is used as the standard typing method. Isolates from notified cases in all counties from 2007 and onwards have been analysed, and comparisons with isolates from previous years have also been performed. Only a minor set of strains from Stockholm county was available for analysis, but exchange of information has taken place to elucidate the epidemic situation.

From this national strain collection and PFGE database it could be shown that the *Enterococcus faecium* with *vanB* gene causing the outbreak situation 2007-2009 had not been detected before 2007. It has been named SE-EfmB-0701 to indicate species (Efm), resistance gene (B), year of detection (07) and a serial number (01). Several smaller outbreaks in Sweden during 2000 – 2006 were caused by strains of different PFGE-types, and they have been given names accordingly. In 2010, one extensive outbreak has occurred in Västernorrland county, and the PFGE pattern of this strain was named SE-EfmB-1001.

Sporadic cases with *Enterococcus faecium* with *vanA* gene have been notified since 2000. PFGE analyses of those indicate that the majority are single cases with unique PFGE patterns. However, at least two small outbreaks occurred in 2010, caused by SE-EfmA-1003 in Norrbotten and SE-EfmA-1007 in Västmanland, Table 4.6.

Data on invasive isolates reported to ECDC/EARS-Net

Enterococcus faecalis and *Enterococcus faecium* have been reported to EARSS/EARS-Net since 2001 (Appendix 5). The main focus has been on vancomycin resistance, but also on high-level resistance to aminoglycosides (HLAR).

In 2003 the first four Swedish vancomycin-resistant invasive isolates of *Enterococcus faecium* were reported (2.2% of all), followed by three isolates (1.2%) in 2004, two isolates (0.3%) in 2006, five isolates (1.5%) in 2008, one isolate (0.4%) in 2009 and one isolate (0.3%) in 2010, Tables 4.7 and 4.8. Molecular typing of these vancomycin-resistant isolates showed that the isolates from 2008 all had the same PFGE pattern as the recent epidemic strain described above, whereas the others were singletons.

HLAR was more prevalent in *Enterococcus faecium* (21.8%) than in *Enterococcus faecalis* (14.5%) in 2010. This shift was seen already in 2008. From 2006 and onwards all laboratories who reported HLAR used gentamicin (GEN) as test disk for detection.

TABLE 4. 7. Resistance among invasive isolates of *Enterococcus faecalis* (number of strains and percentage). Data from Sweden 2001-2010 reported to ECDC/EARS-Net.

Year	Vancomycin-R (%)	HLAR (%)	Total number (number tested for HLAR 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)
2008	0	20.1	720 (703)
2009	0	19.6	718 (627)
2010	0	14.5	776 (687)

TABLE 4.8. Resistance among invasive isolates of *Enterococcus faecium* (number of strains and percentage). Data from Sweden2001-2010 reported to ECDC/EARS-Net.

Year	Vancomycin-R (%)	HLAR (%)	Total number (number tested for HLAR 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)
2008	1.5	24.8	333 (331)
2009	0.4	27.4	311 (274)
2010	0.3	21.8	339 (319)

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Streptococcus pyogenes

Annual Resistance Surveillance and Quality Control (RSQC) programme

Streptococcus pyogenes was not included in the RSQC programme in 2010.

Surveillance on invasive isolates additional to EARS-net

Data on consecutive blood isolates were obtained from 11 laboratories. One hundred and eighteen of 12.296 (1.0%) were *Streptococcus pyogenes* (GAS). This was in the same order of magnitude as in the previous three years with 1.8, 1.2 and 1.2% GAS, respectively. All GAS isolates were susceptible to penicillin. Two isolates (1.7%) were resistant to erythromycin and clindamycin, indicating that they possessed *erm* genes (MLS_B type of resistance). This was a slight decrease compared with 2.2% in 2009. Fifteen isolates (12.7%) were resistant to tetracycline which was similar to the previous three years (range 8.0 -14.6%). A majority of the isolates were retrieved from adults (> 50 years), and only 4.2% of the isolates were from children 0-9 years.

Streptococcus agalactiae

Surveillance on invasive isolates additional to EARS-net

166/12.296 (1.4%) of consecutive blood isolates from the participating 11 laboratories were *Streptococcus agalactiae* (GBS). This was in the same order of magnitude as the previous three years with 1.0, 1.3 and 1.1% GBS, respectively. All GBS isolates were susceptible to penicillin/ampicillin. Thirteen of the isolates (7.8%) were resistant to erythromycin, nine of those were also resistant to clindamycin. This indicates, but has not been confirmed, that the isolates harbour either *erm* genes (MLS_B type of resistance affecting both erythromycin and clindamycin) or *mef* genes (efflux-mediated resistance affecting only erythromycin). The figure for 2010 was comparable to those from the previous three years (range 6.5 - 8.8%). A majority of the isolates were retrieved from adults (> 50 years), but 22 (13.2%) were isolated from children less than 2 months, an increase from 2009 (9.2%). None of the isolates from newborns were resistant to erythromycin.

Haemophilus influenzae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Haemophilus influenzae was included in the RSQC programme on antibiotic resistance in 2010 as a follow-up to 2008 and 2009 when a marked increase in rates of penicillin-resistant and trimethoprim-sulfamethoxazole-resistant isolates was seen, Figure 4.12. In 2010, because of methodological changes (Appendix 4), only 20 laboratories provided data, and approximately 2400 isolates were included in the analysis. The methodological changes introduced made figures for betalactam resistance more difficult to interpret, and for penicillin the bars for 2008-2010 therefore represents betalactamase-positive isolates only, in contrast to the previous years. The average resistance rates, as retrieved from ResNet, are shown in Figure 4.12.

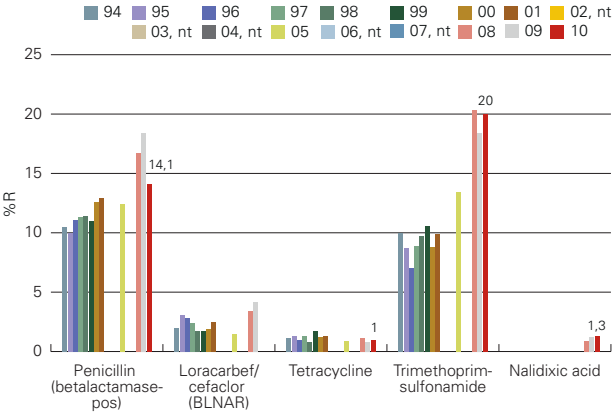

FIGURE 4.12. Resistance rates for *Haemophilus influenzae* 1994-2010 (data from the annual RSQC programme, approximately 3000 isolates per year). Penicillin resistance caused by betalactamase production only is shown for 2008-2010. Data for BLNAR 2010 was not available.

In 2010 the high rate of resistance remained for trimethoprim-sulfamethoxazole, but the rate of beta-lactamase-producing strains was slightly lower than in 2009. The data presented here should be considered preliminary and further investigations are needed. Tetracycline resistance in *Haemophilus influenzae* was still rare (approximately 1%). A few isolates with fluoroquinolone resistance, detected by the nalidixic acid screening disk, were found.

Surveillance on invasive isolates additional to EARS-Net

Of data on consecutive blood isolates from the participating 11 laboratories, 75/12.296 (0.6%) were *Haemophilus influenzae*. Two of these isolates were from cerebrospinal fluid. Only seven isolates (9.3%) were ampicillin-resistant and five of those were betalactamase-producing. This was much lower than the 20-25% betalactamase-producing isolates noted in the previous two years, but the observation that two blood isolates had chromosomally mediated beta-lactam resistance (BLNAR)

was new. Ten isolates (13.3%) were resistant to trimethoprim-sulfamethoxazole, comparable to the results in 2008 and 2009. A majority of the isolates were retrieved from adults (> 50 years), but 3 were isolated from children 0-9 years.

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Extended spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL)

Background

ESBL-producing *Enterobacteriaceae* became notifiable according to the Communicable disease act in February 2007. Notifications of ESBL-producing bacteria are limited to clinical laboratories. As a result, epidemiological information on ESBL cases is restricted to data on age, gender and cultured material while information on reasons for sampling or place of acquisition is not available. In 2007, Strama proposed an action plan with the aim that the proportion of *Escherichia coli* and *Klebsiella pneumoniae* producing ESBL in blood isolates should not exceed a maximum of 1%, respectively, and that ESBL-producing bacteria should not affect the current treatment recommendations for lower urinary tract infections. During 2009, a supplement to the action plan was published where the definition of ESBL was broadened, and the definition of an ESBL valid from 2010 now includes not only classical ESBLs which are inhibited by clavulanic acid (=$ESBL_A$) but also plasmid-mediated AmpC-betalactamases (= $ESBL_M$) and metallo-betalactamases / carbapenemases (= $ESBL_{CARBA}$).

All Swedish clinical microbiology laboratories were requested to report ESBL according to the new definition from January 2010, either as $ESBL_A$, $ESBL_M$ or $ESBL_{CARBA}$.

Notifications according to the Communicable Disease Act

A total of 4983 cases were notified during 2010, an increase with 33% compared with the 3754 cases in 2009. Reports came from all 21 counties of Sweden, corresponding to a national incidence of 53 cases per 100 000 inhabitants, Figure 4.13. Almost all Swedish counties had an increased incidence, the highest incidence 2010 found in Jönköping county (114 cases per 100 000 inhabitants).

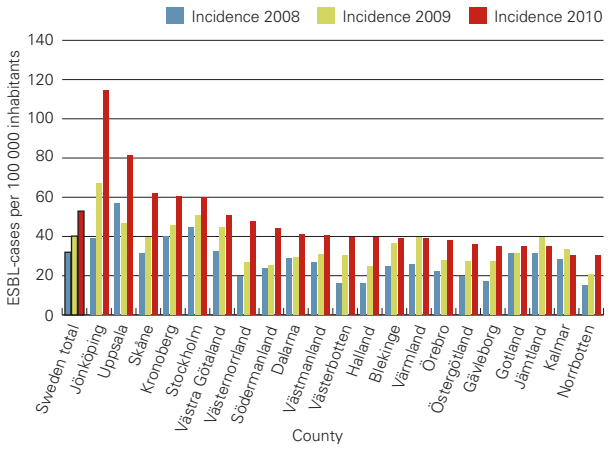

FIGURE 4.13. The incidence of ESBL in Swedish counties 2008-2010, arranged according to incidence 2010.

The most commonly reported species with ESBL was *E. coli*, accounting for 81% of all cases, followed by *K. pneumoniae* with 8%, Table 4.9.

TABLE 4.9. Distribution of species among cases of ESBL-producing bacteria 2010.

Escherichia coli	4167
Klebsiella pneumoniae	412
Proteus mirabilis	31
Citrobacter species	32
Salmonella species	17
Miscellaneous *Enterobacteriaceae*	241
Species not reported	240
Total number reported	5140*

* In 137 patients two or more ESBL-producing species were reported resulting in a higher number of isolates than number of cases reported.

ESBL-producing bacteria were detected in urine samples in 65% of the cases. The second most common source was faecal samples with 15%. Isolates from rectum and wound samples constituted 5.5% and 3% respectively, and blood isolates 3% of the cases. Invasive infections with ESBL-producing bacteria, all in blood and cerebrospinal fluid, were notified in 225 persons during 2010, as compared with 186 persons (all in blood) in 2009. Among these, 204 were new cases for 2010 and 21 were known carriers of ESBL, notified during the previous year.

The type of ESBL according to the extended definition was reported only in 9% of all cases. Out of those 9 %, 346 cases were of $ESBL_A$-type and 98 cases of $ESBL_M$-type. Seven cases were reported as $ESBL_{CARBA}$. In 6 cases more than one type of ESBL was reported.

The incidence in age groups and gender differed between species and is shown in Figures 4.14 and 4.15. ESBL-producing *E. coli* were derived from women in 68% of all *E. coli* cases. They had a median age of 53 years compared with 62 years for men. The *K. pneumoniae* ESBL cases were equally distributed between sexes, with median ages of 63 years both for women and men.

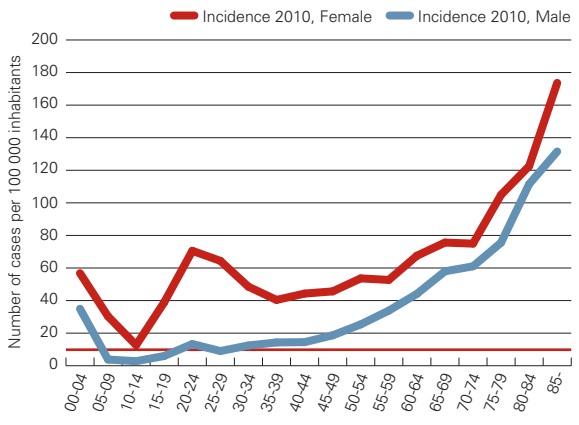

FIGURE 4.14. Age and gender distribution of E.coli ESBL cases 2010.

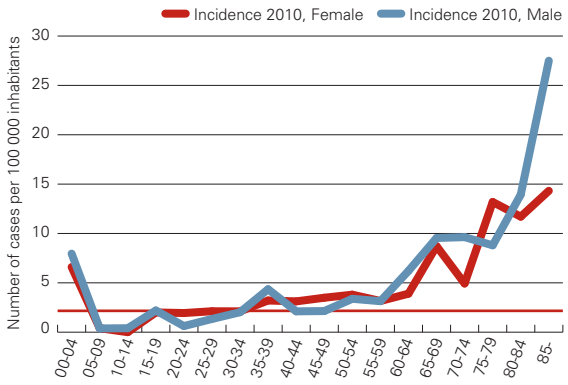

FIGURE 4.15. Age and gender distribution of *K. pneumoniae* ESBL cases 2010.

Carbapenemases, the most recent threat

The nation-wide problem with ESBL-producing bacteria in Sweden continues to be a larger problem than MRSA, both in numbers of cases and severity of infections. Concomitant resistance to several other antibiotics in many isolates (data not shown) limits the options for treatment. As described above there are several types of ESBLs, and their common feature is that they confer resistance to broad-spectrum cephalosporins.

Betalactamases which also affect carbapenem antibiotics, so called carbapenemases, pose an even greater threat because they limit the treatment options even further. Carbapenemases as we know them today are of two kinds, either KPC (*K. Pneumoniae* Carbapenemase) or MBLs (Metallo-BetaLactamases). Both types are included in $ESBL_{CARBA}$ according to the newly extended definition of ESBL.

In Sweden to date we have encountered 18 cases of $ESBL_{CARBA}$. In 2007 the first isolate of *K. pneumoniae* with KPC-2 was detected, and later there have been another 3 cases with KPC-2 and 5 cases with KPC-3. All these were healthcare related and probably acquired either in Greece or Italy.

Six cases of *K. pneumoniae* or *E. coli* carrying a VIM-enzyme, one of the most common types of MBLs, have also been notified, and again there is a relation to countries around the Mediterranian.

Particularly alarming is the world-wide emergence of the recently described MBL named NDM-1 (New Delhi Metallo-betalactamase). In Sweden there have been three cases so far, all with connections to India or Pakistan.

All isolates with $ESBL_{CARBA}$ were also multiresistant, leaving very few 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 national surveillance program several times since 1996 and every year since 2001. Resistance to commonly prescribed oral antibiotics for treatment of urinary tract infections (UTI) has been tested each year. The number of isolates tested by each laboratory was increased from 100 to 200 from 2006 in order to achieve data that would be statistically more valid for trend analyses. In 2010, because of methodological changes (Appendix 4), only 20 laboratories provided data, and approximately 4000 isolates were included in the analysis. The average resistance rates to ampicillin have increased yearly, from 17 to 30%, Figure 4.16. A similar trend has been seen for trimethoprim, for which the rates have increased from 10 to 20%. Fluoroquinolone resistance, detected by the nalidixic acid screening disk since 2002, has also increased during this period and is now close to 13%. Resistance to cephalosporins (cefadroxil tested), although much less prevalent than ampicillin resistance, has continued to increase and reached 3.5% already in 2009. This data is a mirror of the increasing incidence of ESBL-producing bacteria as seen from the notified cases (above) and reports to EARS-Net (below). Also for nitrofurantoin there has been a slight increase in resistance rate, although from a much lower level than for the other antibiotics. Nitrofurantoin resistance is possibly associated with some strains of ESBL-producing *E. coli*, thereby explaining the concomitant increasing resistance rates.

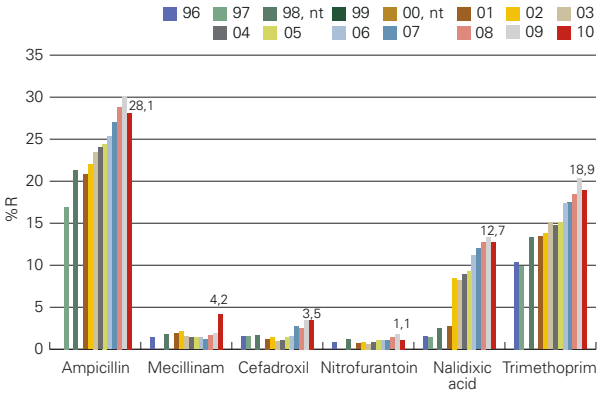

FIGURE 4.16. Resistance rates for UTI antibiotics in *E. coli* 1996-2010. Between 1996-2001 fluoroquinolone resistance was detected with norfloxacin, from 2002 and onwards with nalidixic acid.

Extended RSQC programme 2009

In 2009 the RSQC programme was extended by asking all laboratories to collect consecutive cefadroxil-resistant (R < 13 mm) isolates of *E. coli* and *K. pneumoniae* during a one-month period and send them to SMI for further analysis. The final result for *E. coli* in this investigation is summarised here. A total of 344 *E. coli* were collected and tested with phenotypic and genotypic methods. 78% of the collected isolates had $ESBL_A$, 5% had $ESBL_M$, and 16% had no ESBL-activity. Among the ESBL, CTX-M belonging to group 1was most prevalent (78%), followed by CTX-M group 9 (22.5%), CTX-M group 2 (0.7%) and SHV (1.5%). *E. coli* isolates with $ESBL_M$ harboured plasmid-mediated AmpC-enzyme of the type CIT (originating from *Citrobacter* species).

Data on invasive isolates reported to ECDC/EARS-Net

Escherichia coli derived from invasive infections (blood isolates) have been part of the European Antimicrobial Resistance Surveillance System (EARSS/EARS-Net) since 2001. The surveillance system has focused on resistance to beta-lactam

antibiotics, especially ESBL, and on resistance to aminoglycosides and fluoroquinolones. Results for 2001-2010 are presented in Table 4.10.

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 tested in the RSQC programme, 34% versus 28%. However, the data for blood isolates was incomplete since one third of participating laboratories did not include ampicillin in susceptibility testing of invasive isolates. The 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 cefalosporins among blood isolates was 3.2% in 2010, thus a small increase from 3% in 2009. In the majority of the cefotaxime-R isolates resistance was attributed to the presence of ESBLs of CTX-M type.

Aminoglycoside resistance in *E. coli* has shown an increasing trend for the last couple of years and reached 4.5% in 2010. Resistance genes coding for aminoglycoside resistance often co-exist with genes coding for ESBL enzymes and other resistance markers which make these bacteria multiresistant.

Reduced susceptibility and resistance to fluoroquinolones (I+R) has increased every year, but was found to be slightly lower in 2010 (14%) than in 2009 (15.5%).

TABLE 4.10. Resistance among invasive isolates of *Escherichia coli* (number of strains and percentage). Data from Sweden 2001-2010, reported to ECDC/EARS-Net.

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
2008	31.9	1.9 / 0.4	2.2	14.3	4028
2009	32.8	3	3.7	15.5	4423
2010	34	3.2	4.5	14	4991

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

Klebsiella pneumoniae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Klebsiella pneumoniae is one of the most important bacterial species from a hospital infection control point of view. It has been included in the RSQC programme and in EARSS/EARS-Net since 2005.

As for *E. coli*, the RSQC 2010 programme for *K. pneumoniae* was mainly focused on urine samples, Figure 4.17. Resistance to commonly prescribed oral antibiotics for treatment of urinary tract infections was tested in 2010, but because of methodological changes (Appendix 4), only 20 laboratories provided data, and approximately 2000 isolates were included in the analysis. The results indicated that the levels of resistance to all tested antibiotics were the same or slightly lower than in 2009.

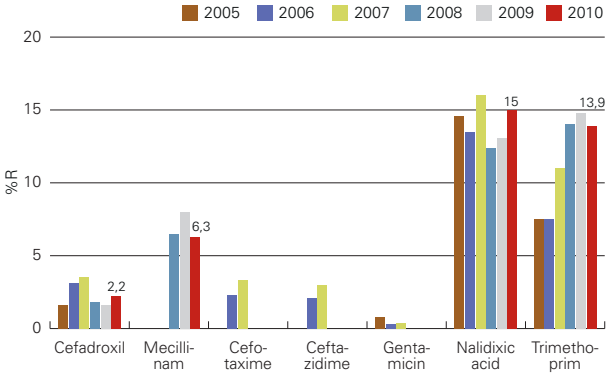

FIGURE 4.17. Resistance rates (resistant isolates in percent of all *Klebsiella pneumoniae* Isolates) for UTI antibiotics 2005-2010.

Extended RSQC programme 2009

In 2009 the RSQC programme was extended by asking all laboratories to collect consecutive cefadroxil-resistant (R < 13 mm) isolates of *E. coli* and *K. pneumoniae* during a one-month period and send them to SMI for further analysis. The final result for *K. pneumoniae* of this investigation was the following: a total of 20 *K. pneumoniae* were collected and tested with phenotypic and genotypic methods. Only $ESBL_A$ was found, represented by CTX-M group 1 (78%), CTX-M group 9 (5%), and SHV (17%).

Data on invasive isolates reported to ECDC/EARS-Net

Klebsiella pneumoniae derived from invasive infections (blood isolates) have been included in the European Antimicrobial Resistance Surveillance System (EARSS/EARS-Net) since July 2005. All cephalosporin resistance was caused by ESBLs of CTX-M type. The rate of aminoglycoside resistance increased whereas fluoroquinolone resistance decreased in 2010.

TABLE 4.11. *Klebsiella pneumoniae* from blood cultures in Sweden 2005-2010, reported to EARSS/EARS-Net. The data for 2005 represent six months from 20 laboratories. From 2006 and onwards the data represent the entire years from 19 laboratories.

Year	Cefotaxime-R (ESBL)	Aminoglycoside-R (%) *	Fluoroquinolone-I/R (%) **	Total number of isolates
2005 (half year)	1.4	1.4	9.8	281
2006	1.5	0.3	8.5	610
2007	1.4	1.1	10.8	649
2008	2.3	1.1	12.9	826
2009	1.8	1.0	12.2	755
2010	2.3	2.0	8.5	908

*gentamicin or tobramycin, ** ciprofloxacin

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Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pseudomonas aeruginosa was reentered in the RSQC programme on antibiotic resistance in 2009.

Laboratories were asked to test 100 consecutive isolates of *P. aeruginosa* with the exclusion of respiratory isolates. Resistance to the tested antibiotics showed fluctuating but low levels of resistance over the years, Figure 4.18. Aminoglycosides (gentamicin and tobramycin) seemed stable around 1%, ceftazidime resistance was slowly increasing but still below 5%, carbapenems (imipenem and meropenem) were at the 5%-level except for the higher rate of 7.7% for imipenem resistance in 2010, and ciprofloxacin seemed stable around 10%.

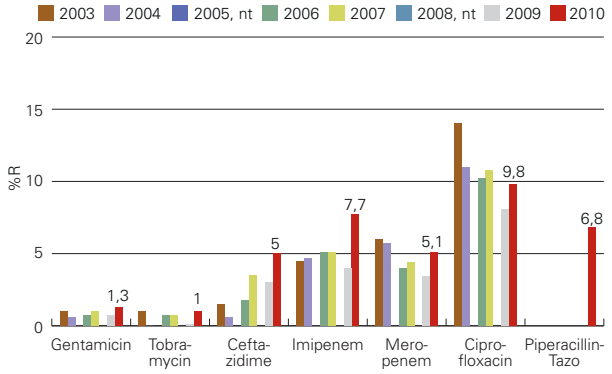

FIGURE 4.18. Resistance rates (resistant isolates in percent of all *Pseudomonas aeruginosa* isolates) for four groups of antibiotics 2003-2010. Data were not collected in 2005 and 2008.

Data on invasive isolates reported to ECDC/EARS-Net

Pseudomonas aeruginosa derived from invasive infections (blood isolates) have been included in the European Antimicrobial Resistance Surveillance System (EARSS/EARS-Net) since July 2005. From Sweden a total of 149 isolates from 20 laboratories were tested during the second half of 2005, and these data are compared with complete data sets for 2006-2010 in Table 4.12. The levels of resistance to beta-lactam antibiotics (ceftazidime and carbapenems) were in the range 3-7% for all five years. No change in resistance rates had occurred for fluoroquinolones (10.5%), but aminoglycoside resistance at 3% was a new finding. This level was higher compared with the RSQC data (see above) and should be investigated further.

TABLE 4.12. *Pseudomonas aeruginosa* from blood cultures in Sweden 2005-2010, reported to EARS-Net.
* imipenem, meropenem, ** gentamicin, tobramycin, *** ciprofloxacin

Year	Ceftazi-dime-R (%)	Carbape-nem-R (%) *	Amino-glyco-side-R (%) **	Fluoro-quino-lone-I/R (%) ***	Total number of isolates
2005 (half year)	4.7	Insuffi-cient data	0	9.0	149
2006	2.6	4.4	0.5	10.4	296
2007	4.5	7.0	0	10.4	342
2008	5.1	4.0	0	8.1	282
2009	3	7.5	0	10.1	352
2010	3.2	6.7	3	10.5	389

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Clostridium difficile

The *Clostridium difficile* surveillance programme in Sweden

A national surveillance programme for *Clostridium difficile* was initiated by the Swedish Institute for Communicable Disease Control (SMI) in 2009. The programme included both a voluntary laboratory reporting system of all new cases of *C. difficile* infection (CDI) through SmiNet2 and a determination of resistance and epidemiological typing of isolates from the clinical microbiology laboratories. All *C. difficile* strains isolated during weeks no. 11 and 39 were sent to SMI for typing by PCR ribotyping and antibiotic susceptibility testing. Primarily metronidazole and vancomycin resistance was monitored, i.e. the recommended treatment choices for CDI. However, since use of antibiotics is a risk factor for acquiring CDI we also tested susceptibility to other antibiotics as an indicator of selective pressure, currently moxifloxacin, clindamycin and erythromycin. All isolates were tested using Etest on Mueller Hinton agar.

Distribution of resistant *Clostridium difficile* isolates in 2010

In the national surveillance programme 2010 a total of 334 isolates from 25/28 laboratories were characterised, which is slightly lower than the 364 isolates from all 28 laboratories collected in 2009. No isolate was resistant to metronidazole or vancomycin, i. e. the recommended choices for treatment of CDI. The proportion of *C. difficile* isolates resistant to moxifloxacin, clindamycin, erythromycin was 16%, 17% and 20%, respectively, Table 4.13. These numbers were comparable to those found in 2009, and most resistant isolates were associated with four types: PCR ribotype 012, 017, 046 and 231/SE37. However, there were more susceptible isolates of type 046 found in 2010 than in 2009, and the proportion of resistant isolates of this type thus decreased. Of other resistant isolates, type 078 was often associated with resistance to these antibiotics. Similar to what was found in 2009, *C. difficile* isolates with

combined resistance to all three antibiotics were clustered in geographical regions ($p < 0.001$, Fisher's exact test), Figure 4.19. Also, as found in 2008 and 2009, the extent of moxifloxacin use was not uniform in Sweden, Figure 4.20. There was an overall positive correlation between the rate of moxifloxacin use and the proportion of moxifloxacin resistant isolates (not shown). However, it is important to stress that such correlations must be confirmed in a case-control study to exclude confounding factors.

TABLE.4.13. *Clostridium difficile* types resistant to erythromycin, clindamycin and moxifloxacin in Sweden 2010 (n=334). R- Breakpoints were as follows: moxifloxacin MIC > 4, clindamycin MIC > 16 and erythromycin MIC > 2. MIC = Minimum inhibitory concentration.

PCR ribotype	no. of isolates tested	moxifloxacinR	clindamycinR	erythromycinR
012	26	19	21	21
017	6	4	4	4
046	18	8	6	6
231/SE37	6	4	4	4
Other	278	18	23	31
Total	334	53	58	66

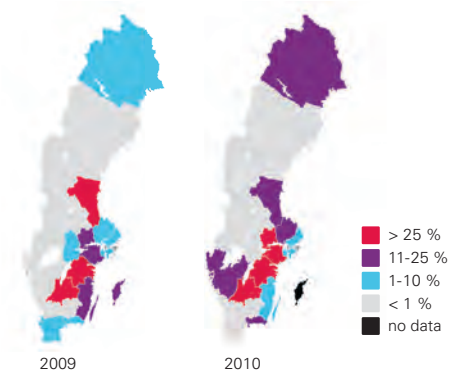

FIGURE 4.19. Proportion of *Clostridium difficile* isolates with combined resistance to erythromycin, clindamycin and moxifloxacin per county 2009-2010.

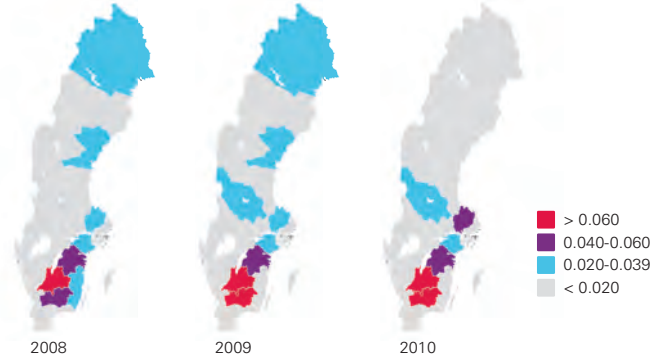

FIGURE 4.20. Sales of moxifloxacin in Sweden 2008-2010 per county. Numbers indicate DDD/1000 inhabitants and day.

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Helicobacter pylori

Annual Resistance Surveillance and Quality Control (RSQC) programme

Helicobacter pylori derived from gastric biopsies has not until 2001 been included in the annual RSQC programme but has been monitored locally at a few laboratories. In vitro resistance to metronidazole has been reported in 10-40 % of Scandinavian isolates. Resistance to clarithromycin is less common (3 %) but is increasing and has locally at one laboratory reached over 10% for three years in a row. Frequencies of resistance to clarithromycin and metronidazole in clinical isolates from southwest of Sweden are presented in Table 4.14, representing a population of approximately 300 000. Resistance to tetracycline is less than 1 % and resistance to amoxicillin has only been described in a few strains and only outside Scandinavia.

TABLE 4.14. Resistance rates of *Helicobacter pylori* lested at University Hospital MAS, Malmö, Sweden 1994-2010, %R

Year	Total number	Clarithromycin %R	Metronidazole %R
1994	536	1.0	29.0
1995	588	2.9	32.1
1996	381	3.9	35.2
1997	331	7.7	39.8
1998	116	6.7	34.3
1999	149	6.1	33.1
2000	216	7.8	30.5
2001	188	8.8	40.2
2002	124	9.0	44.1
2003	112	7.2	42.6
2004	151	11.6	41.0
2005*	217	11.2	nt
2006	257	16.0	nt
2007	375	9.8	nt
2008	156	5.2	nt
2009	151	10.6	nt
2010	175	15.9	nt

* Molecular biology technique from 2005

Mats Walder

Salmonella and *Shigella* spp

Annual Resistance Surveillance and Quality Control (RSQC) programme

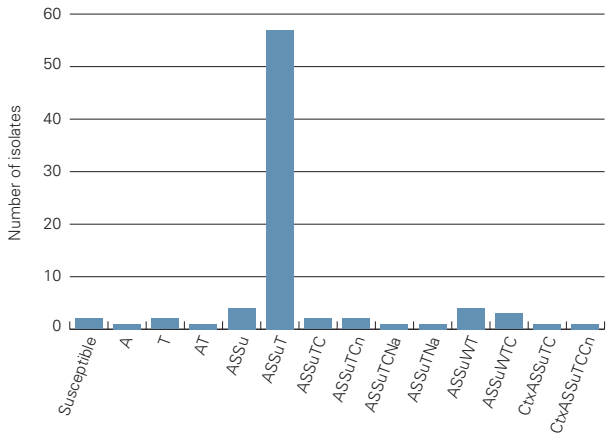
Salmonella spp. and *Shigella* spp. derived from faecal cultures were not included in the annual RSQC programme until 2002 but have been monitored locally by a few laboratories. Since most of the *Salmonella* and more than 90% of the *Shigella* strains isolated in Sweden originate from tourists returning home, the resistance patterns reflect the geographical origin. Too few strains are included in the Swedish survey to obtain conclusive results. However fluoroquinolone resistance is high, between 20-25%, among *Salmonella* strains, and between

15-20% among *Shigella* spp. The fluoroquinolone resistance is not only seen in ESBL producing strains.

Antibiotic resistance in domestic *Salmonella* serovar

This specific serovar of *Salmonella* is also referred to as monophasic Typhimurium. The serovar lacks the second phase H antigen and it seems to increase in importance both domestically and internationally. This new emerging serotype is also associated with multiresistance. In 2010 it was the third most common serotype in Sweden. In a specific project at SMI in 2010, domestic isolates (n=82) that were sent to the laboratory for typing were also analysed for antibiotic resistance. Susceptibility testing by disk diffusion was performed according to the European guidelines (EUCAST). The tested antibiotics were chosen because of clinical and epidemiological relevance but also with regard to the panel of antibiotics tested by the veterinarians (SVARM report), in order to make data comparable. The antibiotics included were ampicillin (A), cefotaxime (Ctx), nalidixic acid (Na), gentamicin (Cn), streptomycin (S), chloramphenicol (C), tetracycline (T), trimethoprim (W) and sulphonamides (Su).

Only 3% were susceptible to all antibiotics tested. 69% of the tested isolates had the R-profile ASSuT. This profile is the most common reported also internationally. Furthermore, 19% were resistant to ≥ 5 of the tested antibiotics, Figure 4.21.



FIGUR 4.21. Antibiotic resistance in domestic Salmonella serovar 2010. A=ampicillin, Ctx=cefotaxime, Na=nalidixic acid, Cn=gentamicin, S=streptomycin, C=chloramphenicol, T=tetracycline, W=trimethoprim, Su=sulphonamides.

Cecilia Jernberg, Cecilia Svensson, Mats Walder

Campylobacter spp

Annual Resistance Surveillance and Quality Control (RSQC) programme

Campylobacter spp. derived from patients with diarrhoea were not included in the annual RSQC programme until 2001 but has been monitored locally at a few laboratories. Approximately 50% of *Campylobacter* strains are imported. Since resistance to fluoroquinolones is of major concern worldwide it is interesting to notice that the small decline in quinolone resistance among *Campylobacter* isolates noticed a few years ago has now regained the former level of about 50%. 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*, Table 4.15.

TABLE 4.15. Campylobacter jejuni/coli, University Hospital MAS, Malmö, Sweden,1995-2010, %R

Year	Nalidixic acid	Ciprofloxacin	Tetracycline	Erythromycin
1995		22	27	4
1997		23	30	3
1998		34	33	2
1999		45	35	1
2000		55	45	1
2001	32	30	28	1
2002	29	28	30	0,5
2003	48	46	22	0
2004	50	47	29	2
2005	57	52	18	1
2006	50	44	21	4
2007	49	45	31	7
2008	65	62	36	7
2009	57	52	21	1
2010	50	48	26	8

Mats Walder

Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable infection/disease and in 2010, 842 cases (8.94 cases per 100 000 inhabitants) of the infection were reported. Most of the cases were identified in the three largest counties of Sweden, which comprise the cities Stockholm, Gothenburg, and Malmö, respectively. Clinical isolates are in the present report described from the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Swedish Institute for Infectious Disease Control [SMI]), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, Örebro and Karolinska University Hospital, site Huddinge and site Solna, Stockholm.

In 2010, in total 618 *N. gonorrhoeae* strains from the notified cases were completely characterised at these laboratories, representing more than 70% of the notified cases.
Susceptibility testing was performed according to 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) and The European Committee on Antimicrobial Susceptibility Testing (EUCAST; http://www.eucast.org). Production of betalactamase was examined by using Nitrocefin discs.

TABLE 4.16. Antibiotic resistance rates (%) and betalactamase production of Swedish *Neisseria gonorrhoeae* strains from 2005 to 2010. * for cefixime, ceftriaxone and azithromycin, new SIR breakpoints were introduced in 2009 and the results from previous years have been recalculated.

	2005 (n=497)	2006 (n=352)	2007 (n=406)	2008 (n=447)	2009 (n=384)	2010 (n=618)
betalactamase pos.	23	30	30	28	44	29
Ampicillin	23	30	30	28	44	31
Cefixime*	0	0	<1	1	5	6
Ceftriaxone*	0	0	0	<1	0	2
Azithromycin*	<1	5	7	13	6	12
Ciprofloxacin	49	61	70	63	75	56
Spectinomycin	0	0	0	0	0	0

Results for 2010 are compared with those from 2005 to 2009 in Table 4.16. Notable, the levels of resistance to all antimicrobials previously used in the traditional gonorrhoea treatment (penicillins and ciprofloxacin) are exceedingly high. The levels of resistance to azithromycin, cefixime, and in 2010 also to ceftriaxone have substantially increased the recent years.

Magnus Unemo, Hans Fredlund

Neisseria meningitidis

Notifications according to the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease and in 2010 a total of 68 clinical cases of the disease were reported. All together 56 clinical isolates (one per patient) from blood or cerebrospinal fluid (one per patient) were analysed at the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Swedish Institute for Communicable Disease Control), Department of Laboratory Medicine/ Clinical Microbiology, Örebro University Hospital.

Susceptibility testing was performed according to standardized methodology using Etest on Mueller Hinton II agar with 5% horse blood and NAD for determinations of MICs of bensylpenicillin, cefotaxime, meropenem, chloramphenicol, ciprofloxacin and rifampicin. Production of betalactamase was examined by Nitrocefin discs.

None of the isolates produced betalactamase. Eight isolates (14%) had reduced susceptibility to bensylpenicillin (MIC>0.064 mg/L). All isolates had MICs of cefotaxime ≤0.016 mg/L, all had MICs of ciprofloxacin ≤0.008 mg/L except one with 0.125. The range of meropenem MICs was 0.004-0.032 mg/L, chloramphenicol MICs 0.25-2 mg/L, and rifampicin MICs ≤0.5 mg/L.

Reduced susceptibility to ciprofloxacin is mediated primarily by mutations in the *gyrA* gene, resulting in low-level resistance. By DNA sequencing of the *gyrA* gene one of the previously described substitutions threonine to isoleucine at position 91 (T91I) was identified in the isolate with MIC 0.125.

Per Olcén

Mycobacterium tuberculosis

During 2010 in total 683 cases of tuberculosis (TB) were reported compared with 642 cases during 2009 which is an increase of 6%.

The number and proportion of culture confirmed cases were 527(77%) in 2010 compared with 515(80%) in 2009. *Mycobacterium tuberculosis* was identified in 524 cases, *Mycobacterium africanum* in one patient and *Mycobacterium bovis* in two patients. In three of the cultures with confirmed *M. tuberculosis* it was not possible to do a drug resistance test due to poor growth of the strain. The proportions of cases diagnosed with isoniazid resistant TB in 2010 were 10.9% (57/523) and MDR 3.4% (18/523).

Isolates of *M. tuberculosis* and *M. africanum* resistant to at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) were identified in 68 patients corresponding to 13% of the 523 with culture confirmed TB, see Table 4.17. The two patients with *M. bovis* were not included since these strains are naturally resistant to pyrazinamid. As always the most common resistance found was against isoniazid. Among the patients born in Sweden 10.1% (8/76) had resistant TB and 5 of these were resistant to isoniazid. More than 85% of the TB patients in Sweden are born in another country. In this group 13.4% (60/447) had some kind of resistant TB and 18 of those 60 had MDR-TB, which is 4.0% (18/447). Six percent (34/523) of the culture confirmed cases had a history of previous treatment for TB after 1949 since when effective medication has been available. Out of these 34 cases 35.3% (12/34) had strains resistant to any of the first line drugs including 20.6% (7/34) MDR-TB. The corresponding figures for cases with no reported previous treatment were 11.4% (56/489) out of which 2.2% (11/489) were MDR-TB.

None of the 18 cases of MDR-TB were born in Sweden. One lives in Sweden since 1992 but frequently spends long periods in his native country. The majority (15/18) came to Sweden 2007 or later. In total 14 of the 18 cases had pulmonary manifestations among whom nine were smear positive.

Genetic typing with RFLP (restriction fragment length polymorphism) has been performed on 56 of the 70 resistant strains so far. The typing of the remaining 14 is ongoing. This is done to help detect clusters which could indicate ongoing spread of resistant strains. Thirty-one of the 56 examined strains belong to 24 different clusters with two or more patients in each cluster. For two patients there is a close geographical connection and for two others a close family connection. The majority of the clustering cases belong to clusters with no resistant strains which make recent spread unlikely, the common factor in the cluster most often being the same country of origin.

The proportion of patients with *M. tuberculosis* resistant against isoniazid has gradually increased from an annual average of 5% during the 1990 to 9% in the period 2000–2006 and then to 12.7% in 2007. Since then the proportion has dropped and is now 10.9 %. In parallel the annual proportion of MDR-TB increased from 0.8% in 2006 to 4.2% in 2007, dropped in 2009 but increased again to 3.4% in 2010. The increase in the number of cases from Somalia has continued but the proportion of resistant TB in this group is similar to immigrants from the rest of the world during 2010.

Jerker Jonsson

TABLE 4.17. Drug resistant *Mycobacterium tuberculosis* in Sweden 2001-2010.

Year of diagnosis	**2002**		**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**		**2010**	
Culture confirmed *M. tuberculosis* or *M. africanum*	346		345		368		448		395		361		434		510		523	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Any resistance	36	10,4	32	9,3	43	11,7	52	11,6	43	10,9	49	13,6	57	13,1	58	11,4	68	13,0
Isoniazid	34	9,8	26	7,5	35	9,5	46	10,3	38	9,6	46	12,7	51	11,8	51	10,0	57	10,9
Rifampicin	4	1,2	10	2,9	6	1,6	5	1,1	6	1,5	15	4,2	15	3,5	14	2,7	20	3,8
Ethambutol	1	0,3	5	1,4	3	0,8	3	0,7	1	0,3	7	1,9	6	1,4	7	1,4	12	2,3
Pyrazinamid	4	1,2	7	2,0	12	3,3	6	1,3	6	1,5	11	3,0	18	4,1	15	2,9	20	3,8
Isoniazid + rifampicin (MDR)	4	1,2	8	2,3	5	1,4	4	0,9	3	0,8	15	4,2	14	3,2	13	2,5	18	3,4

Appendix 1 – Abbreviations

ABU	Asymptomatic bacteriuria
AST	Antibiotic susceptibility testing
ATC	The Anatomical Therapeutic Chemical classification system
BLNAR	Betalactamase negative ampicillin resistant
CDCDC	County Department for Communicable Disease Control
DDD	Defined daily dose
DST	Drug susceptibility testing
EARSS/ EARS-Net	European Antimicrobial Resistance Surveillance System/Network
ESBL	Extended spectrum beta-lactamase
GAS	Group A streptococci or *Streptococcus pyogenes*
GBS	Group B streptococci or *Streptococcus agalactiae*
ICU	Intensive care unit
MDR	Multidrug resistance
MIC	Minimal Inhibitory concentration
MRB	Multiresistant bacteria
MRSA	Methicillin resistant *Staphylococcus aureus*
PFGE	Pulsed-field gel electrophoresis
PNSP	Penicillin non-susceptible pneumococci, MIC ≥ 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
SSTI	Skin and soft tissue infection
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
TB	Tuberculosis
UTI	Urinary tract infection
VRE	Vancomycin resistant enterococci
UK-NEQAS	United Kingdom National External Quality Assessment Service

Appendix 2 – Demographics and denominator data

TABLE APP 2.1.Population by county and age group, December 31st 2010.

	0-6 y	7-19 y	20-59 y	60-79 y	80 -	All ages
Stockholm	187909	303100	1111516	331577	85080	2019182
Uppsala	27569	51726	177067	60538	14998	331898
Södermanland	21025	42844	131341	58826	15017	269053
Östergötland	33239	66754	219361	84187	23565	427106
Jönköping	26974	55137	167462	66480	19991	336044
Kronoberg	14373	28616	91987	37096	11090	183162
Kalmar	15858	35694	113205	53790	15092	233639
Gotland	3803	8912	28326	12894	3286	57221
Blekinge	11394	22680	74969	34312	9236	152591
Skåne	101499	184085	643656	235726	66096	1231062
Halland	24312	48479	146720	60823	16491	296825
Västra Götaland	126715	240405	822707	296856	82775	1569458
Värmland	18955	41407	134898	60754	17243	273257
Örebro	21355	43653	140137	57705	16032	278882
Västmanland	19091	39256	125535	53283	14188	251353
Dalarna	19886	42804	133956	62402	17406	276454
Gävleborg	19719	42048	134997	62702	16754	276220
Västernorrland	18059	36461	118040	55699	14783	243042
Jämtland	9454	18914	62553	27695	8050	126666
Västerbotten	19453	39620	133693	51970	13812	258548
Norrbotten	17074	37664	124349	56532	13400	249019
Sweden	757716	1430259	4836475	1821847	494385	9340682

TABLE APP 2.2. Population in Sweden 2000-2010. Numbers represent the population by December 31st the previous year.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Population	8861265	8882831	8909322	8940744	8975669	9011391	9047803	9113297	9182923	9256347	9340682

TABLE APP 2.3. Number of admissions and patient-days in somatic medical care, 2009. Numbers represent production by hospitals in the counties.

	Patient-days	Admissions
Stockholm	1 104 604	266223
Uppsala	320 163	61145
Södermanland	194 289	39164
Östergötland	292 144	66165
Jönköping	250 113	53433
Kronoberg	138 968	25919
Kalmar	167 430	39542
Gotland	42 331	9686
Blekinge	114 912	22109
Skåne	939 300	190235
Halland	193 422	42428
Västra Götaland	1197030	243021
Värmland	189 633	38275
Örebro	231 717	49674
Västmanland	206178	36818
Dalarna	209 067	47828
Gävleborg	199981	43449
Västernorrland	170 565	36818
Jämtland	91 857	17996
Västerbotten	284 796	52149
Norrbotten	185 390	38447
Sweden	6 723 890	1420524

TABLE APP 2.4. Denominator data from the microbiological laboratories. NP = test not performed. NA = data not available.

	Number of analyses 2010									Number of positive samles 2010	Number of positive cultures 2010				
Laboratory	**Blood (pair of bottles)**	**Cerebro-spinal fluid (CSF)**	**Nasopharynx**	**Throat**	**General culture**	**Screen MRB**	**Urine**	**Faeces SSYC**	**Faeces *Clostridium difficile* (toxin)**	**Blood (pair of bottles**	***Staphylococcus aureus***	***Streptococcus pneumoniae***	***Streptococcus pyo-genes***	***Escherichia coli***	***Clostridium difficile* (toxinpositive)**
Borås	15968	154	3983	3460	6599	1693	25535	6382	1967	2583	4354	710	580	7072	197
Eskilstuna (Unilabs)	10597	213	6195	4088	9014	1578	24629	4890	2536	1320	4036	720	661	5976	337
Falun	15673	404	3340	2087	10414	2840	27380	4145	1815	1691	4565	548	515	7423	299
Gävle	11102	185	2323	1031	9312	2031	23377	3286	1725	1478	4050	473	401	7237	157
Göteborg	34850	1442	2926	3134	18466	37148	71160	12900	4497	5024	9657	740	743	16884	856
Halmstad	10475	156	2246	2339	8843	10087	23692	5343	1807	1418	3333	428	514	6665	241
Karolinska Stockholm	70549	3346	29113	9698	71242	213387	140083	20471	10986	9075	26860	3182	2843	37008	1306
Jönköping	17208	190	3945	3466	13814	18758	35200	6700	2848	2289	6118	594	824	10152	740
Kalmar	9949	180	3496	2549	7186	9532	26627	4310	1392	1256	4193	501	538	7707	216
Karlskrona	5532	56	1355	1798	5243	1200	14505	2461	1492	636*	2042	225	371	4150	341
Karlstad	14859	124	1504	2458	11181	5747	32367	3838	1731	1293	5345	351	441	8448	210
Linköping	19548	1000	5569	3433	17477	8660	38479	6786	3933	3388**	6780	636	678	9895	761
Lund	36935	1523	16409	11170	35648	24448	99445	18332	6770	5166	14706	2654	2019	25604	905
Malmö	23240	299	5455	6131	14938	53023	63532	11644	4114	2880	9531	1330	1176	16151	542
Aleris Medilab	648	0	10222	5081	10559	17320	41314	8855	1445	88	4417	1071	959	9753	257
St:Göran (Unilabs)	8184	151	7139	3899	14197	36483	39516	8536	4161	1042	5836	724	979	10968	141
Skövde (Unilabs)	10334	125	2838	2870	10576	7673	42644	6168	2161	1311	4626	382	544	9767	322
Sunderby Luleå	8884	144	1883	2962	8136	3286	26990	3422	1485	NA	3104	390	447	7818	276
Sundsvall	10427	167	2548	1611	7236	6129	26240	3832	1904	1483	3998	453	440	7585	232
NÄL Trollhättan	16817	172	1714	2485	8434	5597	34563	4537	1553	1911	4361	345	397	9347	186
Umeå	14266	530	3629	2506	6052	7825	33592	3578	1654	1461	4500	503	621	9499	123
Uppsala	19870	855	5605	2577	15026	13979	33721	5766	3457	2177	5507	661	607	8995	791
Visby	3644	337	2028	484	2597	NP	6496	1121	651	80	1136	264	151	2037	70
Västerås	11040	163	2291	1862	9719	11995	27999	4736	1698	1543	3784	245	384	7994	300
Växjö	7494	101	2082	1820	6419	2898	19992	3222	1415	942	2952	342	463	5306	160
Örebro	15858	265	9353	1909	14704	5680	33162	4752	2514	1551	5989	1091	593	8019	238
Östersund	6789	100	2278	1333	7809	3621	16141	2566	867	354	2853	359	413	5418	100
Total	430740	12382	141469	88241	360841	512618	1028381	172579	72578	49416	158633	19922	19302	272878	10304

*number of positive samples

**not pair

MRB = multiresistant bacteria

SSYC = Salmonella, Shigella, Yersinia and Campylobacter spp.

Appendix 3 – Surveillance of antibiotic consumption

Sources of data

Data on sales of antibiotics in outpatient care is obtained from Apotekens Service AB, the core infrastructure supplier for all pharmacies in Sweden. Measures used are defined daily doses per 1000 inhabitants and day (DDD/1000 and day) and prescriptions per 1000 inhabitants. Every purchase of a medicine prescribed in outpatient care is also recorded in the Prescribed Drug Register, held by the Swedish National Board of Health and Welfare. This register provides the opportunity to link each prescription to an individual, which makes it possible to investigate the actual number of individuals or the fraction of the population treated with a specific medicine.

Antibiotic use in hospital care is measured as DDD/1000 and day and DDD/100 patient-days or 100 admissions to hospitals. The number of DDDs is obtained from Apotekens Service AB and from local medicines statistics systems in the counties. The National Board of Health and Welfare has provided data on patient-days and admissions to hospitals.

When this report is compiled, data on patient-days and admissions in 2010 is not available. Therefore, data from 2009 is used. The number of patient-days and admissions represent production of somatic medical care by each county (to be distinguished from consumption of the county's inhabitants). This gives a more accurate comparison of antibiotic use in hospitals, since the amount of medicines used is related to the quantity of medical care produced.

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 Apotekens Service 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 and 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. Out-patient care data includes 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 and day or number of prescriptions/1000 inhabitants. Hospital care data includes drugs delivered by all hospital pharmacies to the hospital departments. The system also produces sales statistics for each hospital department and on national and county sales to hospitals. The sales are expressed as cash value, number of packages and number of defined daily doses.

Following the re-regulation of the pharmacy market in Sweden in July 2009, the responsibility for collection of medicines statistics was transferred to the core infrastructure supplier for all pharmacies, Apotekens Service AB.

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 outpatient 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 and 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. Since data for 2010 is not available until August denominator data from 2009 and sales data from 2010 are used in some figures in this report. The number of admissions and patient-days in Swedish medical care 2009 is shown in Appendix 2, Table App 2.3. The National Board of Health and Welfare keeps a searchable database at the web, http://www.socialstyrelsen.se/statistik.

Appendix 4 – Antibiotic Susceptibility testing

The **agar or broth dilution methods** are the reference methods in Swedish susceptibility testing to which other methods are compared. Clinical microbiological laboratories in Sweden have 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** (intermediate) and **R** (resistant).

The disk diffusion method has been successfully standardized by the Swedish clinical microbiology laboratories in collaboration with the SRGA-M. Up til 2009 all laboratories used the methodology based on ISA medium and a semi-confluent bacterial inoculum as recommended by SRGA-M. From 2010 several laboratories have already adopted to the new European method as described by EUCAST, based on Mueller Hinton agar and an almost confluent inoculum (equivalent to a 0.5 McFarland turbidity standard). This disk diffusion method is used as the routine method for susceptibility testing. It is also used 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 (e.g. betalactam resistance in pneumococci, chromosomally mediated betalactam resistance in *Haemophilus influenzae*), and still in others by methods for enzyme detection (e.g. beta-lactamase detection in *Haemophilus influenzae* and *Neisseria gonorrhoeae*).

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 (preferably on a daily basis) 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 and www.eucast.org). External quality control is often done by participation in UK-NEQAS and/or other international programmes, whereas quality assurance is one of the features of the Swedish "100-strains or RSQC programme".

Appendix 5 – National surveillance of antibiotic resistance

Surveillance regulated in the Communicable Disease Act

Statutory notifications of certain communicable diseases are regulated in the Communicable Disease Act (SFS 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 (smittskyddsläkare) and to the Swedish Institute for Communicable 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 colonisation) with different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with bensylpenicillin 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, SmiNet2. At the SMI, the clinical and laboratory notification for each case are merged and checked for errors. If data are missing, contact persons in the counties are asked to supplement the information. As an important complement to the notifications, the MRSA, VRE and PNSP isolates are sent to SMI for epidemiological typing. For MRSA *spa*-typing is the primary typing method, for VRE it is pulsed-field gel electrophoresis (PFGE), and for PNSP serotyping. Depending on needs also other molecular biology methods are used, e.g. MLST.

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 feedback of notification data is done monthly on the SMI homepage (http://www.smi.se) and yearly in "Communicable Diseases in Sweden – the Yearly Report (in Swedish)" 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 at present 28 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 defined set of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. Since 2001 *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* 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 aggregated data from the laboratories and, following approval of registered data by one of two web administrators, instantly display it in the form of resistance frequencies on the geographical areas on a map 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 turned into EARS-Net

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 performed 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.

During 2009 a transition of the EARSS management from RIVM in the Netherlands to ECDC in Stockholm was prepared, and from 1st January 2010 the network, renamed as EARS-Net, is coordinated from ECDC.

Data collected by EARS-Net should be routinely generated quantitative data (MICs or inhibition zones), but the data presented is in the format of susceptibility cathegories (SIR). External quality assurance exercises have so far been carried out by EARSS/EARS-Net in cooperation with UK-NEQAS once every year. Results of those exercises have shown that participating laboratories were capable of delivering good quality susceptibility data, indicating that the overall resistance rates as monitored through EARSS/EARS-Net are accurate. Although not perfect, this network of networks forms a solid base for surveillance of resistance and is constantly extended and improved.

The participation from twenty laboratories in Sweden is coordinated through the SMI, where electronic data collection, validation and verification of specific resistance mechanisms are performed. 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 EARS-Net.

Surveillance of invasive isolates additional to EARS-Net 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 at present 4.1 millions, thus representing more than 40% of the Swedish population. From these laboratories data for the pathogens specified by the EARS-net network are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In the SWEDRES reports from 2007 to2010 data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* are presented.

Sentinel surveillance

Susceptibility testing of gastrointestinal pathogens such as *Salmonella*, *Shigella*, *Campylobacter* spp. 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.

Appendix 6 – Recent publications (2008-2010)

3. Use of antibiotics

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Guidelines

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Websites

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