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A Report on Swedish Antimicrobial Utilisation and Resistance in Human Medicine

Strama
Swedish Strategic Programme against Antibiotic Resistance

SMITTSKYDDSINSTITUTET
Swedish Institute for Infectious Disease Control

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

Strama

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

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Editors:
Ulrica Dohnhammar and Barbro Olsson-Liljequist

Address:
Swedish Institute for Infectious Disease Control
SE 171 82 Solna, Sweden
Phone: +46 8 457 23 00
Fax: +46 8 30 06 26
E-mail: smi@smi.se
www.smi.se
www.strama.se

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Björn Lundquist AB, Malmö

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Edita Västra Aros AB

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Content

1. Preface

WELCOME to the eight 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.

In 2009 Strama published three suggested national targets for antibiotic prescriptions in outpatient care. The total number of prescriptions should not exceed 250 prescriptions per 1000 inhabitants per year, the proportion of fluoroquinolones prescribed for female urinary tract infections (UTI) in ages 18-79 years should not exceed 10 % and penicillin V should constitute 80% of all prescriptions of antibiotics primarily used for respiratory tract infections (RTI) in children 0-6 years. Sales statistics showed that there are great variations in the country with regard to these indicators and that the overall prescription, despite decreasing by 6%, still is too high, the average being 392 prescriptions/1000 inhabitants and year. The average proportion of fluoroquinolones in UTI-treatment of women was 16% and that of PcV in RTI-treatment of children was 64%. This shows that work still remains to be done to improve compliance to existing recommendations.

The situation with regard to antibiotic resistance is becoming increasingly worrisome year by year. A major problem is that it is difficult to assess the burden antibiotic resistance is causing, but several deaths related to ESBL-producing *enterobacteriaceae* are known to have occurred. A nationwide outbreak of vancomycinresistant *Enterrococcus fecium van*B is still ongoing since 2007, albeit at a lower intensity. The number of community acquired MRSA infected domestically is increasing and the number of reported cases with ESBL-producing *enterobacteriaceae* has almost doubled since notification was introduced 2007. Of particular concern are reports of a few cases infected with *Klebsiella* producing carbapenemases or metallobetalactamases.

While much attention has been given to improve hospital staff's compliance to basic hygiene during the last decade, similar attention needs to be given to antibiotic stewardship and compliance to therapeutic recommendations. The zoonotic potential, including risk for transmission through the food chain of some resistance genes calls for continued and strengthened intersectorial collaboration between authorities and stakeholders in human and veterinary medicine.

2.1 Summary

Use of antibiotics

After several years of small changes, 2009 showed a marked decrease (5.5%) in sales of antibiotics. The number of prescriptions per 1000 inhabitants in outpatient care was much lower in the last quarter of the year, compared with the same period in previous years. The decrease encompasses all age groups, all counties and almost all antibiotics. The greatest reduction was seen in the age group 0-6 years where the sale decreased with 17.2%. Several reasons have been suggested in the analysis of this decrease, one of the major being the increased awareness in infection control issues and hand hygiene evoked by the outbreak of the pandemic influenza 2009. Many daycare centers have also developed hygiene curricula after initial studies of the use of hand sanitizers showing promising results with less absence due to sickness.

30% of all children aged 0-6 years were treated with at least one course of antibiotics in 2009. Ten percent of all purchases of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years, are followed by an additional course within 14 days.

Beta-lactamase sensitive penicillins together with tetracyclines are the most commonly used antibiotics in outpatient care. Treatment of respiratory tract infections has been the subject of information campaigns last year and this is reflected in the sale of antibiotics commonly used to treat respiratory tract infections. Doxycycline is the most frequently used tetracycline and a substance mainly used to treat respiratory tract infections. The total sale of tetracyclines decreased in 2009 and the seasonal variation was less pronounced.

Treatment of lower urinary tract infections in women has been the subject of information campaigns for several years. The total proportion of the two first line recommended substances increased for every year and represents nearly 70% of the sale of antibiotics commonly used to treat urinary tract infections in this group in 2009.

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 continues and is in fact even more pronounced in 2009. However, there are still large differences between counties in this aspect. 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

During the past five years we have seen the arrival of many new antifungal drugs. The total amount of antifungals used in hospitals have only increased with 10%, but there is a shift from narrowspectrum drugs such as fluconazole towards broadspectrum drugs like the echinocandins and late generation azoles. This development becomes even more evident if we also confer prescriptions of voriconazole och posaconazole to hospital use. The total amount of antifungals in hospitals is still low, 55 DDD/10^6 inhabitants and day, but with increasing reports of resistance and a shift towards non albicans species it is important to closely monitor both resistance and consumption of antifungals, both at a national and a local level.

Antibiotic resistance

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

Staphylococcus aureus: A total of 1480 cases of MRSA were notified in 2009, a 13% increase compared to 1307 cases in 2008. Almost half of the reported cases (48%, n=711) had acquired MRSA in Sweden, and one-third (35%, n=517) had acquired the infection abroad. Eight of the Swedish counties had an incidence of notified MRSA cases above the average country incidence of 15.8 cases/100 000 inhabitants. Community-acquired infections dominated among domestic cases (64%) but were less frequent among imported cases (38%). Hospital-acquired infections were comparatively more common in imported cases (41%) than among domestic cases (12%), indicating continued good compliance to basal hygiene principles.

Invasive isolates of MRSA were as few in 2009 (n=18) 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 EARSS.

Epidemiological typing of all MRSA isolates is performed primarily by spa-typing. The five most commonly encountered spa-types in 2009 were t008 (n=157), t044 (n=108), t002 (n=106), t019 (n=59) and t015 (n=58), comprising one third of all isolates. The prevalence of MRSA with PVL toxin was 34% 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 betalactam antibiotics and to three or more other categories of antibiotics, was a rare phenomenon. Most cases could be correlated to six 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 antibiotics in > 95% of

cases. The fusidic acid resistant strain causing bullous impetigo, which has spread all over Sweden during the last decade, seems to decline and the epidemiology is described in detail.

Streptococcus pneumoniae: In 2009 there were 446 notifications of PNSP (*Streptococcus pneumoniae* with MIC of penicillin ≥ 0.5 mg/L) in Sweden, a decrease by 21% compared with 2008. PNSP have decreased in annual incidence (cases per 100 000 population) from around 10 in 1997 to values between 5 and 7 since 2007. 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 14 cases the PNSP isolates came from invasive sites, i.e. blood and/or spinal fluid. 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, 23F, 9V, 19A, and 6B.

For five antibiotics tested on *Streptococcus pneumoniae* in the yearly RSQC programme 2009 the rates of resistance were slowly increasing, 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 than in the nasopharyngeal isolates from the RSQC programme, and in 2009 also resistance to macrolide antibiotics was lower, 3.2% compared to 4.6-5.7% in 2001-2008.

Enterococcus faecalis and *Enterococcus faecium*: Enterococci, and more specifically vancomycin-resistant enterococci (VRE), have been important causes of nosocomial outbreaks in many parts of the world, but have until 2007 been rare in Sweden. In 2007 there were 53 notified cases, in 2008 618 cases, and in 2009 402 cases of VRE. These high notification rates were attributable to the spread of *van*B-carrying *Enterococcus faecium* not only in Stockholm county, but also in the counties of Halland and Västmanland. Intensive infection control efforts, implementation of screening programmes, contact tracing, and also other measures undertaken have contributed to the reduction in new cases in 2009. The strain of *Enterococcus faecium* with the *van*B gene, affecting all three counties, was a new strain according to epidemiological typing using PFGE.

There were only four new cases of invasive vancomycin-resistant *Enterococcus faecium* in 2009. Of those four, only one was reported from an "EARSS-laboratory", thus resulting in 0.8% as reported to EARSS. In this case there was no connection to the widely disseminated new Swedish strain, neither geographically nor by epidemiological typing. Among invasive isolates of both *Enterococcus faecalis* and *Enterococcus faecium* high-level resistance to aminoglycosides (HLAR) was more common with 20% and 25%, respectively.

Streptococcus pyogenes: Data were obtained on 134 invasive isolates in 2009 (data derived from eleven laboratories using ADBact laboratory information system). Three isolates (2.2%) were resistant to erythromycin and clindamycin, indicating resistance caused by *erm* genes. Thirteen isolates (9.7%) were resistant to tetracycline, a marked decrease compared to 2008 when 14.6% of the isolates were resistant.

Streptococcus agalactiae: Data were obtained on 131 invasive isolates in 2009 (data derived from eleven laboratories using ADBact laboratory information system). Nine isolates (6.9%) were resistant to erythromycin and clindamycin, a figure similar to those from 2006-2008.

Haemophilus influenzae: Data were obtained in the RSQC programme in 2009 and was compared to results from 2008. In 2009 the high frequencies of resistance remained with 23.3% for penicillins (including both beta-lactamase producing strains, BLPAR, and chromosomally mediated resistant strains, BLNAR) and 18.4% for trimethoprim-sulfamethoxazole. The frequency of BLNAR alone had increased from 3% to 4.2%. Betalactam-resistant strains from all laboratories and from both 2008 and 2009 were selected for further analysis. Co-resistance between trimethoprim-sulfamethoxazole and betalactams was more frequent among BLNAR than among BLPAR strains. Preliminary data on epidemiological typing of these selected strains also indicated a wide variety of strains and not a clonal dissemination of one strain. *Haemophilus influenzae* was rarely found among blood isolates, only 49 cases in 2009 derived from eleven laboratories using ADBact laboratory information system. Ten of these (20.4%) were beta-lactamase producing, and seven were resistant to trimethoprim-sulfamethoxazole.

Enterobacteriaceae producing extended spectrum beta-lactamases (ESBL) were made notifiable by the laboratories from February 2007. A total of 3754 cases were notified during 2009. Reports came from all 21 counties of Sweden, corresponding to a national incidence of 40 cases per 100 000 inhabitants. When comparing the second halfs of 2008 and 2009, respectively, a 27% increase of ESBL cases was noted for 2009. The most commonly reported species was *Escherichia coli* with 82% of all cases, followed by *Klebsiella pneumoniae* with 7%. Most ESBLs were found in urine samples (69%). 186 cases of invasive infections with ESBL-producing bacteria were noted in 2009. 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 included in the EARSS network 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 (33% and 30%) in 2009. The level of resistance to third generation cephalosporins among blood isolates has increased to 3%, 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 (13.3 vs. 15.5%) in 2009.

Klebsiella pneumoniae has also been monitored in the RSQC

programme and through the EARSS network since 2005. The rates of resistance to tested antibiotics were comparable between the two surveillance programmes. Almost 2% of *Klebsiella pneumoniae* were cephalosporin resistant and ESBL-producing, thus no increase from 2008. In 2007 the first isolate of *K. pneumoniae* with KPC-2 (*K. pneumoniae* carbapenemase) was detected in Sweden. In 2008 one isolate with a KPC-3 betalactamase was identified, and in 2009 there were reports of three isolates in Stockholm, one identified as KPC-2 and two as KPC-3. All the cases were healthcare related.

Pseudomonas aeruginosa has been monitored in the RSQC programme and through the EARSS network since 2005. The rates of resistance to tested antibiotics were comparable between the two surveillance programmes, but carbapenem resistance was more frequent in invasive isolates (7.5%) than among "all" isolates in the RSQC surveillance (4%). Fluoroquinolone resistance was approximately 10%.

A national surveillance program for *Clostridium difficile* was initiated by SMI in 2009. The program included both a voluntary laboratory reporting system of all new cases and determination of resistance and epidemiological typing of collected isolates. On isolates from 25 laboratories, collected during weeks 11 and 39, susceptibility tests and PCR ribotyping was performed. Type 014 was most frequent followed by types 020, 001, 023, 078 and 012. One isolate of type 027 was detected; however this isolate was susceptible to moxifloxacin, which is otherwise a typical marker for the virulent type 027 that has spread world-wide. In summary, there was geographical clustering of certain *C. difficile* types that were also resistant to several antibiotics.

Helicobacter pylori have been monitored locally at a few laboratories, but consistent data was only retrieved from one laboratory (University Hospital MAS, Skåne). Following a steady increase since 1994 and a peak of 16% in 2006, the rate of resistance to clarithromycin was 10.6% in 2009. In *Campylobacter jejuni/coli* 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.

Neisseria gonorrhoeae. Gonorrhoea is a notifiable disease, and in 2009 611 cases of the disease were reported. Isolates from 387 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 63% of the notified cases. In 2009 44% of these isolates were beta-lactamase producing and ampicillin resistant, and 75% were resistant to ciprofloxacin.

Mycobacterium tuberculosis. The total number of new cases of TB diagnosed in Sweden 2009 were 642, an increase of 16% compared with 2008. The numbers of cases diagnosed with isoniazid resistant TB in 2009 were 38/515 (7,4%) and with MDR-TB 13/515 (2,5%). Genetic typing with RFLP (restriction fragment length polymorphism) was completed on 50 of the 58 resistant strains of *Mycobacterium tuberculosis* or *M. africanum* and is ongoing on the remaining 8. Sixteen of the 50 examined isolates belong to 12 different clusters with two or more patients in each cluster.

2.2 Sammanfattning

Antibiotikaförbrukning

Efter flera år av små skillnader i antibiotikaförsäljningen minskade försäljningen markant (6 %) under 2009. I öppenvården var antalet recept mycket lägre under sista kvartalet 2009 jämfört med samma månader föregående år. Minskningen omfattar alla åldrar, alla län och de flesta preparaten. Barn 0-6 år är den åldersgrupp som uppvisar störst minskning (17,2%) av antibiotikaförsäljning under 2009. Många orsaker kan ligga bakom den minskade antibiotikaförsäljningen. En trolig orsak som diskuteras i analysen är den ökade medvetenheten om infektionsspridning som väckts av informationskampanjer under våren 2009 på grund av den nya influensan. Många förskolor har också skaffat sig goda hygienvanor efter studier som visar på mindre sjukfrånvaro vid användning av handsprit.

30 % av alla barn 0-6 år behandlades med minst en antibiotikakur under 2009. I 10,3 % av alla köp av luftvägsantibiotika till barn 0-6 år köptes en ny kur av luftvägsantibiotika inom 14 dagar.

Betalaktamaskänsliga penicilliner och tetracykliner är de antibiotika som oftast förskrivs på recept. Behandling av luftvägsinfektioner har varit i fokus för informationsaktiviteter senaste året vilket avspeglas i försäljningsstatistiken. Doxycyklin är den tetracyklin som förskrivs mest och en substans som oftast används mot luftvägsinfektioner. Under 2009 minskade den totala försäljningen av tetracykliner och säsongsvariationen av doxycklin minskade kraftigt.

Behandling av nedre urinvägsinfektioner hos kvinnor har varit i fokus för informationsinsatser under flera år. Andelen av de två rekommenderade förstahandspreparaten ökar för varje år och utgör nästan 70% av förskrivningen av antibiotika som ofta används vid urinvägsinfektioner.

Senaste åren har antibiotikaanvändningen i slutenvården växlat från ett stort användande av cefalosporiner till ett ökat användande av smalspektrumantibiotika. Trenden fortsätter och är under 2009 ännu tydligare. Trots detta ses en stor skillnad mellan länen.

Förbrukning av svampmedel

Under de senaste fem åren har utbudet av systemiska läkemedel mot svampinfektioner ökat, och man har sett en ökad användning av främst echinocandinerna, men också av de nyare azolerna. Den totala förbrukningen har ökat med 10 % sedan 2006, men det finns en tendens att smalspektrumantimykotika, dvs flukonazol minskar och att bredspektrumantimykotika tar motsvarande andel. Denna utveckling ses än tydligare om man även inkluderar receptförsäljning av voriconazole 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 55 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

Vissa former av antibiotikaresistens anmäls enligt smittskyddslagen men den frivilliga rapporteringen av resistensdata från de svenska kliniskt mikrobiologiska laboratorierna utgör basen för resistensövervakningen. Alla laboratorier deltar i den årliga insamlingen av data till ResNet, och tre fjärdedelar av laboratorierna bidrar också med data avseende de invasiva isolat som definierats av EARSS. För vissa mikroorganismer sammanställs data av laboratorier med referensfunktion och/eller med speciellt intresse för dessa arter (till exempel *Neisseria*-arter). I denna rapport presenteras resistensdata från 2009 och analyseras tillsammans med föregående års data.

Staphylococcus aureus: Totalt 1480 fall av MRSA anmäldes 2009, en ökning med 13 procent från 2008 då 1307 fall noterades. Nästan hälften av fallen hade blivit smittade i Sverige (711 fall), och en tredjedel (517 fall) hade blivit smittade utomlands. I åtta län/regioner var incidensen av MRSA-fall högre än riksgenomsnittet (15,8 fall per 100 000 invånare). Antalet invasiva isolat av MRSA var lika få 2009 (n=18) som föregående år, vilket medför att Sverige fortfarande är ett av de få länder i Europa som ännu ej nått nivån 1 procent av alla invasiva *Staphylococcus aureus* enligt rapportering till den europeiska resistensövervakningen EARSS.

Från och med 2006 har spa-typning utgjort den primära typningsmetoden. De fem vanligast förekommande spa-typerna var t008 (n=157), t044 (n=108), t002 (n=106), t019 (n=59) och t015 (n=58). Förekomsten av MRSA med PVL-toxin var 34 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. Detta gällde även fusidinsyra, beroende på att den tidigare spridda fusidinsyra-resistenta stammen som orsakade bullös impetigo kraftigt har minskat.

Streptococcus pneumoniae: Under 2009 noterades 446 fall med nedsatt känslighet för penicillin (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 5-7 sedan år 2007. De flesta fallen identifierades genom nasofarynxodling. Majoriteten av PNSP-fallen var i åldersgruppen 0-4 år. I 19 fall påvisades PNSP från blod och/eller spinalvätska. Multiresistens (resistens mot penicillin och minst två ytterligare antibiotika) var vanlig hos PNSP. De vanligast förekommande serotyperna/grupperna var 19F, 23F, 9V,19A och 6B. Enligt data rapporterade i ResNet sågs en långsam ökning av resistens mot testade antibiotika. Frekvensen PNSP var lägre hos invasiva isolat än hos nasofarynx-isolat, och detta gällde även frekvensen makrolidresistens som var 3,2 procent jämfört med tidigare års 5-6 procent.

Enterococcus faecalis och *Enterococcus faecium*: Enterokocker, särskilt de med resistens mot vankomycin (VRE), har varit frekvent förekommande vid sjukvårdsrelaterade utbrott i många delar av världen och har ofta omfattat riskpatienter. Från att ha varit ovanliga i Sverige, indikerade ökningen av anmälda fall 2007 ett skifte. Under 2008 rapporterades 618 fall och 2009 402 fall. Det stora antalet fall kunde tillskrivas förekomst och spridning av en *van*B-innehållande *Enterococcus faecium* som uppträdde inte enbart i Stockholm utan också i Halland och Västmanland. Intensiva vårdhygieniska åtgärder, kontaktspårning och screening är alla faktorer som har medverkat till att antalet nya fall 2009 ändå har minskat. Genom epidemiologisk typning med PFGE framkom att den aktuella VRE-stammen sannolikt inte hade förekommit i Sverige före 2007. Endast fyra invasiva VRE har noterats 2009, och av dessa var det bara ett som ingick i rapportering till EARSS 2009 vilket då gav 0,8 procent resistens. Hos invasiva isolat av både *Enterococcus faecalis* och *Enterococcus faecium* förekom också höggradig aminoglykosidresistens (HLAR), i 20 respektive 25 procent av isolaten.

Streptococcus pyogenes: Data för 134 invasiva isolat, erhållna från elva ADBact-laboratorier under 2009, visade något ökad förekomst av makrolid-resistens, 2,2 procent jämfört med 0,5 procent 2008. Tetracyklinresistensen var lägre 2009 (10 procent) än 2008 (15 procent).

Streptococcus agalactiae: Data för 131 invasiva isolat, erhållna från elva ADBact-laboratorier under 2009, visade att 7 procent var makrolid-resistenta, vilket var samma nivå som 2006-2008.

Haemophilus influenzae: Data från övervakningen i ResNet, som genomfördes 2008 och 2009 efter ett uppehåll på tre år, visade på en kraftigt ökad förekomst av betalaktamas-producerande (ampicillin-resistenta) isolat och också av trimetoprim-sulfa-resistenta isolat. Siffrorna är nu på nivån runt 20 procent. Andelen cefalosporinresistenta (ej betalaktamasproducerande) utgjorde cirka 4 procent av alla betalaktamresistenta. Preliminära resultat på utvalda isolat som typats med PFGE visar att det förekommer flera olika resitenta stammar, ofta med bara lokal spridning.

Haemophilus influenzae var ett sällsynt fynd bland invasiva isolat, och endast 49 fall fanns registrerade från de elva ADBakt-laboratorierna 2009. Tio av dessa var betalaktamas-producerande (20 procent), och sju var resistenta mot trimetoprim-sulfa.

Enterobacteriaceae som producerar betalaktamaser med utvidgat spektrum, så kallade ESBL, blev anmälningspliktiga i februari 2007. Totalt 3754 fall rapporterades under 2009. Samtliga landsting rapporterade, och den genomsnittliga incidensen i Sverige (fall per 100 000 invånare) var 40. Vid jämförelse mellan andra halvåret 2009 med samma period 2008 noterades en 27-procentig ökning av fall 2009. De flesta isolaten återfanns i urinprover (69 procent) och var *Escherichia coli* (82 procent), och de hade oftast ESBL av CTX-M-typ. Multiresistens var ett vanligt fynd hos dessa isolat.

Escherichia coli, huvudsakligen från urinvägsinfektioner, har övervakats enligt det nationella programmet (ResNet) sedan 1996, och blodisolat har inkluderats i EARSS sedan 2001. Ampicillinresistens, oftast orsakad av plasmidmedierad betalaktamasproduktion av TEM-typ, återfanns i ökande utsträckning både hos blodisolat och urinisolat 2009 (33 procent och 30 procent). Frekvensen blodisolat med resistens mot 3:e generationens cefalosporiner var 3 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 t ex aminoglykosider och kinoloner. Resistens mot kinoloner har ökat årligen och var hos både blodisolat och urinisolat 13-15 procent 2009.

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 KPC-2 i Sverige, under 2008 ytterligare ett, och under 2009 har tre KPC-producerande isolat påträffats. I samtliga dessa fall fanns en bakomliggande historia med sjukvård i södra Europa.

Hos *P. aeruginosa* var karbapenemresistensen vanligare hos invasiva isolat (7,5 procent) än hos övriga (4 procent), och kinolonresistensen var generellt cirka 10 procent.

Helicobacter pylori har övervakats regelbundet vid ett laboratorium. Resistens mot klaritromycin har ökat stadigt under flera år men från 2007 och framåt har en minskning skett till 11 procent 2009.

Hos *Campylobacter jejuni/coli* 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 2009 rapporterades 611 kliniska fall. Isolat från 387 (63 procent) av dessa har undersökts vid det svenska referenslaboratoriet i Örebro eller vid laboratoriet för klinisk bakteriologi, Karolinska Universitetssjukhuset Huddinge, Stockholm. 2009 var 44 procent av isolaten beta-laktamasproducerande och därmed ampicillinresistenta, och 75 procent var resistenta mot kinoloner (ciprofloxacin testat).

Mycobacterium tuberculosis. Antalet anmälda nya fall av tuberkulos var 642 under 2009, en ökning med 16 procent från 2008. *M. tuberculosis* med resistens mot minst två antibiotika (MDR-TB) rapporterades hos 2,5 procent av alla odlingsverifierade fall(13/515). Epidemiologisk typning med RFLP av de resistenta TB-isolaten visade att de tillhörde 12 olika kluster med två eller fler patienter i varje.

2.3 Contributors

Otto Cars, Strama,
otto.cars@strama.se

Ulrica Dohnhammar, Strama,
ulrica.dohnhammar@strama.se

Charlotta Edlund, Medical Products Agency,
charlotta.edlund@mpa.se

Petra Edquist, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
petra.edquist@smi.se

Jesper Ericsson, Strama,
jesper.ericsson@strama.se

Hans Fredlund, Communicable Disease Control, National Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital,
hans.fredlund@orebroll.se

Christian Giske, Department of Clinical Microbiology, Karolinska University Hospital, Solna,
christian.giske@ki.se

Henrik Hallin, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
henrik.hallin@smi.se

Jenny Hellman, Strama,
jenny.hellman@strama.se

Birgitta Henriques Normark, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
birgitta.henriques@smi.se

Sven Hoffner, Department of Bacteriology, Swedish Institute for Infectious Diseases Control,
sven.hoffner@smi.se

Jerker Jonsson, Department of Epidemiology, Swedish Institute for Infectious Disease Control,
jerker.jonsson@smi.se

Gunnar Kahlmeter, National Reference Laboratory for Antibiotic Resistance, Central Hospital, Växjö Hospital,
gunnar.kahlmeter@ltkronoberg.se

Christer Norman, Strama,
christer.norman@strama.se

Per Olcén, National Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Clinical Microbiology, University Hospital,
per.olcen@orebroll.se

Barbro Olsson-Liljequist, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
barbro.liljequist@smi.se

Ulf Persson, Medical Products Agency,
ulf.persson@mpa.se

Cecilia Svensson, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
Cecilia.svensson@smi.se

Johan Struwe, Department of Epidemiology, Swedish Institute for Infectious Disease Control,
johan.struwe@smi.se

Tomas Söderblom, Department of Epidemiology, Swedish Institute for Infectious Disease Control,
tomas.soderblom@smi.se

Karin Tegmark Wisell, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
karin.tegmark-wisell@smi.se

Magnus Unemo, National Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital,
magnus.unemo@orebroll.se

Mats Walder, Department of Clinical Microbiology, Malmö University Hospital,
mats.walder@mikrobiol.mas.lu.se

Thomas Åkerlund, Department of Bacteriology, Swedish Institute for Infectious Disease Control,
thomas.akerlund@smi.se

Strama's group for analysis of antibiotic sales data: **Ingrid Brännström, Jonatan Dahlqvist, Mats Erntell, Maria Grünewald, Mikael Hoffmann, Pinelopi Lundquist** and **Christer Norman**.

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Data on antibiotic use in relation to number of admissions and number of patient days in somatic hospital somatic care during 2006-2009 have kindly been provided by pharmacists in local Strama-groups.

Rickard Ljung and **Pinelopi Lundquist**, The National Board of Health and Welfare, has kindly provided individually based data on the use of antibiotics.

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. Most people living in nursing homes still get their medicines by prescription, and data on this consumption are managed as outpatient care. However, there are also nursing homes where medicines are bought by the institution and then dispensed to the residents. That consumption is not included in outpatient statistics but in hospital care. 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 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.

Total sales of antibiotics

Due to the large decrease of antibiotic use in outpatient care, the total use of antibiotics in Sweden was 6% lower in 2009 than in 2008, Table 3.1.1.

Outpatient care

The number of prescriptions on antibiotics in outpatient care decreased with 7.4% in 2009. This is the greatest decrease since 1995 calculated as a percent. The decrease encompasses all age groups and is most evident among the youngest children, Figure 3.1.4. Over the last two decades, antibiotic prescribing to this age group has shown a significant change. After the 40% decrease between 1992 and 1997 sales have continued to decline, albeit at a slower pace.

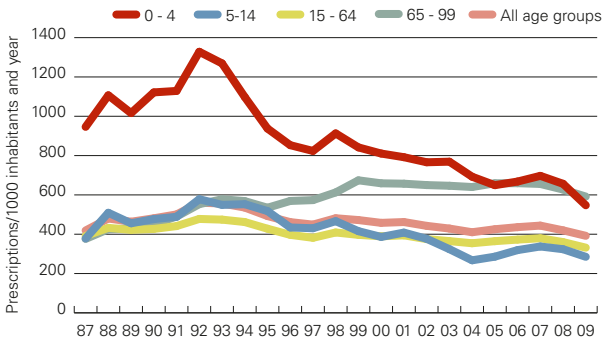

FIGURE 3.1.4. The sales of antibacterial drugs for systemic use in outpatient care 1987-2009, different age groups, prescriptions/1000 inhabitants and year.

Seasonal variations in antibiotic use have been less pronounced during the last years and this trend continues in 2009. This could be regarded as an indicator of good quality in prescribing, Figure 3.1.5.

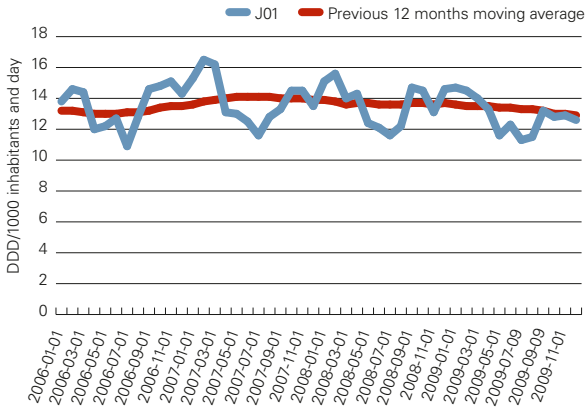

FIGURE 3.1.5. Antibiotics in outpatient care 2006-2009, DDD/1000 inhabitants and day. Monthly sale and 12 months moving average.

TABLE 3.1.1. Sales of antibiotics in outpatient and hospital care 2000-2009, DDD/1000 inhabitants and day. Total sales include outpatient care, hospital care and antibiotics dispensed by open specialist surgeries.

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

Antibiotic use in human and veterinary medicine

IN A GLOBAL PERSPECTIVE, bacteria in the environment are exposed to antibiotics from human medicines, veterinary medicines, foodstuffs and industrial products. Legislation in this area differs widely between countries and reliable data on use of antibiotics in the food industry is scarce. However, in this year's SWEDRES, an approach is done to somehow illustrate and relate the use of antibiotics in human and veterinary medicine to each other. Data collection and analysis have been done in collaboration between Strama and the corresponding programme for veterinary medicine and food, Strama VL.

The figures on total use of antibiotics sold for systemic use in humans were retrieved as defined daily doses and calculated to amounts of active substance. Figures on sales of antibiotics for use in animals (QJ01) are those presented in SVARM 2009. Sales for aquaculture are not included, nor are sales of medicines authorized for humans but sold for use in animals.

In 2009, around 64.5 tons of active substances from products classified as ATC J01 were sold for humans and around 14.7 tons of QJ01 to animals. Below are two diagrams showing a more detailed view of the relation between antibiotic use in humans and animals. Antibiotics that are used in both disciplines and which had a sales amount exceeding 1000 kg are included, Figures 3.1.1 and 3.1.2. Please note the difference in indexation of the x-axis.

Figure 3.1.1 displays the sales of beta-lactam antibiotics. These substances are by far the most used antibiotics in both human and veterinary medicine, but from an environment and resistance perspective they are relatively harmless. The substances presented in Figure 3.1.2 are sold in much smaller quantities, but their impact on both antibiotic resistance and the environment is more pronounced due to their pharmacological and chemical properties.

Antibiotic use in relation to body weight in humans and animals is presented and discussed in SVARM 2009 (www.sva.se).

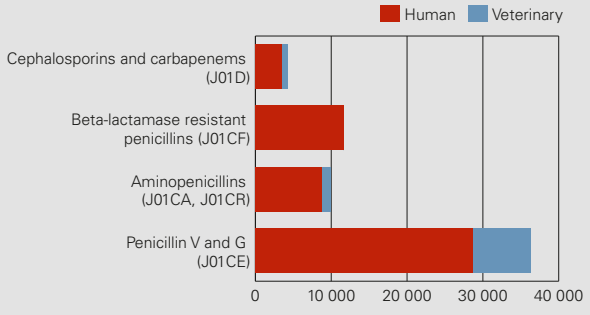

FIGURE 3.1.1. Amount of beta-lactam antibiotics in human and veterinary medicine, kg substance 2009.

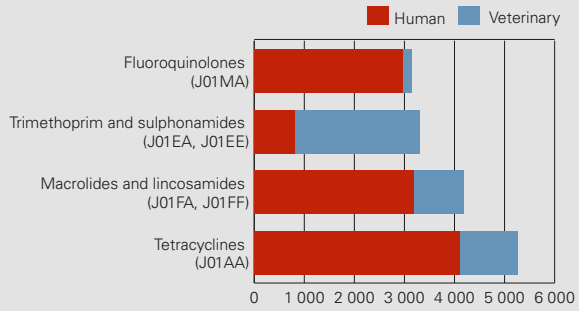

FIGURE 3.1.2. Amount of fluoroquinolones, macrolides, lincosamides, trimethoprim and sulphonamides and tetracyclines in human and veterinary medicine, kg substance 2009.

Human use makes up more than three quarters of all classes except trimethoprim and sulphonamides, where veterinary use represents 76 percent, Figure 3.1.3. An additional antibiotic group that is used in both disciplines is the aminoglycosides of which approximately 9 percent is used in human medicine.

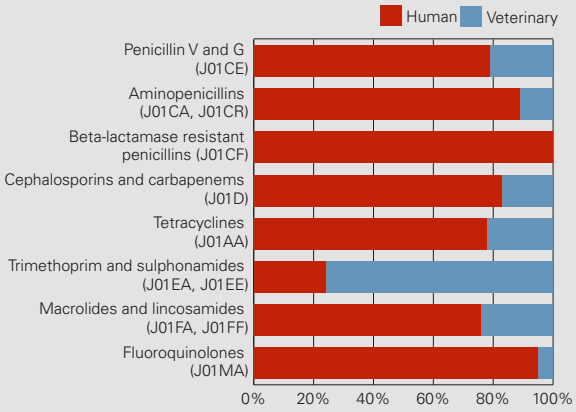

FIGURE 3.1.3. Proportions of certain antibiotic classes in human and veterinary medicine 2009.

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Christina Greko, National Veterinary Institute

The decrease in sales encompasses all antibiotic groups except nitrofurantoin and pivmecillinam. Penicillins with extended spectrum with the exception of pivmecillinam (J01CA) and cephalosporins (J01DB-DE) are the two antibiotic groups with the greatest decrease expressed in percent. Beta-lactamase sensitive penicillins (J01CE) together with tetracyclines (J01AA) are the most commonly used antibiotics in outpatient care 2009, Figure 3.1.6, and these groups show the largest decrease in absolute numbers.

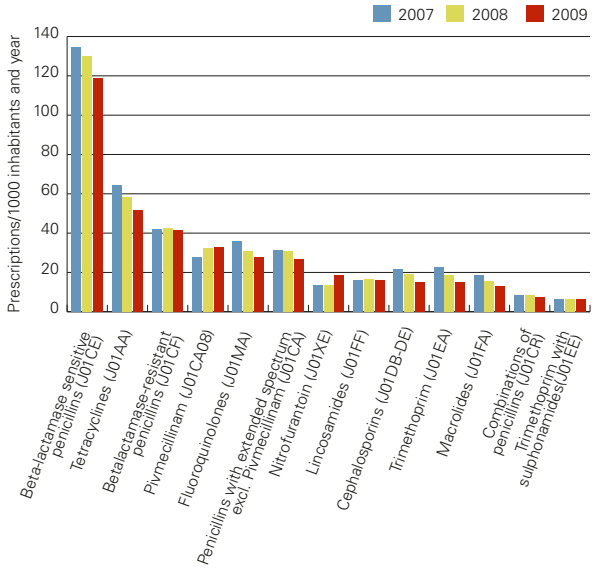

FIGURE 3.1.6. Antibiotics in outpatient care 2007-2009, Prescriptions/1000 inhabitants and year.

Tetracyclines

Doxycycline is the most frequently used tetracycline measured as prescriptions/1000 inhabitants and stands for 75.6% of the sale of tetracyclines in 2009. This substance is mainly used to treat respiratory tract infections, which can be one explanation to the great seasonal variation. In Figure 3.1.7 the seasonal variation in use of tetracyclines during the period 2006-2009 is shown. However, during the winter 2009 the use of tetracyclines was less than previous winter seasons. This may be an effect of the new treatment guidelines for respiratory tract infections launched by Strama and The Swedish Medical Products Agency in April 2008 and the distribution of these guidelines in a pocket format to all doctors in September 2009. 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.

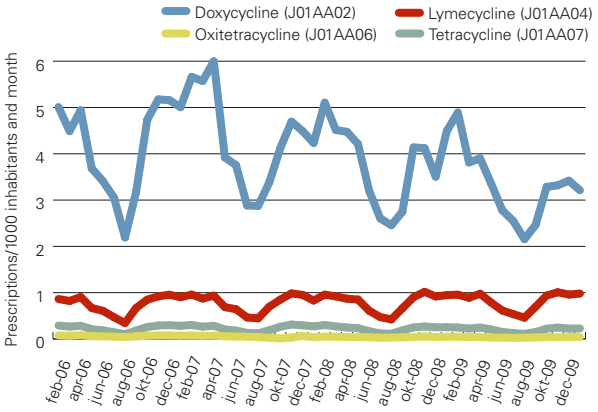

FIGURE 3.1.7. Seasonal variation of tetracyclines, outpatient care 2006-2009, prescriptions /1000 inhabitants and month.

Sales of tetracyclines measured as prescriptions and DDDs decreased by 11% and 6% respectively in outpatient care in 2009. This indicates an increasing fraction of prescription with a larger number of DDDs. The reduction encompasses all age groups measured as prescriptions per 1000 inhabitants. However, while measured as DDDs per 1000 inhabitants and day, an increased use in teenagers is seen, Table 3.1.2.

Teenagers, 13-19 years, is the age group with the highest number of DDDs per prescription (ranging from 15 for doxycycline to 51 for lymecycline). This is probably due to treatment of acne for which long-term treatment often is prescribed. The number of prescriptions of tetracyclines per 1000 teenagers range from 60 in Uppsala county to 38 in Gotland county. The diversity seems mostly relate to the substances commonly used to treat acne, Figure 3.1.8.

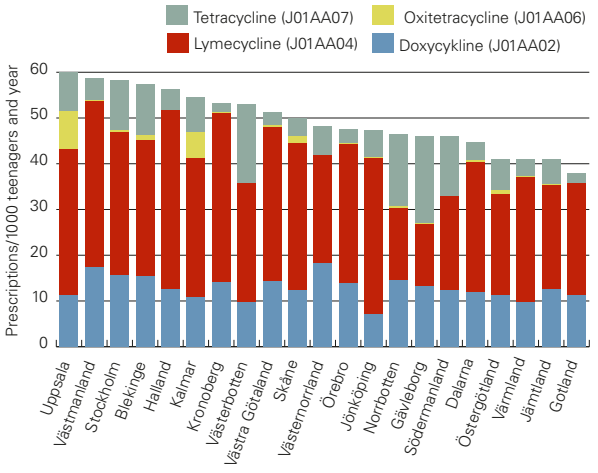

FIGURE 3.1.8. Tetracyclines in outpatient care per county, Prescriptions/1000 teenagers, 13-19 years, 2009.

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: from 258 in Stockholm to 146 in Västerbotten, Figure 3.1.9.

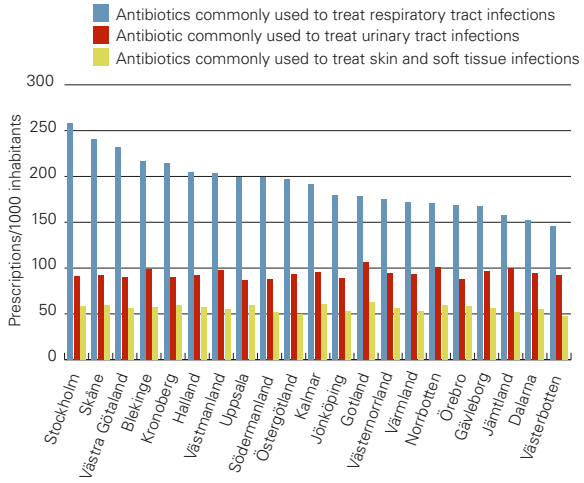

FIGURE 3.1.9. Antibiotics commonly used to treat respiratory tract infections (J01AA02, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infection (J01CA08, J01 EA01, J01MA02, J01MA06 and J01XE01) and skin and soft tissue infections (J01FF01 and J01CF05) in outpatient care 2009, per county. Both sexes, all ages, prescriptions/1000 inhabitants and year.

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 nearly 70% of all antibiotics commonly prescribed to treat this condition. Pivmecillinam is prescribed almost twice as often as nitrofurantoin. In all, the number of nitrofurantoin prescriptions to women increased by 37% in 2009, while the number of DDDs only increased by 11%, Table 3.1.2. This can be explained by the introduction of a new package adapted to the recommendations mentioned above. Simultaneous to an increased use of pivmecillinam and nitrofurantoin, the use of trimethoprim and fluoroquinolones has decreased drastically during recent years, Figure 3.1.10. Taken together, sales of antibiotics commonly used to treat urinary tract infections in women have decreased every year since 2006. Read more about Strama's prescribing goal for urinary tract infections in page 17.

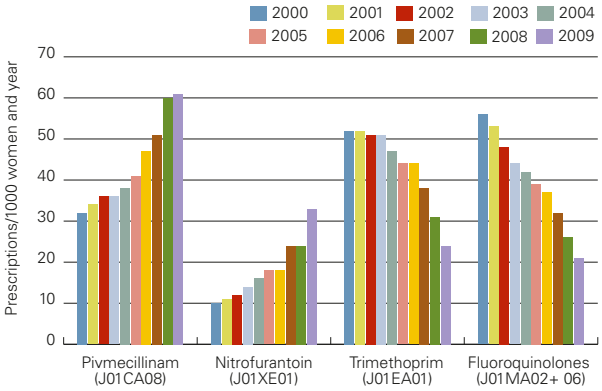

FIGURE 3.1.10. Antibiotics commonly used to treat lower urinary tract infections in women, 2000-2009, prescriptions/ 1000 women and year.

County and municipality data

The fraction of people treated with any kind of antibiotic (users per 1000 inhabitants) has decreased by 6% in 2009, Table 3.1.2. However, the fraction of people treated with antibiotics varies within Sweden, from 255 users per 1000 inhabitants in Stockholm county to 181 users per 1000 inhabitants in Västerbotten county, Figure 3.1.11. A comparison of age and gender standardized sales data from the counties shows that the use is highest in the big cities and their surroundings.

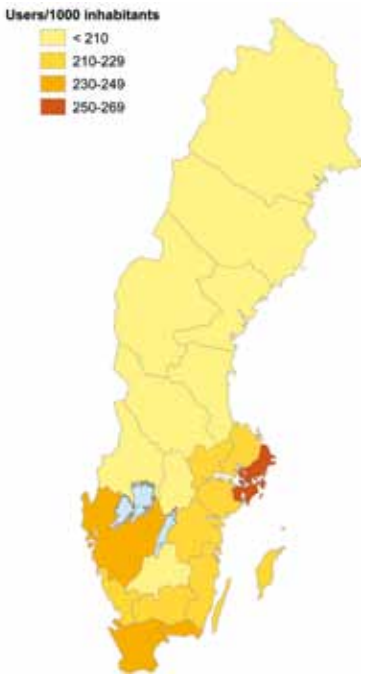

FIGURE 3.1.11. Fraction of people treated with at least one course of antibiotics in 2009, users/1000 inhabitants.

There are 290 municipalities in Sweden and Figure 3.1.12 presents the ten municipalities with the highest prescription of antibiotics and the ten with the lowest, in all age groups, in outpatient care 2009. Analyses of antibiotic prescriptions at municipality level generate even more pronounced differences within the country than analyses at county level. The number of prescriptions per 1000 inhabitants range from 485 in Upplands Väsby to 270 in Robertsfors. A comparison of age and gender standardized data at municipality level shows no big differences regarding ranking. However data at municipality level are more sensitive for variation in the population's composition because of the small denominator.

Read more about Strama's prescribing goal in outpatient

care in page 17.

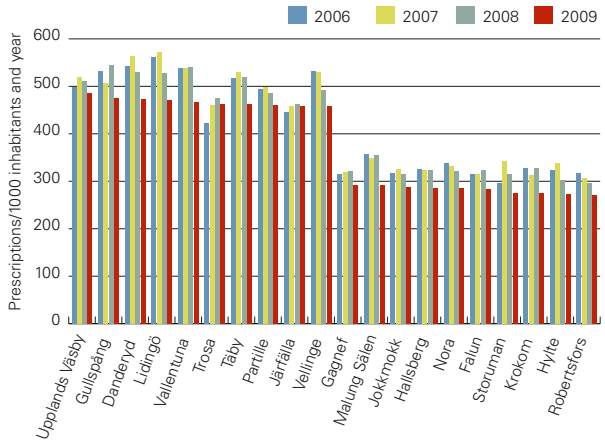

FIGURE 3.1.12. Swedish municipalities with highest and lowest prescription of antibiotics, all age groups, in outpatient care 2009. Prescriptions/1000 inhabitants and year.

Antibiotic consumption in children

The fraction of children treated with any kind of antibiotic range from 342 users per 1000 children in Stockholm county to 199 users per 1000 children in Jämtland county, Figure 3.1.13. Taken together in Sweden the fraction of children treated with antibiotics was 298 users per 1000 children, which is 10% lower than in 2008, Table 3.1.2.

FIGURE 3.1.13. Fraction of children aged 0 to 6 years treated with at least one course of antibiotics in 2009, users/1000 children.

Prescriptions of antibiotics to children aged 0-6 years decreased with 17.2% in 2009. The great fall concerns all counties and all antibiotic groups except pivmecillinam, nitrofurantoin and lincosamides. Combinations of penicillins had the greatest decrease (27%) in number of prescriptions per 1000 children of all antibiotic groups, Table 3.1.2.

Different kinds of penicillins are the most commonly prescribed antibiotics. Amoxicillin-clavulanate, amoxicillin and penicillin V represent 75% of all antibiotics to children aged 0-6 years in outpatient care 2009.

Consumption of antibiotics among children varies greatly within the country. The number of prescriptions range from 606 prescriptions per 1000 children in Stockholm county to 297 prescriptions per 1000 children in Jämtland county, Figure 3.1.14. Even counties with the lowest numbers of prescriptions decreased to a great extent in 2009.

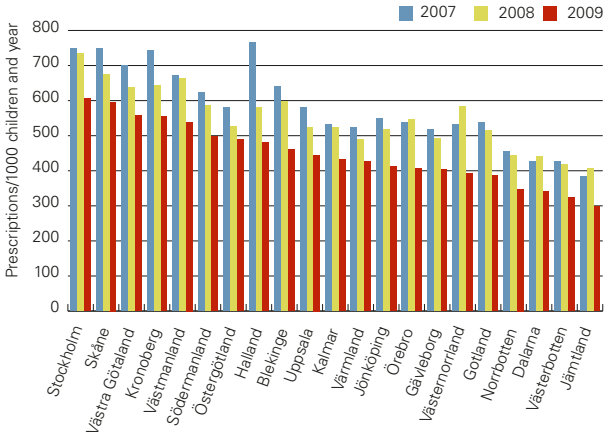

FIGURE 3.1.14. Antibiotics in outpatient care to children aged 0-6 years, per county 2007-2009. Prescriptions/1000 children and year.

Antibiotic use in children has been in focus of Strama's information activities the last year. The great reduction in sales of antibiotics may have several explanations. Hand hygiene has been the subject of many campaigns during 2009. One study has shown that using alcohol-based hand disinfection in preschools reduces absence from Swedish day care centers with 12%. Social insurance office reported a 7% less parental leave measured as days of parental leave per children aged 1-6 years in 2009. This may indicate fewer infections in children.

Antibiotics in dentistry

Dentists account for approximately 8% of all antibiotic prescribing in outpatient care. After several years of increase, the prescription of antibiotics by dentists decreased by 7% in 2009. Penicillin V is the most commonly prescribed antibiotic and represents 80% of all antibiotics prescribed by dentists. Lincosamides comprise a small proportion of dentists' prescribing, but has increased from 1 prescription/1000 inhabitants and year in 2000 to nearly 3 prescriptions/1000 inhabitants and year in 2009.

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TABLE 3.1.2. Antibiotics in outpatient care, classes of antibiotics and age groups. DDD/1000 inhabitants and day and prescriptions/1000 inhabitants and year. 2004-2009. Users/1000 inhabitants and year.

Age group (years)	DDD/1000 and day						Prescriptions/1000 and year						Users/1000 and year			
	2004	2005	2006	2007	2008	2009	2004	2005	2006	2007	2008	2009	2006	2007	2008	2009
Tetracyclines (J01AA)																
0-6	0.00	0.00	0.00	0.00	0.00	0.00	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.02	0.01
7-19	2.36	2.71	3.12	3.23	3.26	3.31	25.4	28.9	32.7	33.9	32.0	31.6	20.4	21.5	19.64	19.16
20-59	3.36	3.52	3.56	3.68	3.50	3.26	62.9	67.2	66.3	68.3	61.3	53.7	51.8	53.4	47.61	41.72
60-79	3.90	4.15	4.11	4.29	4.05	3.64	91.7	99.7	96.3	99.3	90.1	78.3	71.6	74.4	67.18	60.08
80 -	2.83	3.04	2.89	2.93	2.78	2.43	75.8	82.6	76.4	77.8	71.7	62.2	60.1	62.0	56.83	49.69
All age groups	3.06	3.26	3.33	3.44	3.29	3.08	58.6	63.2	62.6	64.3	58.3	51.7	46.9	48.6	43.7	38.82
Penicillins with extended spectrum (J01CA) excl. pivmecillinam																
0-6	1.25	1.41	1.59	1.74	1.71	1.52	84.7	85.0	86.9	95.2	90.8	72.7	64.6	70.5	66.74	56.31
7-19	0.32	0.38	0.45	0.46	0.43	0.39	10.8	12.5	14.1	14.5	13.6	11.8	12.4	12.8	11.54	10.08
20-59	0.64	0.72	0.72	0.77	0.75	0.66	16.8	18.3	18.4	19.4	18.7	16.5	16.0	16.7	15.1	14.15
60-79	1.43	1.56	1.59	1.62	1.63	1.52	39.3	41.2	41.4	42.0	41.3	37.9	32.3	32.9	29.9	30.05
80 -	1.65	1.80	1.81	1.79	1.83	1.76	45.3	47.5	47.3	46.8	46.5	44.0	38.3	38.0	32.87	35.39
All age groups	0.84	0.94	0.98	1.02	1.02	0.93	27.4	29.0	29.6	31.0	30.5	26.9	23.4	24.5	22.47	21.08
Pivmecillinam (J01CA08)																
0-6	0.01	0.01	0.01	0.01	0.01	0.01	0.3	0.4	0.5	0.5	0.7	0.8	0.4	0.5	0.61	0.74
7-19	0.14	0.15	0.17	0.19	0.24	0.24	7.4	8.7	10.7	12.4	15.5	16.1	9.6	11.0	13.58	13.89
20-59	0.32	0.31	0.34	0.36	0.43	0.44	15.4	16.9	20.1	22.2	26.9	27.3	17.3	19.0	22.52	22.99
60-79	0.72	0.70	0.71	0.74	0.84	0.85	33.4	36.2	40.3	43.0	49.5	49.9	31.2	33.1	37.3	38.09
80 -	2.05	1.90	1.84	1.84	1.95	1.92	97.4	100.0	106.7	109.3	116.6	115.8	80.1	81.8	85.14	83.94
All age groups	0.43	0.42	0.43	0.46	0.53	0.54	20.5	22.3	25.5	27.6	32.2	32.8	20.7	22.3	25.56	25.95
Beta-lactamase sensitive penicililns (J01CE)																
0-6	3.32	3.35	3.59	4.03	4.14	3.56	307.9	310.5	327.3	350.7	343.7	287.4	230.8	244.3	235.92	210.74
7-19	2.92	3.01	3.38	3.68	3.64	3.46	120.6	121.5	135.0	142.5	135.0	123.3	113.1	117.3	110.21	100.69
20-59	4.16	4.18	4.28	4.49	4.42	4.00	105.5	105.2	107.9	112.8	108.4	97.7	91.6	95.2	90.86	83.75
60-79	4.33	4.27	4.46	4.57	4.51	4.25	104.8	102.9	107.0	109.0	106.1	99.6	88.0	89.4	86.95	84.50
80 -	3.32	3.39	3.33	3.36	3.51	3.38	86.8	87.1	84.2	84.2	85.7	81.7	71.4	72.2	72.39	69.91
All age groups	3.90	3.92	4.09	4.30	4.26	3.96	122.6	122.5	128.1	134.3	130.0	118.6	104.0	108.1	103.74	95.96
Beta-lactamase resistant penicillins (J01CF)																
0-6	0.33	0.31	0.35	0.33	0.33	0.31	34.3	32.2	35.6	32.9	32.8	30.8	26.7	25.2	24.82	24.22
7-19	0.67	0.65	0.70	0.69	0.80	0.79	32.0	30.7	33.6	31.9	31.9	31.2	27.5	26.4	26.2	25.36
20-59	0.88	0.88	0.95	0.96	1.14	1.13	31.7	31.7	33.5	33.3	33.2	32.6	26.9	26.7	26.45	26.24
60-79	1.94	1.91	2.04	2.04	2.37	2.29	54.5	54.4	57.4	56.3	56.9	55.0	37.7	37.1	37.31	37.05
80 -	4.47	4.38	4.44	4.40	5.01	4.92	124.2	122.0	123.4	122.6	122.1	119.4	68.7	67.9	66.75	65.46
All age groups	1.18	1.18	1.25	1.25	1.46	1.45	40.9	40.5	42.9	42.2	42.3	41.7	31.2	30.7	30.52	30.11
Combinations of penicillins (J01CR)																
0-6	0.68	0.73	0.73	0.75	0.67	0.52	48.5	51.8	51.2	52.7	46.4	33.7	34.4	35.2	30.89	24.00
7-19	0.17	0.20	0.22	0.21	0.20	0.18	5.1	6.0	6.4	6.4	6.0	5.4	5.1	4.9	4.54	4.07
20-59	0.15	0.17	0.18	0.20	0.21	0.20	3.3	3.8	3.9	4.4	4.6	4.3	3.5	3.9	4	3.70
60-79	0.17	0.20	0.22	0.25	0.27	0.28	3.5	4.2	4.5	5.1	5.5	5.7	3.6	4.1	4.38	4.57
80 -	0.11	0.15	0.15	0.17	0.20	0.22	2.4	3.0	3.0	3.4	4.1	4.3	2.3	2.7	3.21	3.40
All age groups	0.19	0.22	0.24	0.26	0.26	0.24	6.9	7.8	8.0	8.5	8.3	7.2	6.1	6.5	6.26	5.53
Cephalosporins (J01DB-DE)																
0-6	0.53	0.50	0.52	0.52	0.46	0.36	49.7	46.4	49.0	49.7	43.6	34.1	37.6	38.0	33.86	28.12
7-19	0.30	0.29	0.30	0.29	0.27	0.21	20.9	19.6	20.6	20.2	18.4	14.9	17.4	17.2	15.71	12.64
20-59	0.30	0.30	0.29	0.28	0.25	0.20	16.9	16.6	16.8	16.2	14.5	11.4	14.2	13.7	12.2	9.77
60-79	0.48	0.47	0.46	0.40	0.36	0.29	23.6	23.1	22.6	20.2	17.7	13.8	17.1	15.5	13.49	10.66
80 -	0.79	0.77	0.73	0.65	0.54	0.41	42.6	42.3	40.5	35.4	29.4	22.7	30.9	27.4	22.86	17.88
All age groups	0.40	0.38	0.37	0.35	0.31	0.25	23.4	22.5	22.5	21.5	19.0	15.2	17.9	17.2	15.3	12.29

Age group (years)	DDD/1000 and day						Prescriptions/1000 and year						Users/1000 and year			
	2004	2005	2006	2007	2008	2009	2004	2005	2006	2007	2008	2009	2006	2007	2008	2009
Trimethoprim (J01EA)																
0-6	0.12	0.11	0.12	0.12	0.10	0.09	15.6	14.8	16.0	15.4	14.0	12.6	11.1	10.6	9.82	9.67
7-19	0.21	0.20	0.21	0.18	0.15	0.11	12.4	11.9	12.4	10.9	8.9	7.0	10.8	9.5	7.75	6.02
20-59	0.36	0.33	0.33	0.29	0.24	0.18	18.7	17.3	17.4	14.6	11.8	8.7	14.7	12.4	9.89	7.25
60-79	0.92	0.86	0.84	0.76	0.64	0.52	44.6	41.7	40.7	35.2	29.2	23.1	29.7	25.6	20.97	16.65
80 -	2.48	2.28	2.19	1.91	1.58	1.30	136.0	125.6	120.1	104.5	84.7	69.6	73.3	61.6	49.08	38.59
All age groups	0.53	0.49	0.49	0.43	0.36	0.29	28.2	26.4	26.3	22.8	18.8	14.9	19.8	16.9	13.77	10.73
Trimetoprim with sulphonamides (J01EE)																
0-6	0.15	0.15	0.16	0.16	0.14	0.13	18.4	18.1	18.1	18.8	16.7	14.8	13.2	13.5	12.03	10.70
7-19	0.09	0.10	0.10	0.10	0.11	0.11	4.0	4.1	4.0	4.1	4.2	4.3	2.7	2.6	2.65	2.55
20-59	0.12	0.12	0.13	0.14	0.14	0.15	2.7	2.8	2.9	3.0	3.1	3.3	1.9	1.9	2.02	2.12
60-79	0.33	0.34	0.36	0.39	0.44	0.47	8.2	8.4	8.8	9.2	10.1	10.4	5.8	6.1	6.75	7.13
80 -	0.35	0.34	0.36	0.39	0.43	0.43	11.8	11.5	11.7	12.2	13.1	12.5	8.8	9.1	9.91	9.72
All age groups	0.18	0.18	0.19	0.20	0.21	0.22	6.2	6.2	6.3	6.4	6.5	6.6	4.0	4.1	4.25	4.25
Macrolides (J01FA)																
0-6	0.73	0.80	0.80	0.85	0.68	0.51	34.5	37.4	37.3	38.1	29.9	22.4	29.6	30.4	23.28	18.09
7-19	0.62	0.72	0.76	0.74	0.54	0.45	18.1	21.0	22.1	21.7	15.4	12.7	17.9	17.2	11.82	9.70
20-59	0.54	0.56	0.54	0.55	0.49	0.42	16.3	16.8	16.3	16.5	14.3	12.1	13.0	13.2	11.3	9.61
60-79	0.49	0.51	0.50	0.50	0.47	0.42	14.1	14.8	14.5	14.6	13.0	11.3	11.0	11.0	9.58	8.41
80 -	0.31	0.34	0.34	0.32	0.30	0.29	9.7	9.8	9.3	8.7	8.4	7.4	7.2	6.8	6.35	5.46
All age groups	0.55	0.59	0.58	0.59	0.50	0.43	17.3	18.4	18.2	18.4	15.3	12.8	14.4	14.4	11.74	9.85
Lincosamides (J01FF)																
0-6	0.02	0.02	0.02	0.03	0.02	0.02	4.1	4.5	5.0	5.3	5.0	5.2	3.6	3.9	3.67	3.84
7-19	0.09	0.10	0.11	0.12	0.12	0.12	6.5	6.9	7.8	8.3	8.4	8.2	6.2	6.7	6.85	6.57
20-59	0.24	0.25	0.28	0.29	0.30	0.29	12.6	13.0	14.3	15.6	15.6	15.0	11.1	12.2	12.21	12.00
60-79	0.51	0.53	0.55	0.55	0.57	0.57	21.1	22.1	23.7	24.4	24.6	23.8	15.3	15.9	16.26	16.40
80 -	0.71	0.77	0.75	0.74	0.76	0.72	30.0	32.2	32.6	32.8	33.2	31.0	18.1	18.6	19.21	18.79
All age groups	0.27	0.29	0.31	0.32	0.33	0.32	13.5	14.1	15.4	16.3	16.4	15.9	10.9	11.7	11.85	11.71
Fluoroquinolones (J01MA)																
0-6	0.01	0.02	0.01	0.01	0.01	0.01	0.4	0.8	0.8	0.8	0.7	0.7	0.4	0.4	0.39	0.36
7-19	0.12	0.12	0.12	0.13	0.12	0.12	5.5	5.5	5.5	5.5	4.8	4.3	4.7	4.4	3.85	3.51
20-59	0.81	0.81	0.80	0.76	0.69	0.63	33.1	31.9	30.2	27.8	23.8	20.9	22.0	20.3	17.33	15.43
60-79	2.07	2.08	2.05	1.93	1.75	1.67	88.0	84.6	80.2	73.7	63.9	58.6	52.7	48.7	42.73	40.22
80 -	3.14	3.13	3.00	2.74	2.41	2.25	158.4	149.4	136.8	119.7	98.5	88.2	92.5	81.5	68.14	61.43
All age groups	0.98	0.99	0.98	0.93	0.84	0.80	42.5	41.0	39.0	35.7	30.6	27.8	27.0	24.9	21.47	19.59
Nitrofurantoin (J01XE)																
0-6	0.07	0.07	0.07	0.07	0.06	0.06	6.9	6.4	6.3	6.3	6.2	6.9	4.2	4.2	4.15	4.93
7-19	0.11	0.12	0.12	0.14	0.13	0.15	4.9	5.3	5.2	6.7	6.6	9.2	4.4	5.8	5.78	7.89
20-59	0.17	0.19	0.20	0.24	0.23	0.26	7.4	8.5	8.5	11.0	10.6	14.7	7.0	9.1	8.84	12.16
60-79	0.29	0.34	0.36	0.46	0.47	0.53	11.7	14.1	14.6	19.4	20.6	28.1	10.7	14.3	15.19	20.82
80 -	0.68	0.78	0.78	0.97	0.95	1.05	31.0	36.5	37.2	46.7	47.7	61.7	24.0	30.3	31.17	40.29
All age groups	0.20	0.23	0.24	0.30	0.29	0.32	9.0	10.3	10.5	13.5	13.6	18.5	8.0	10.3	10.4	14.08
All agents (J01 excl. methenamine)																
0-6	7.23	7.49	7.98	8.62	8.34	7.12	605.9	608.8	634.7	666.8	630.8	522.4	335.6	348.5	330.34	298.02
7-19	8.13	8.76	9.79	10.18	10.02	9.66	274.1	283.4	311.1	319.8	301.4	280.8	204.5	208.1	195.83	182.14
20-59	12.09	12.37	12.63	13.04	12.82	11.84	344.2	350.9	357.6	366.1	348.0	318.9	223.9	228.7	217.78	204.07
60-79	17.66	18.02	18.34	18.58	18.46	17.37	541.0	550.0	554.5	553.7	531.0	497.7	288.8	289.6	279.04	269.55
80 -	23.01	23.20	22.74	22.33	22.37	21.18	856.3	854.2	833.3	807.9	765.1	723.5	379.4	372.5	356.15	340.11
All age groups	12.77	13.13	13.51	13.87	13.70	12.88	418.2	425.6	436.1	443.8	423.1	391.9	249.8	254.1	242.53	228.02

Strama's prescribing goal in outpatient care

OF ALL ANTIBIOTIC SALES 90 percent is prescribed in outpatient care including primary care, open specialist surgeries, dentists and parts of nursing homes. There is no medical reason to the wide regional variations in the use of antibiotics that are seen within the country. National studies show that antibiotic prescribing not always is done according to guidelines. Given the rapid and serious development of antibiotic resistance Strama has proposed three goals for antibiotic use in outpatient care. The aim is to preserve the relatively favorable resistance situation in Sweden as long as possible.

Find more information about Stramas prescribing goals in outpatient care at Stramas webpage www.strama.se

The total number of antibiotic prescriptions in Sweden

The total number of antibiotic prescriptions in Sweden should not exceed 250 prescriptions per 1000 inhabitants and year by 2015. The goal includes all antibiotics for systemic use excluding methenamine (J01 excl. J01XX05). The goal cannot however be applied by a single care unit but it can provide a measure at the county level.

It is mainly estimated from an analysis of electronic patient records of visits for respiratory tract infections in primary care in Kalmar county. All patients diagnosed with respiratory tract infections between the year 2000 and 2005 were included. In addition, electronic patient records from 21 Health centres covering all visits diagnosed as an infection (respiratory tract infections, urinary tract infections and skin- and soft tissue infections) between the year 2007 and 2009 has been analysed (unpublished data). The management of all patient visits was compared to current indications for antibiotic treatment according to national recommendations.

In primary care, respiratory tract infections stands for approximately 60%, urinary tract infections 20% and skin- and soft tissue infections 15% of all antibiotic prescriptions. Since GPs prescribe approximately 60% of all prescriptions in outpatient care in Sweden, the number of prescriptions that should cover the need of antibiotic treatment according to current recommendations in outpatient care was estimated to be approximately 250 prescriptions/1000 inhabitants and year.

This level of prescribing of antibiotics in outpatient care is currently existing in the Netherlands. However, it is important to emphasize that still all patients benefiting from antibiotics should be treated according to current guidelines.

In 2009 the average use of antibiotics in outpatient care in Sweden was 392 prescriptions per 1000 inhabitants. Still, there are great regional differences within the country. Prescriptions per 1000 inhabitants range from 430 in Stockholm county to 311 in Västerbotten county. The use of antibiotics decreased in all counties in 2009, Figure 3.1.15.

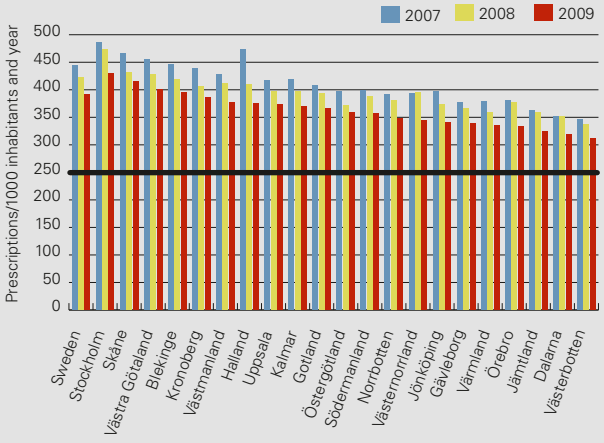

FIGURE 3.1.15 Sales of antibiotics in outpatient care 2007-2009, prescriptions/1000 inhabitants. The black line indicates Strama's goal at 250 prescriptions/1000 inhabitants in outpaitent care.

Further more Strama's goals are:

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 (J01CE 02) and the denominator is amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulanate (J01CR02), cephalosporins (J01DB-DE) and macrolides (J01FA). This qualityindicator is also used by The National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions (SALAR) in their annual benchmarking of medical treatments and procedures.

In 2009 the proportion of penicillin V of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years was 64% on a country level and the proportion of penicillin V increased in the majority of all counties. Värmland county had the greatest proportion, 78%, and Stockholm the lowest, 58%, Figure 3.1.16.

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).

The total number of prescriptions of antibiotics commonly used to treat urinary tract infections in women 18-79 years decreased by 1% in 2009 while the prescription of fluorquinolones decreased by 18%.

In Sweden the average proportion of fluorquinolones was 16% in 2009. Kronoberg was the county with the highest proportion (19%) and Jämtland was the county with lowest proportion (13%), Figure 3.1.17.

The Swedish Association for General Medicine (SFAM) has developed quality indicators. These indicators are prima-

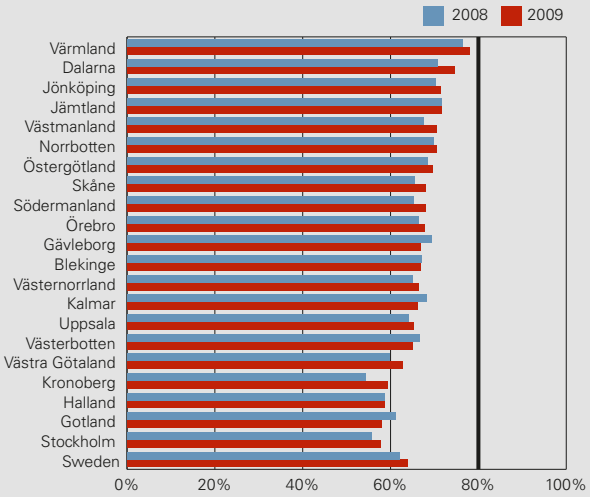

FIGURE 3.1.16. Proportion penicillin V of antibiotics commonly used to treat respiratory tract infections* in children 0-6 years, per county. The black line indicates Strama's goal at 80%.
*Prescriptions of amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulanate (J01CR02), macrolides, (J01FA) and cephalosporins (J01DB-DE).

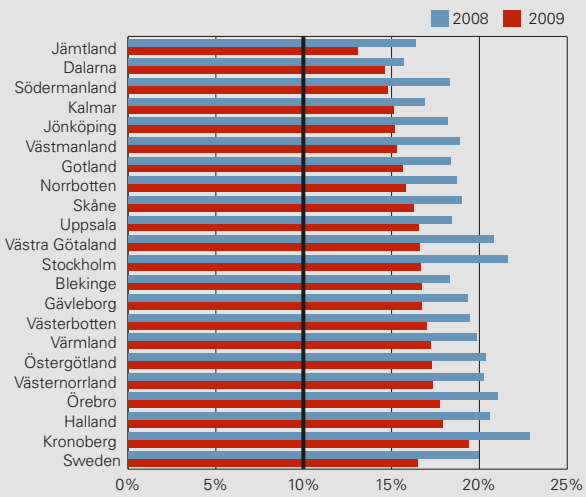

FIGURE 3.1.17. Proportion fluoroquinolones of antibiotics commonly used to treat urinary tract infections* in women aged 18-79 years, per county. The black line indicates Strama's goal of maximum 10%.
*Prescriptions of pivmecillinam (J01CA08), nitrofurantoin (J01XE01), trimethoprim (J01EA01), ciprofloxacin (J01MA02) and norfloxacin (J01MA06).

rily intended as tools for the individual physician or clinic/family doctors to review their own prescribing. One of these indicators is the proportion of fluorquinolones and cephalosporins of antibiotics commonly used to treat lower urinary tract infections in women aged 18 years or older.

Of great importance when promoting a reduced use of antibiotics is to ensure that this does not bring about increased morbidity. Figure 3.1.18 shows the incidence of pneumonia in relation to antibiotic prescribing in outpatient care and Figure 3.1.19 shows the incidence of mastoiditis in children in Sweden 1987-2008. Despite the great decrease in antibiotic sales the last years, complications in bacterial infections have not increased attributable to less antibiotic treatment. No correlation between the decreasing use of antibiotics and the incidence of pneumonia is seen.

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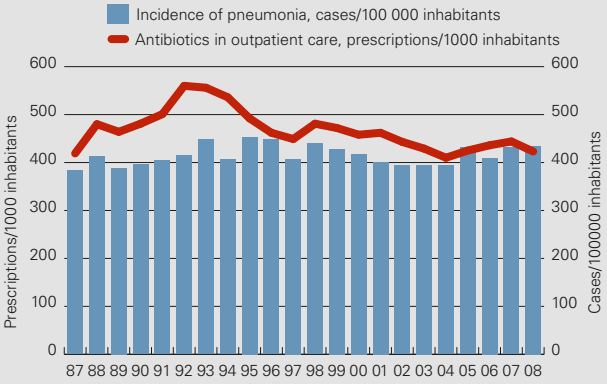


FIGURE 3.1.18. Hospital admissions for pneumonia and sale of antibiotics (J01 excl methenamine) in outpatient care, 1987-2008. Data from the national registry of diagnosis in hospital care

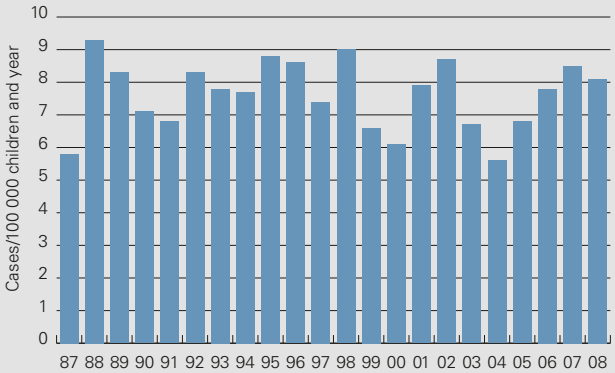


FIGURE 3.1.19. Hospitals admissions for mastoiditis in children aged 0-6 years, 1987-2008. Data from the national registry of diagnosis in hospital care.

Hospital care

As reported in earlier issues of Swedres, a more reasonable use of broad spectrum antibiotics has been one of Strama's objectives for a long time. The communication of this issue has been intensified in 2009 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 Swedish Reference Group for Antibiotics has published a list of "substitutional" antibiotics to be used instead of cefuroxime which has been extensively used for a variety of indications.

The considerable decrease in the use of cephalosporins in the recent years seems to continue also in 2009, Figure 3.1.22. Initially, the decrease was partly explained by a shift from cefuroxime to cefotaxime. The latter has a lower prescribed daily dose in Sweden that is lower than WHO's DDD, so comparison of DDDs showed a too large decrease in use. From 2007 to 2009 the sales of second generation cephalosporins, of which more than 90% was cefuroxime, decreased by 66%. Sales of third generation cephalosporins, mainly cefotaxime and ceftazidime, increased by 87% in the same period. Taken together, the overall decrease in DDDs for cephalosporins indicates that these substances are actually replaced by other antibiotics.

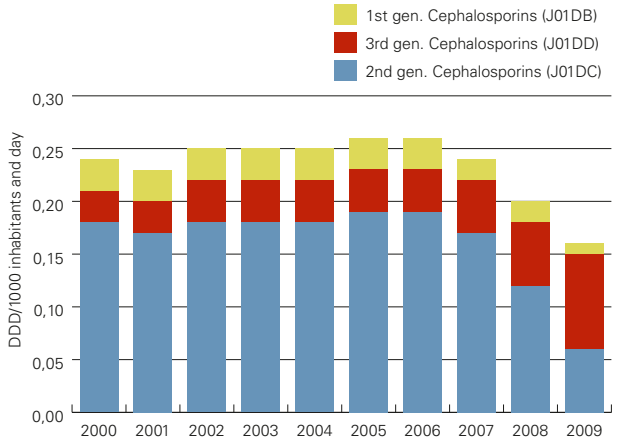


FIGURE 3.1.22. Cephalosporins to all patients, hospital care, DDD/1000 inhabitants and day 2000-2009.

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. Figure 3.1.23 shows the diversity within Sweden. The magnitude of the error of course varies between substance groups; 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. On the national level, the proportion of inpatient antibiotics actually used in hospitals is about 75%, and has been so for the last four years.

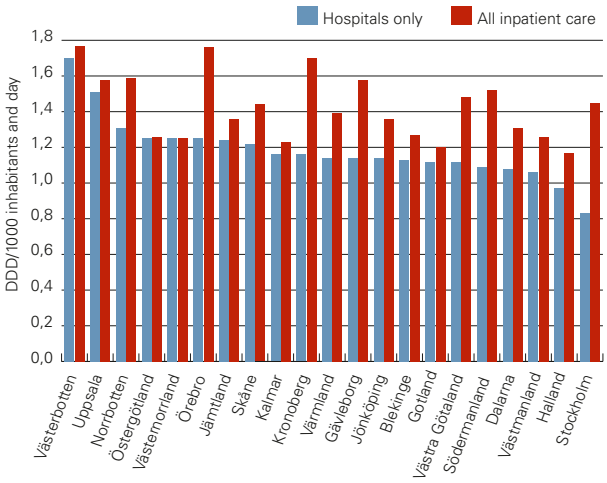


FIGURE 3.1.23. Antibiotic use in hospitals and in all inpatient care in the counties, DDD/1000 inhabitants and day 2009.

Despite the fact that several counties did initiate stock-piling of certain antibiotics to meet increased needs due to severe outbreaks of influenza, the overall sales of antibiotics to hospital care decreased a little between 2008 and 2009. Due to the recent rapid decrease (17% between 2007 and 2008, 21% between 2008 and 2009) in use of cephalosporins, the betalactamase-resistant penicillins (J01CF) are now the largest group of antibiotics in hospital care, Figure 3.1.24. One of these substances, cloxacillin, is largely used as prophylaxis before surgery. Another class of broad spectrum antibiotics, the fluoroquinolones (J01MA), is also decreasing in accordance with recommendations. Piperacillin with tazobactam still represents a small proportion of antibiotic use in hospitals, but it is increasing rapidly. Sales have increased by between 25 and 30% each year since 2006.

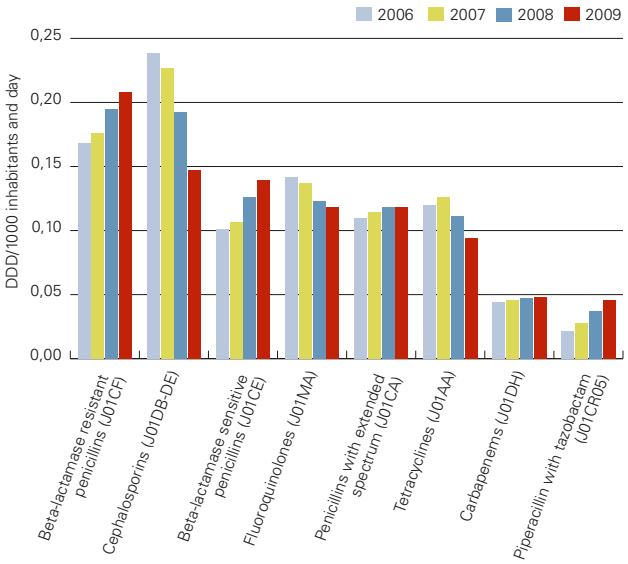


FIGURE 3.1.24. Use of some antibiotic groups in Swedish hospitals 2006-2009, DDD/1000 inhabitants and day.

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. The group J01CR, penicillins with enzyme inhibitors, has more than doubled over these four years. Around 80% of this group constitutes of piperacillin with tazobactam, the rest is amoxicillin with clavulanate. The increasing use of betalactamase sensitive penicillins is evident also with this denominator.

Taken together, the amount of antibiotics used per 100 patient-days or admissions to hospital remains quite stable since 2006 – the former increase by 6% and the latter decrease by 3%, 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 2006-2009.

	2006	2007	2008	2009*
Tetracyclines (J01AA)	5.5	5.7	5.5	4.7
Penicillins with extended spectrum (J01CA)	5.0	5.2	5.8	5.9
Betalactamase sensitive penicillins (J01CE)	4.6	4.8	6.2	6.9
Betalactamase resistant penicillins (J01CF)	7.7	8.0	9.6	10.3
Combinations of penicillins (J01CR)	1.3	1.6	2.3	2.8
Cephalosporins (J01DB-DE)	10.9	10.4	9.5	7.3
Carbapenems (J01DH)	2.0	2.1	2.3	2.4
Trimethoprim (J01EA)	1.3	1.2	1.2	1.0
Trimethoprim with sulphonamides (J01EE)	1.5	1.6	1.9	2.0
Macrolides (J01FA)	1.0	1.0	1.0	1.0
Lincosamides (J01FF)	1.5	1.5	1.7	1.7
Aminoglycosides (J01GB)	0.7	0.7	0.9	1.0
Fluoroquinolones (J01MA)	6.5	6.3	6.1	5.9
Glycopeptides (J01XA)	0.6	0.6	0.7	0.8
Imidazole derivatives (J01XD)	1.6	1.5	1.5	1.3
Methenamine (J01XX05)	0.9	0.9	0.8	0.7
Linezolid (J01XX08)	0.1	0.1	0.1	0.1
All agens (J01)	53.2	53.8	57.6	56.2

*Denominator data from 2008.

TABLE 3.1.4. DDD/100 admissions in somatic medical care 2006-2009.

	2006	2007	2008	2009*
Tetracyclines (J01AA)	28.8	29.9	26.5	22.5
Penicillins with extended spectrum (J01CA)	26.2	27.1	28.2	28.4
Betalactamase sensitive penicillins (J01CE)	24.2	25.2	30.0	33.5
Betalactamase resistant penicillins (J01CF)	40.3	41.8	46.4	49.9
Combinations of penicillins (J01CR)	6.7	8.2	11.0	13.6
Cephalosporins (J01DB-DE)	57.2	53.9	45.8	35.4
Carbapenems (J01DH)	10.6	10.8	11.3	11.6
Trimethoprim (J01EA)	6.7	6.3	5.8	4.8
Trimethoprim with sulphonamides (J01EE)	7.7	8.3	9.1	9.7
Macrolides (J01FA)	5.4	5.3	4.7	4.7
Lincosamides (J01FF)	7.8	8.0	8.2	8.0
Aminoglycosides (J01GB)	3.8	3.8	4.2	4.9
Fluoroquinolones (J01MA)	33.9	32.5	29.4	28.4
Glycopeptides (J01XA)	3.4	3.4	3.4	3.7
Imidazole derivatives (J01XD)	8.4	7.9	7.4	6.5
Methenamine (J01XX05)	4.7	4.5	3.8	3.2
Linezolid (J01XX08)	0.3	0.3	0.3	0.3
All agens (J01)	278.4	279.8	278.0	271.4

*Denominator data from 2008.

When comparing geographical regions, data on patient-days and admissions to hospital are subject to changes that are not easily retrieved and thus difficult to incorporate in the analysis. To minimize the risk for error caused by unreliable denominator data, the figures below display sales of certain substances as proportions of all antibiotics in hospital care in each county.

The proportion of broad and narrow spectrum antibiotics used in hospitals varies greatly between counties, as seen in Figures 3.1.25 and 3.1.26. Only 6% of systemic antibacterials in hospitals in Uppsala county are penicillins V or G, whereas in Värmland county these substances represent more than one-fifth. Less variation is seen in sales of one of the most common broad spectrum groups, the fluoroquinolones, which constitute between 9 and 14% of all antibiotics in the counties. After several years of decreasing use, the cephalosporins make up only 6% of antibiotics in Gotland, Södermanland and Västmanland counties. In Gävleborg county the proportion is more than three times higher.

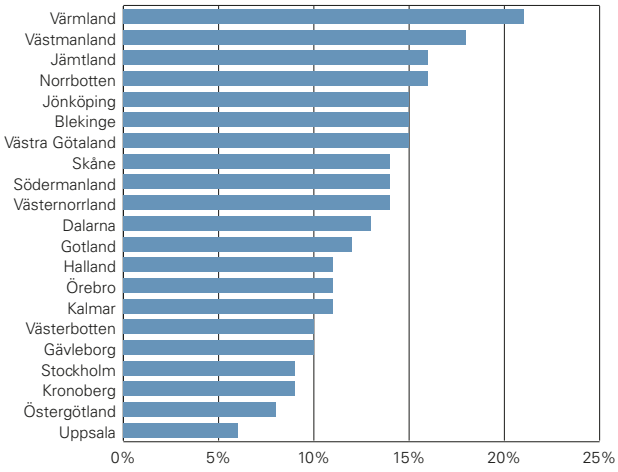


FIGURE 3.1.25. Percentage of narrow spectrum penicillins (penicillin V and G, J01CE) of all antibiotics in Swedish hospitals 2009, per county.

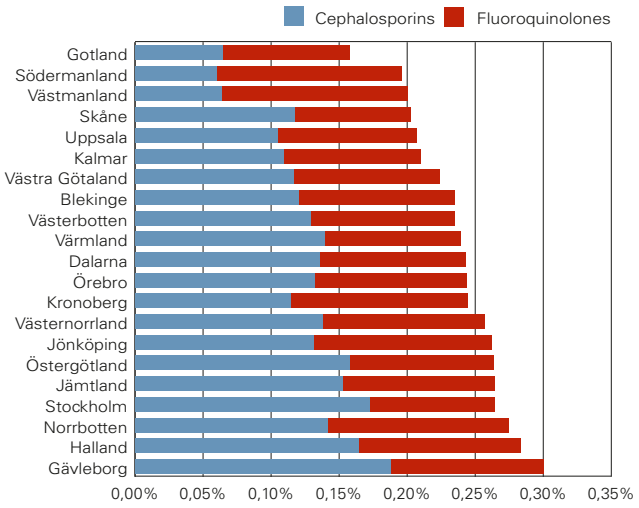
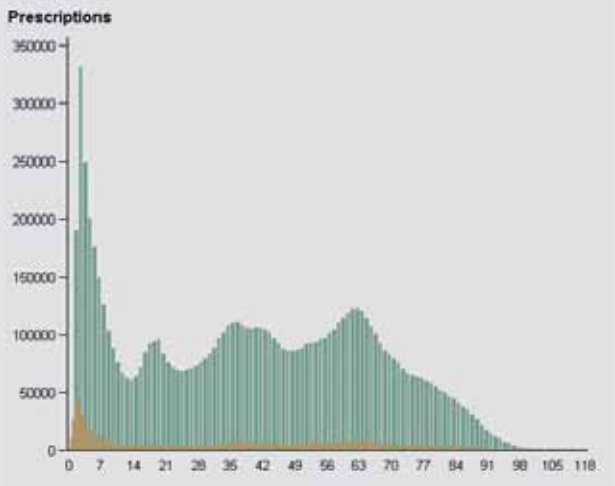


FIGURE 3.1.26. Percentage of broad spectrum antibiotics (cephalosporins, J01DB-DE and fluoroquinolones, J01MA) of all antibiotics in Swedish hospitals 2009, per county.

Respiratory tract infections – repeated courses in outpatient antibiotic use

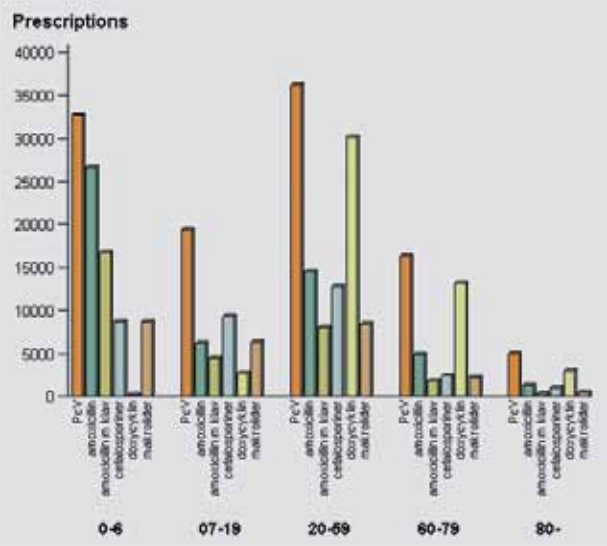
A STUDY PUBLISHED by the National Board of Health and Welfare (available at www.socialstyrelsen.se, only in Swedish) investigates the treatment of respiratory tract infections and to what extent repeated treatments occur within two weeks. Data from the Swedish Prescribed Drug Register were analyzed with respect to 1) what kind of antibiotic was used prior to a further purchase, 2), the choice of antibiotic in a supplementary purchase and 3) the time between purchases.

Children have the highest occurrence of prescription purchases of antibiotics used to treat respiratory tract infections and the largest fraction of repeated courses of antibiotics within 14 days. In the age group 0-6 years, the proportion of prescriptions with supplementary purchases for the same individual within 2 weeks is 10% of the total number of prescriptions on antibiotics used to treat respiratory tract infections (other age groups 5-7%), Figure 3.1.20.



FIGUR 3.1.20. Users treated with antibiotics used to treat respiratory tract infections in outpatient care during the period Sep 2005 – Aug 2009 versus patient age. The different colors indicate the prescriptions with no supplementary purchase for the same individual within 2 weeks (green) and the prescriptions followed by a further purchase within 2 weeks (brown). Antibiotics commonly used to treat respiratory tract infections (Strama): Amoxicillin-clavulanate (J01CR02), cephalosporins (J01DB-DE), doxycycline (J01AA02), macrolides (J01FA), amoxicillin (J01CA04), penicillin V (J01CE02). As medical cause of drug therapy not is indicated in the register, prescriptions for other indications than respiratory tract infections may be included.

In many cases (46%) the repeated course is the same antibiotic as the first. Penicillin V is the most commonly prescribed respiratory tract antibiotic in ages below 60 years and more than half of the repeated purchases are made after penicillin V. The choice of antibiotic that follow after penicillin V varies among different age groups. Figure 3.1.21 illustrates the choice of antibiotic that follows after penicillin V.



FIGUR 3.1.21. The choice of new antibiotic within 2 weeks after penicillin V in different age groups. The bars show the contribution of each sort of antibiotic (all formulations) to the total number of prescriptions that follow after purchases of penicillin V in each age group.

The number of days between purchases within 2 weeks varies with the type of antibiotic that was preceding the new course and the age of the patient. After use of penicillin V in children aged 0-6 years, new purchases of antibiotics often occur after just one day. This pattern has remained unchanged for the last 4 years. Among the other age groups there is a more even spread of purchases over time.

A new course of antibiotics commonly used against respiratory tract antibiotic within a 14-days period may have many explanations including unsuitable formulation (oral suspension, tablets) or unappreciated taste by young children, allergy, relapsed infection or lack of effect (viral or mycoplasma etiology).

One tenth of the prescriptions for antibiotics commonly used to treat respiratory tract infections in young children is followed by a new course within 14 days. The key to improvement might be in the prescribing situation or at the pharmacy for example; advice on how to ease the intake, discuss formulation alternatives, motivate parents of young children, involve the child in drug therapy to ease intake, etc.

The reason why nearly half of all repeated prescriptions results in an additional recipe for a course of the same antibiotic must be further investigated in the ambition to reduce ineffective antibiotic therapy.

Pinelopi Lundquist, National Board of Health and Welfare

Trends in antibiotic use in Swedish Intensive Care Units (ICUs)

Eleven year (1999-2009) report from ICU-Strama and Swedish ICU registry

The ICU-Strama programme was developed eleven years ago and used for regular audit of antibiotic use, antibiotic resistance and infection control procedures in Swedish ICUs. It is a joint project between the Strama-ICU and the Swedish Intensive Care Registry. The purpose of this report is to provide a trend analysis of antibiotic consumption in Swedish ICUs. Regarding data collection see Apppendix 3.

Total antibiotic consumption in Swedish ICUs increased from 1 216 DDD/1000 occupied bed-days (DDD/1000) 1999 to 1 425 in 2009 (p <0.001). Antibiotic consumption varied widely between different units during 2009, ranging between 680 and 2698 DDD/1000 with a median of 1354 DDD/1000. Trend analyses of usage of different classes of antibiotics were performed and showed increased consumption of aminoglycosides, betalactam sensitive penicillins, carbapenems, piperacillin-tazobactam, triazoles and vancomycin (p<0.01). There was no significant change in consumption of cephalosporins for the eleven year period but a trend towards decreased consumption the last three years. No significant correlations between antibiotic consumption and standardised mortality rates were shown for 2008 or 2009.

The four-fold variation in consumption between ICUs can be explained by different case mix, but there were also great variations between ICUs of the same type. The high antibiotic consumption concurs with figures from European and US ICUs in general, but like a few ICUs in our programme, relatively low antibiotic consumption has been reported from The Netherlands and Switzerland. The lower antibiotic consumption suggests that it is possible to reduce antibiotic consumption in the critically ill, but it has to be accompanied with a quality control system to make sure that it does not compromise patient outcomes.

Morgan Edström, Hans Gill, Sten Walther, Håkan Hanberger, ICU-Strama and the Swedish ICU registry

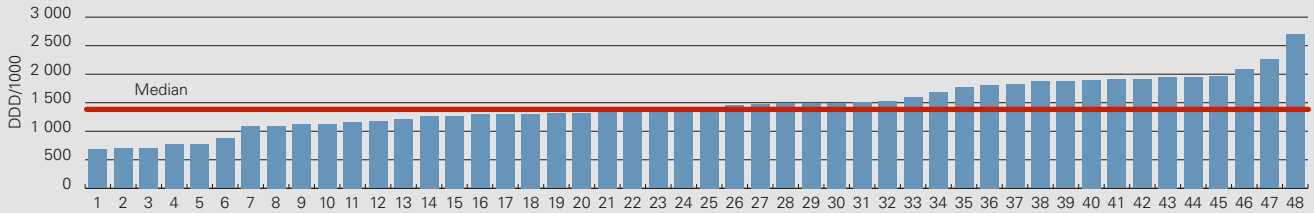


FIGURE 3.1.28. Antibiotic consumption in individual Swedish ICUs 2009, DDD/1000 occupied bed-days.

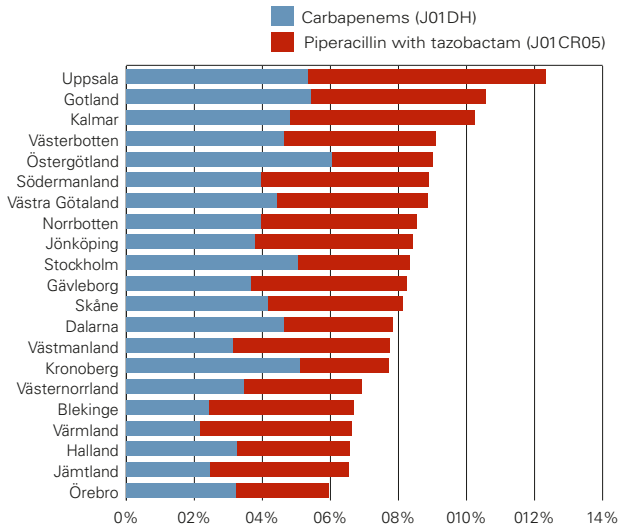


FIGURE 3.1.27. Percentage of carbapenems, J01DH, and piperacillin with tazobactam, J01CR05, of all antibiotics in Swedish hospitals 2009, per county.

As seen in Figure 3.1.24 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 10 percent in others, Figure 3.1.27. The proportion of carbapenems of all antibiotics in hospitals varies threefold, from 2% in Jämtland, Värmland and Blekinge counties to 6% in Östergötland county. Concerning piperacillin with tazobactam, sales vary from 3% in several counties to 7% in Uppsala county.

Ulrica Dohnhammar, 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, 2005–

2009, 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=513), hepato-biliary disorders (n=210), gastrointestinal disorders (n=206), general disorders (n=140), musculoskeletal disorders (n=98), blood disorders (n=123), and neurological reactions (n=120). The majority of the reports (62%) 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. A newcomer in this top-ten-list is amoxicillin.

TABLE 3.1.5. Most reported antibiotic agents to the Swedish Medical Products Agency 2005–2009

Antibiotic	Total number of ADR reports 2005 to 2009	Number of 'serious' reports	Number of fatal cases (causal relationship possible)
Ciprofloxacin	167	93	4
Flucloxacillin	111	70	4
Nitrofurantoin	102	52	1
Fenoxymethylpenicillin	87	40	0
Clindamycin	75	35	0
Trimethoprim	71	29	0
Doxycylin	70	21	2
Sulphamethoxaxol + trimethoprim	65	38	1
Cefuroxime	51	27	1
Amoxicillin	42	16	0

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 was reflected in a decrease in reported adverse events. In recent years the reporting rate has been stable. For nitrofurantoin which was increasingly prescribed a slight corresponding increase in the reporting of adverse reactions was noted. Due to the low number of reports and to the fact that data are based on spontaneous reporting, no clear conclusions can be made 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 2005 - 2009

	2005	2006	2007	2008	2009	2005-2009
Fluoroquinolones						
Total no of reports	56	45	55	35	34	225
Number of reactions						
Musculoskeletal	24	11	15	9	9	68
tendinitis	13	6	7	2	3	31
tendon rupture	5	3	2	5	3	18
Skin- and subcutaneous tissue	11	4	13	4	8	40
Psychiatric disorders	10	8	4	2	1	25
Nitrofurantoin						
Total no of reports	15	20	22	24	21	102
Number of reactions						
Respiratory system	8	12	3	7	9	39
dyspnoea	2	4	0	1	2	9
interstitial pneumonia	2	2	2	2	3	11
pulmonary fibrosis	0	2	0	0	0	2
Skin- and subcutaneous tissue	1	7	8	7	6	29
General disorders	7	8	7	6	7	35
fever	6	4	3	4	4	21

Charlotta Edlund, Ulf Persson

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 proportionally. From 2006 until 2009 there has been a 10% increase from 50.4 DDD/10^6 inhabitants and day to 55.0 DDD/10^6 inhabitants and day.

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 75% 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 fluconazole, both as prophylaxis and as treatment.

The use of voriconazole is still low in absolute numbers (2.49 DDD/10^6 inhabitants and day), but the downward trend that was seen in hospital use last year has been reversed and

the use increased by 9%. 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 broadspectrum antifungal drug that can be given orally and is therefore often used when the initial iv 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 63% in 2009.

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 mikafungin. (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 11% during 2009.

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 remained at the same level as last year.

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.

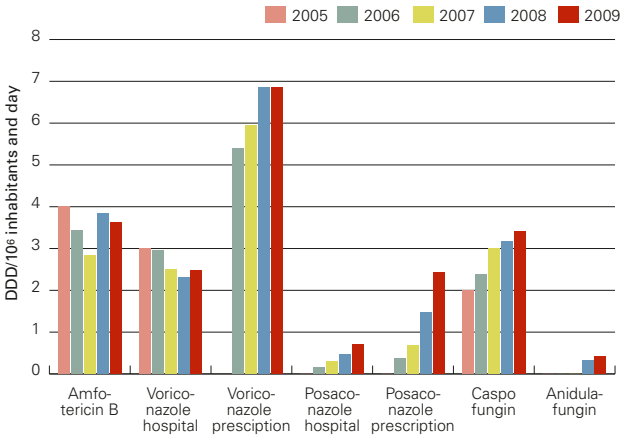


FIGURE 3.1.29. Use of broadspectrum antifungals in hospital care, 2005-2009, DDD/10^6 inhabitants and day.

Outpatient care

70% of all systemically administrated antifungal drugs are sold on prescription. 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 dermatophyte infections 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

SURVEILLANCE of antimicrobial resistance is normally based on testing of clinical samples and samples taken according to screening programmes. Each part of the Swedish surveillance programme is based on data collected from all the clinical microbiology laboratories. In these laboratories testing of clinical isolates for antibiotic susceptibility is routinely performed using the standardized disk diffusion method (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 ESBL-producing *Enterobacteriaceae* 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.

Annual resistance surveillance and quality control (RSQC) programme form the second part of the national surveillance programme and it was initiated in 1994 (Appendix 5). Well-characterized data on resistance in many bacterial species are now available from several years both at regional and national level.

Under the heading **Data on invasive isolates reported to EARSS,** results from the Swedish part of the European Antimicrobial Resistance Surveillance Network are presented. Twenty of twentyeight Swedish laboratories, covering approximately 75% of the population, regularly report susceptibility data on invasive isolates of seven defined bacterial species to EARSS/ECDC 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 EARSS, data on resistance is presented under the heading **Surveillance of invasive isolates in addition to EARSS**.

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 2009 27 of 28 laboratories provided data on MRB- screening.

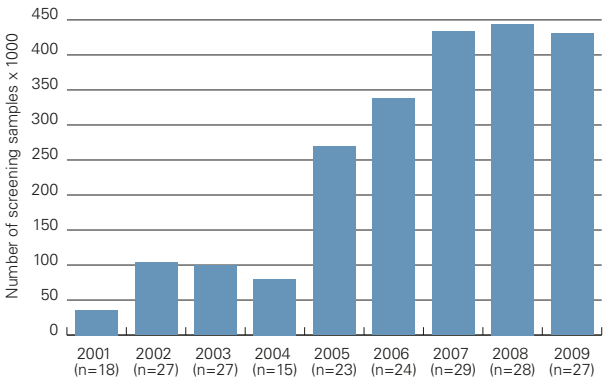


FIGURE 4.1. Annual number of recorded screening samples for multiresistant bacteria, 2001-2009. n refers to the number of participating laboratories.

Table 4.1 shows the rate of positive findings according to the different screening programmes. The categorization of screening programmes vary between laboratories.

TABLE 4.1. Compilation of responses, from 24 responding laboratories, of an inquiry concerning sampling series, sampling and positivity numbers for screening/contact tracing samples for 2009. n refers to the number of responding laboratories.

	Total number of analyses	Number of sampled persons	Total number of positive tests	Number of persons with at least one positive sample
MRB	69 217 (n=11)	13 814 (n=7)	1 603 (n=8)	313 (n=6)
MRSA	286 802 (n=19)	62668 (n=15)	4253 (n=19)	1728 (n=19)
VRE	65 292 (n=17)	24730 (n=15)	749 (n=19)	341 (n=17)
ESBL	14 620 (n=14)	15089 (n=13)	1877 (n=16)	1788 (n=16)
Other	851 (n=1)	126 (n=1)	2 (n=1)	2 (n=1)

Staphylococcus aureus including MRSA

Notifications of MRSA according to the Communicable Disease Act

MRSA was made mandatory notifiable in the year 2000. Infection control programmes have been developed and implemented locally under supervision by 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.

The following presentation is based on data collected in the web-based notification system "SmiNet 2" as recorded at the county level. During the last four 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 2009 a total of 1480 cases of MRSA were notified, an increase by 13% compared with the 1307 cases 2008, Figure 4.2.

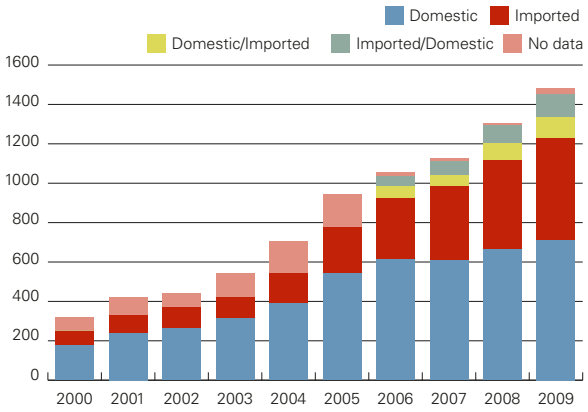


FIGURE 4.2. Number of MRSA notified annually by country of infection, Sweden 2000-2009. "Domestic/Imported" and "Imported/Domestic" indicate several mentioned countries of infection with the most likely mentioned first.

In 2009, eight of the Swedish counties, marked by colour in Table 4.2, (Stockholm, Jönköping, Kalmar, Skåne, Västra Götaland, Örebro, Västmanland, Västernorrland), had a higher incidence than the average national incidence of 15.8 cases/100 000 inhabitants, Table 4.2.

During 2009, 48% (n=711) of all reported MRSA cases were domestically acquired and 35% (n=517) were acquired abroad. China (54 cases), Philippines (44 cases), Iraq (33

TABLE 4.2. MRSA notified in 2000-2009 by county according to the Communicable Disease Act

	2000		2001		2002		2003		2004		2005		2006		2007		2008		2009	
County	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***	**No**	**Inc ***
Stockholm	97	5.3	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
Uppsala	19	6.5	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
Södermanland	2	0.8	1	0.4	4	1.5	2	0.8	8	3.1	11	3.8	9	3.4	26	9.8	20	7.5	23	8.5
Östergötland	2	0.5	7	1.7	7	1.7	14	3.4	14	3.4	101	24.3	48	11.5	49	11.6	43	10.2	45	10.5
Jönköping	7	2.1	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
Kronoberg	1	0.6	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
Kalmar	3	1.3	5	0.9	5	2.1	6	2.6	16	6.8	23	9.7	26	11.1	36	15.4	29	12.4	42	18,0
Gotland	1	1.8	10	17.5	3	5.3	2	3.5	1	1.7	10	17.3	4	6.9	8	14,0	6	10,5	6	10.5
Blekinge	7	4.7	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
Skåne	22	1.9	76	6.7	68	5.9	104	9.1	128	11.3	162	13.9	179	15.5	166	13.8	273	22.5	284	23.1
Halland	10	3.6	26	9.4	13	4.7	13	4.6	9	3.2	21	7.4	23	8.1	18	6.2	16	5.5	45	15.2
Västra Götaland	114	7.6	56	3.7	48	3.2	63	4.2	118	7.8	125	8.1	177	11.6	178	11.5	245	15.7	258	16.4
Värmland	9	3.3	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
Örebro	8	2.9	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
Västmanland	3	1.2	8	3.1	6	2.3	11	4.2	12	4.6	35	13.4	48	18.4	54	21.7	23	9.2	46	18.3
Dalarna	0	0,0	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
Gävleborg	2	0.7	1	0.4	12	4.3	5	1.8	5	1.8	24	8.6	17	6.1	12	4.4	26	9.4	12	4.3
Västernorrland	14	5.7	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
Jämtland	0	0,0	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
Västerbotten	3	1.2	17	6.7	10	3.9	13	5.1	16	6.2	10	3.8	7	2.7	23	8.9	22	8.5	28	10.8
Norrbotten	3	1.2	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
Total	327	3.7	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

* = Incidence (cases/100 000 inhabitants)

cases), Vietnam (32 cases) and USA (27 cases) made up the five most common countries for imported MRSA infection during 2009. In 15% of the cases Sweden and at least one more country were mentioned as possible countries for acquisition of MRSA. When these reported secondary countries were also considered, the three most common countries were still the same (China 55 cases, Philippines 48 cases and Iraq 47 cases), whereas Thailand (35 cases) became number four followed by Vietnam (34 cases). The country for acquisition was reported as "unknown" in 24 cases and in seven cases no country of acquisition was listed.

Among the domestic MRSA cases, an increased incidence was seen in the age group 0-6 years during 2009, Figure 4.3. In contrast, a decrease in incidence was seen for domestic cases 80 years and older. Since 2006, the incidence in age groups between 7 and 79 years has remained stable.

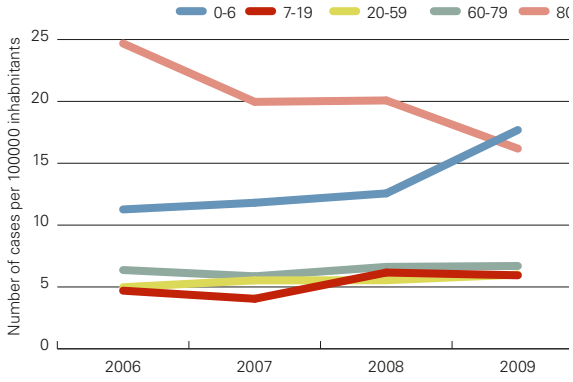


FIGURE 4.3. Age group adjusted incidence of notified domestic MRSA cases (n=711), Sweden 2006-2009.

In 2009, 57% of the domestic cases were identified through contact tracing or targeted screening, and 42% presented with clinical symptoms (Figure 4.4). For imported cases in 2009 the corresponding figures were 65% and 35%. Twenty-two cases with invasive MRSA infection were reported. Eighteen of those were new cases 2009, and four cases were previously known to carry MRSA.

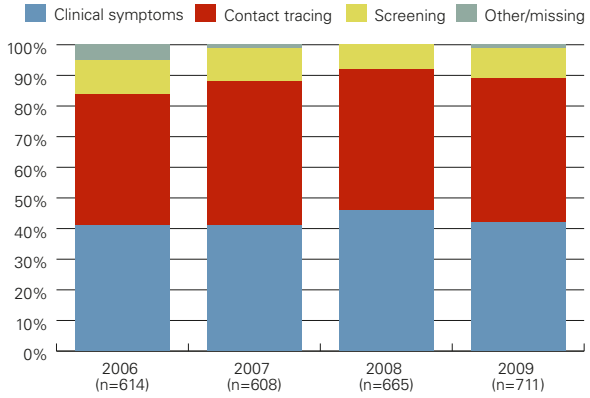


FIGURE 4.4. The reasons for detection of domestic MRSA cases in Sweden 2006-2009. n refers to the number of reported cases.

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.

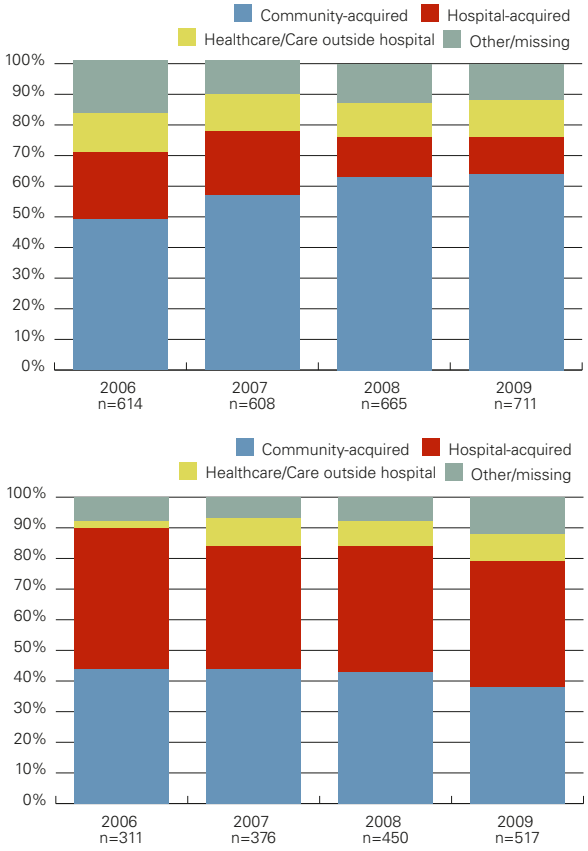


FIGURE 4.5. A and B. Epidemiological classification of the acquisition of domestic (a. top) and imported (b. bottom) MRSA, Sweden 2006-2009.

Community-acquired infections dominated among domestic cases 2009 and comprised 64% (n=458) 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 primarily acquired in the community. Among the imported cases the proportion of community acquired infections was 38% (n=198). Community acquisition was reported for two thirds of the cases for which it was uncertain whether MRSA was acquired domestically or imported (n=231).

Hospital acquired MRSA was comparatively more common in imported cases, 41% (n=212), than among domestic cases, 12% (n=85). Among imported cases a similar proportion of hospital acquired MRSA was seen in 2007 and 2008, but for domestic cases the proportion of hospital acquired MRSA was lower in 2008 and 2009 (12%) than in 2006 and 2007 (20%).

During 2009 only a few minor outbreaks were reported from the Swedish healthcare system and from long-term care facilities. They were reported from several counties.

Typing of MRSA

DNA-based methods have been used for typing of all MRSA isolates in Sweden since the year 2000. During 2000-2005 pulsed field gel electrophoresis (PFGE) was the standard

method. It was replaced by spa-typing in 2006 and this is now the primary typing method. spa-typing is based on sequencing of the polymorphic X-region of the *S. aureus* species-specific protein A gene, spa, and the Ridom StaphType® software is used for analysis.

The ten most common spa-types among notified cases in 2009 were t008 (n=157), t044 (n=108), t002 (n=106), t019 (n=59), t015 (n=58), t437 (n=53), t223 (n=46), t127 (n=44), t032 (n=38), and t037 (n=27) (Table 4.3). The five most common of these types comprised one third, and all ten most common types comprised almost 50% of all cases. The total number of spa-types identified in 2009 was 245, indicating the good discriminatory power of this typing method.

The ten most common spa-types during the last three years are shown in Table 4.3. The most dramatic changes seen were on the one hand the decrease in prevalence of t032 (often equivalent to strain EMRSA-15 or UK E15 according to the Swedish PFGE nomenclature), which is a typically healthcare related strain, and on the other hand the rise and dominance of the PVL-positive, most often community associated strains with spa-types t008, t044 and t019.

TABLE 4.3. Ten most common spa-types in 2007-2009 listed in decreasing order per year.

2007	2008	2009
t032	t002	t008
t008	t008	t044
t044	t044	t002
t002	t019	t019
t037	t032	t015
t015	t127	t437
t437	t437	t127
t690	t024	t223
t024	t015	t032
t019	t037	t037

As in the previous two years, isolates with spa-types t015, t032, t037 and t223 were always negative for the PVL-toxin, whereas isolates with spa-type t044 were always positive. Among isolates of the other common spa-types both PVL-positive and –negative ones were found. In total, 491 (34%) of all tested isolates from 2009 were PVL-positive. This was in line with results from the last couple of years, when PVL-positive isolates have represented more than 30% of all MRSA cases. Among the PVL-positive isolates, those of spa-type t008 were most frequently encountered in 2009, followed in decreasing order by t044, t019, t437, t002, t355, t852, t024, t657 and t318.

Since 2006 there has been focus on the zoonotic potential of MRSA and especially occurrence of the livestock associated MRSA belonging to clonal complex CC398 as reported from several European countries (see also SVARM). However, in humans in Sweden 2006-2009, only few cases of MRSA with spa-types correlating to CC398 were found. These were five cases with t011, two cases with t108, five cases with t034, and two cases with t571, all of them PVL-negative. An additional twelve cases of PVL-positive t034 have been identified, but they seem to be unrelated to the livestock associated MRSA. The epidemiological information on these cases is however scarce, and only in one case the connection between animal (horse) and man has been confirmed.

Antibiotic resistance in MRSA

All MRSA isolates were investigated with regard to resistance to antibiotics other than betalactam antibiotics, Table 4.4. The antibiotic categories were fluoroquinolones (ciprofloxacin tested), macrolides (counting erythromycin and clindamycin as one category), fusidic acid, aminoglycosides (gentamicin tested), and rifampin. Out of 1158 isolates tested (MRSA from all counties except Skåne and Örebro), 508 (44%) had no other resistance marker than the *mec*A 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 fusidic acid, resistance to gentamicin, and to a lesser degree resistance to rifampicin or to mupirocin. The general trend described in SWEDRES 2008 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 84 strains meeting these criteria. Six different spa-types were frequently found to be multiresistant and are described in Table 4.4.

TABLE 4.4. Characteristics of the six most frequent spa-types among multiresistant MRSA 2009

Spa type	No of strains	Acquisition	Route of transmission	Antibiogram[a]	CC/ST[b]
t037	27	Sweden/ abroad	Healthcare	CDEFGR CDEG	CC8 /ST239, worldwide
t041	7	Abroad	Healthcare	CDEG	CC5 /ST228, Germany, Italy
t189	6	Sweden/ abroad	Healthcare/ Community	CDEG	ST188, worldwide (also as MSSA)
t062	5	Sweden/ abroad	Healthcare/ Community	CDEG	CC5 /ST5
t149	5	Abroad	Healthcare/ Community	CDEG	CC5 /ST5, Europe
t1081	7	Sweden/ abroad	Healthcare	CDEG	CC45 /ST45, Europe

[a] C = ciprofloxacin, D = clindamycin, E = erythromycin, F = fusidic acid, G = gentamicin, R = rifampicin. [b] Information retrieved from Ridom SpaServer (www.spaserver.ridom.de).

Is the epidemic of fusidic acid resistant *Staphylococcus aureus* causing bullous impetigo over?

SINCE THE MID-1990s there has been an increased incidence, later described as a clonal spread, among Swedish children of a *Staphylococcus aureus* strain resistant to fusidic acid. This strain caused bullous impetigo in small children, necessitating treatment. Fusidic acid ointment has long been used in Sweden, but this use was questioned when the epidemic potential of the resistant strain was understood. Not only Sweden but also other northern European countries have witnessed this epidemic (1-3).

In Sweden this epidemic has been thoroughly investigated regarding both its epidemiology and microbiology, and its effect on the sales of fusidic acid ointments has also been studied. In previous SWEDRES reports we have briefly commented upon the epidemic in relation to the yearly prevalence studies on antibiotic resistance in *S. aureus*.

In 2009 it was feasible for those counties providing information to the previous two studies to once again retrieve microbiological data on fusidic acid resistance in *S. aureus* from children (0-12 years) compared to adults (13-99 years). In Figure 4.7 it is clearly shown that the frequencies of resistance among children are decreasing in all counties and are approaching the levels around 10% seen throughout in the adult population. The sales statistics of fusidic acid to children 0-12 years are presented in Figure 4.8.

It is assumed that the resistance levels should be back at "normal" levels in a year or two, however national guidelines still recommend that fusidic acid shall be avoided.

Gunnar Kahlmeter, National Reference Laboratory for Antibiotic Resistance; Barbro Olsson-Liltjequist, Swedish Institute for Infectious Disease Control and the FURSA study group

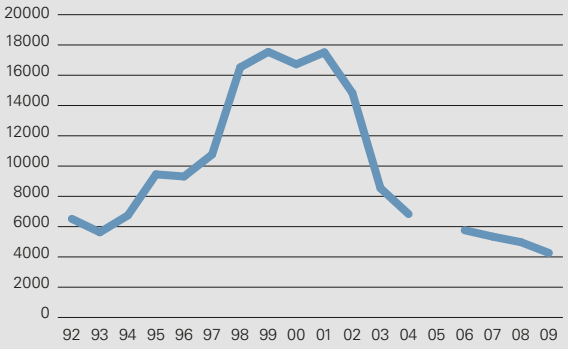


FIGURE 4.8. Sales statistics of fusidic acid to children 0-12 years in Sweden 1992-2009.

References

Österlund A, Eden T, Olsson-Liljequist B, Haeggman S, Kahlmeter G; Swedish Study Group on Fusidic Acid-resistant *Staphylococcus aureus*. Clonal spread among Swedish children of a *Staphylococcus aureus* strain resistant to fusidic acid. Scand J Infect Dis 2002;34:729-34.

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Tveten Y, Jenkins A, Kristiansen B-E. A fusidic acid-resistant clone of *Staphylococcus aureus* associated with impetigo bullosa is spreading in Norway. J Antimicrob Chemother 2002; 50:873-876.

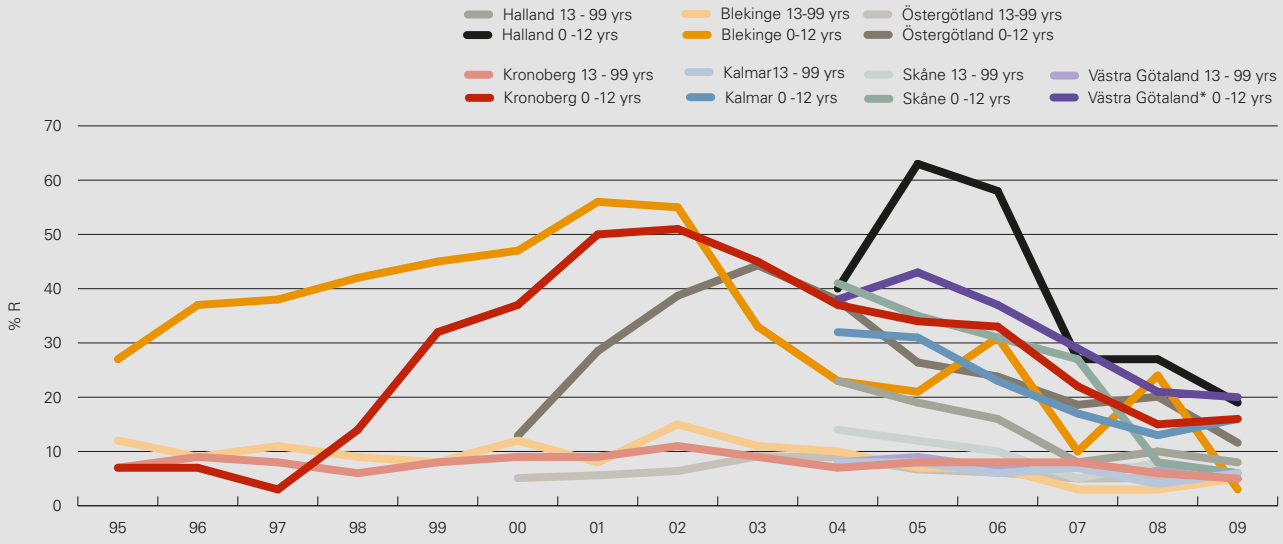

FIGURE 4.7. *Staphylococcus aureus* with fusidic acid resistance in patients 0-12 years and 13-99 years in 7 Swedish counties 1995-2009.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Staphylococcus aureus from wound infections has been included in the annual RSQC programme since 2001 (Appendix 5). Twenty-eight laboratories regularly provide data on consecutive isolates using the disk diffusion method for cefoxitin (from 2004 used as screening disk for detection of MRSA), clindamycin, fusidic acid, aminoglycoside (gentamicin or tobramycin) and vancomycin. Erythromycin (group representative for macrolide antibiotics) and a fluoroquinolone (ciprofloxacin or norfloxacin) have also been tested since 2004. The average resistance rates, as retrieved from ResNet, are shown in Figure 4.6.

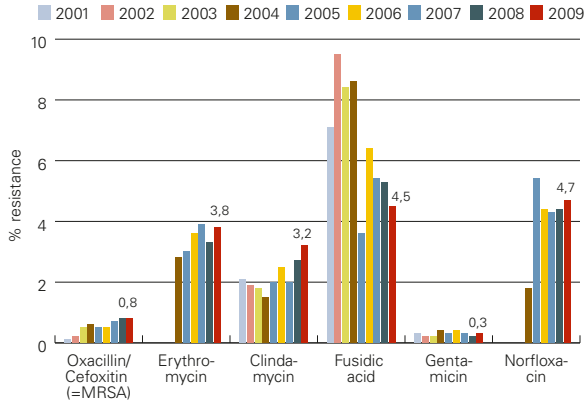

FIGURE 4.6. Resistance rates in *Staphylococcus aureus* 2001–2009 (data from the annual RSQC programme, approximately 3000 isolates per year). In 2005 resistance rates were recorded in *S. aureus* isolated from skin and soft tissue infections from elderly (> 65 years) people only.

The frequency of MRSA in skin and soft tissue infections (SSTI) (cefoxitin used as test compound) has increased slowly but the level in 2009 still remained below 1%. The resistance rate for erythromycin (3.8%) was only slightly higher than that for clindamycin (3.2%). 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 reduced to below 5%. The story of the fusidic acid resistant clone causing bullous impetigo in children is described in detail, see HIGHLIGHT page 30. Almost no resistance to aminoglycosides was seen in bacteria from SSTI. Fluoroquinolone resistance was stable at 4-5%.

Data on invasive isolates reported to EARSS

In 2009, 0.9% of the invasive *S. aureus* isolates were MRSA (identified by the cefoxitin screen disk test and confirmed by detection of the *mec*A gene), Table 4.5. This low level has remained during the nine years of mandatory reporting, indicating that infection control measures to prevent MRSA from spreading in the hospital environment have been successful. Fifteen spa-types were identified among the 18 newly discovered invasive MRSA isolates in 2009, indicating that these cases were sporadic.

TABLE 4.5. *Staphylococcus aureus* susceptibility results (number of strains and percentage) in blood isolates by the disk diffusion method and by confirmation of the *mec*A gene. Data reported from SMI to EARSS.

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%)

Johan Struwe, Tomas Söderblom, Gunnar Kahlmeter, Barbro Olsson-Liljequist

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 2009 there were 446 notifications of PNSP in Sweden, Figure 4.11, a decrease by 21% compared with 2008. Fifty-three percent of the cases had been infected domestically and 16% of the cases in a foreign country. In the remaining 138 cases no country for acquisition was given.

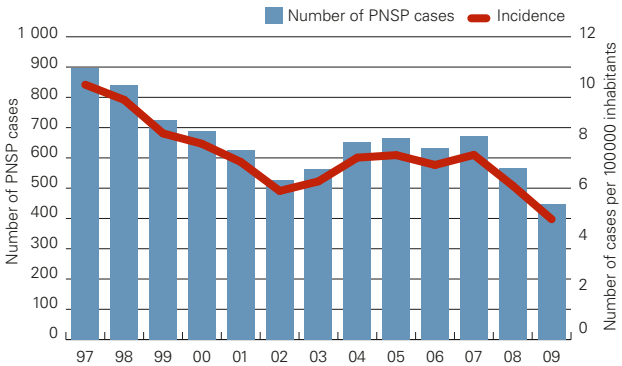

FIGURE 4.11. Number of cases of *S. pneumoniae* with reduced susceptibility to penicillin, MIC ≥ 0.5 mg/L (left) and cases per 100 000 inhabitants (right), Sweden 1997-2009.

The PNSP incidence in Sweden was 4.8 cases per 100 000 inhabitants 2009. Previous analyses have indicated that the declining incidence has been 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 4.12. Compared with 2008 the decrease in number of reported cases was found primarily in

Staphylococcus aureus among blood isolates: proportions and types

CONSECUTIVE DATA on blood isolates are obtained from 20 laboratories participating in the Swedish EARSS Network. These laboratories deliver data on seven pathogens, namely *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. From eleven of these 20 laboratories information is available on all their positive blood cultures (one isolate per patient), allowing for analysis on more microorganisms than the seven "EARSS"-bacteria. These sets of data are complete from 2005 and onwards and have been used to gather information on for instance *Streptococcus pyogenes* and *Streptococcus agalactiae* to previous SWEDRES reports.

However, the two most frequently found pathogens in blood cultures were *E. coli* and *S. aureus*, save for the commonly isolated coagulase negative staphylococci. We investigated the proportions of these two bacterial species in relation to the total numbers of positive cultures and also looked for trends. The total numbers of blood cultures taken (pairs of bottles) increased every year in all of the eleven laboratories as can be seen in Figure 4.9. This might indicate a general awareness of infectious diseases and an increased adherence to guidelines. However, the percentage of positive blood cultures did not change during these five years. It ranged between 7.6% and 7.9% in 2005-2009.

The proportions of *S. aureus* (this chapter) were further analysed for geographical differences or changes over time. In Figure 4.10 is shown the percentage of *S. aureus* of all positive blood cultures per laboratory/county and year. A rough estimate of the overall average was 11%.

There were small differences between laboratories/counties, but there were only few examples of trends within laboratories/counties. One county (Dalarna) had a proportion above 11% during all five years, whereas the other ten varied around 11% through the years. In one county (Kronoberg) there was a continuous rise in the proportions of *S. aureus*, whereas in the other laboratories / counties the levels fluctuated between the years.

Invasive *Staphylococcus aureus* – a snapshot of spa-types

Molecular typing methods are only rarely applied on *S. aureus* isolates, invasive or others. However, one recent European overview of invasive *S. aureus* isolates was performed through an initiative by the EARSS network together with Seqnet.org. National EARSS-representatives agreed to create a working group of *S. aureus* reference laboratories across Europe. This working group supported a structured survey for the identification of the strain composition of *S. aureus* isolates that cause invasive infections in Europe. During a 6 month period 2006-2007, 2890 methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) isolates from invasive infections of patients treated in 450 European healthcare institutions from 26 European countries have been systematically collected and analysed by spa-sequence typing. This collection provides a genetic snapshot of the *S. aureus* population causing invasive disease in Europe including MSSA as well as MRSA strains (Grundmann *et al.* 2010). In the report there is a mapping platform providing a widely applicable research tool for geographic tracking of strains/clones with particular public health importance. It enables viewing the spatial distribution of spa-types across the EARSS network.

Sweden contributed information and spa-typing results on 200 isolates, 5 of which were MRSA. These five had spa-types t002, t021, t032, t041 and t455. Among the 195 MSSA a total of 93 spa-types were identified. The ten most common of these were, in decreasing order, t015, t084, t012, t021, t002, t160, t050, t026, t005 and t008. These spa-types are also commonly found among MRSA isolates both in Sweden and in Europe.

Barbro Olsson-Liljequist, Gunnar Kahlmeter and the Swedish EARSS laboratories

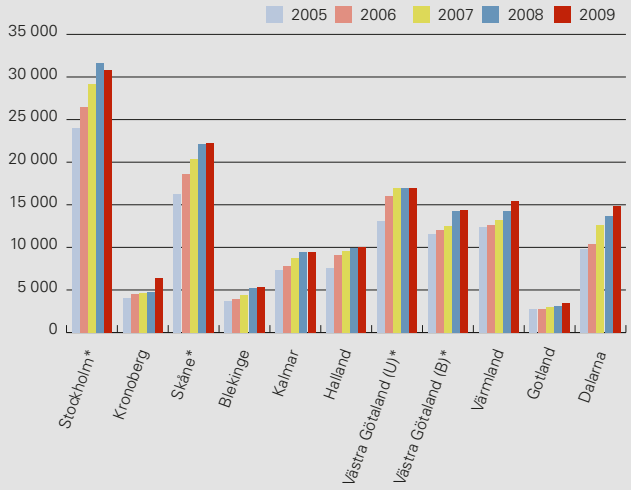

FIGURE 4.9. Number of blood cultures per laboratory 2005 -2009. *Data representing part of county.

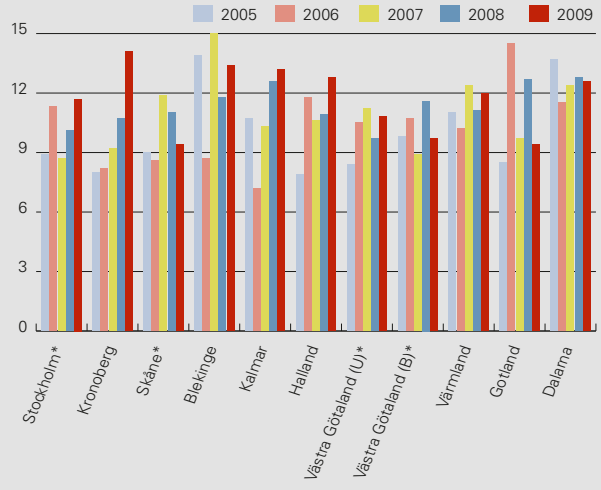

FIGURE 4.10. Proportions of *S. aureus* among positive blood cultures from eleven laboratories representing counties or parts of counties (*) 2005-2009. *Data representing part of county.

this age-group. There was no difference in the proportion of the reported cases with regard to sex.

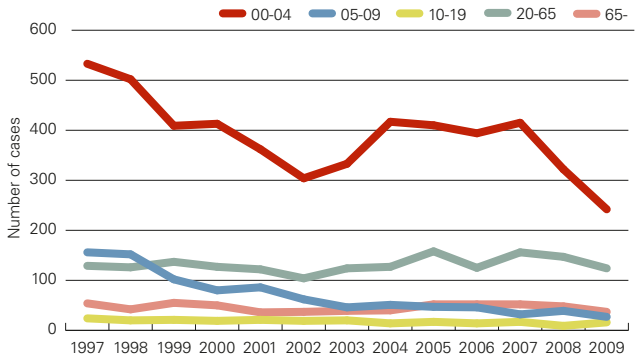

FIGURE 4.12. Age-group distribution among all cases reported with PNSP in Sweden 1997-2009.

PNSP were reported from all 21 counties with Stockholm (144 cases) and Skåne (135 cases) accounting for 63% of all notifications. In these two counties, the notifications have decreased by 22% and 38%, respectively. Remaining counties reported 1-36 cases each. Due to regional differences in general culturing propensity, case finding intensity as well as presence of targeted screening programmes, a comparison of regional incidence rates is not meaningful. The majority, 82% of all notifications of PNSP, were found in cultures from nasopharynx. In 43% of all cases the detection of PNSP was due to clinical infection, and in 28% due to targeted screening including contact tracing. In the remaining cases another reason for sampling was stated or the information was missing. Of all PNSP cases during 2009, 53% (n=236) were domestic cases and 16% were imported. Information was missing in 138 cases.

In 2009, 14 cases were reported to have invasive PNSP infections, 14 cases in blood and in one of those also in cerebrospinal fluid. For 11 of these cases the serotypes were reported, and six had serotype 9, two serotype 14, and one each had serotypes 6, 23 and 35. The most commonly found serotypes among all PNSP were, in decreasing order, type 19F (29%), followed by type 23F (12%), 9V (9%), 19A (7%), 6B (7%), and non-typeable 7%. The distribution of serotypes has thus changed and serotype 9V was less dominant. Based on these results the potential coverage rates of the 7-, 10- and 13-valent vaccines were 64%, 64% and 77%, respectively.

Annual Resistance Surveillance and Quality Control (RSQC) programme

The isolates collected during the RSQC surveys are mainly derived from nasopharyngeal cultures. Approximately 3000 consecutive isolates per year from all the clinical laboratories have been tested for susceptibility to penicillin (by means of oxacillin 1 µg screen disk), erythromycin, clindamycin (from 2004), tetracycline, trimethoprim-sulfamethoxazol, and norfloxacin (from 2005, used as indicator for fluoroquinolone resistance) using the disk diffusion method. The national summary of the results is shown in Figure 4.13. For all tested antibiotics except norfloxacin there has been a steady increase in rates of resistance every year.

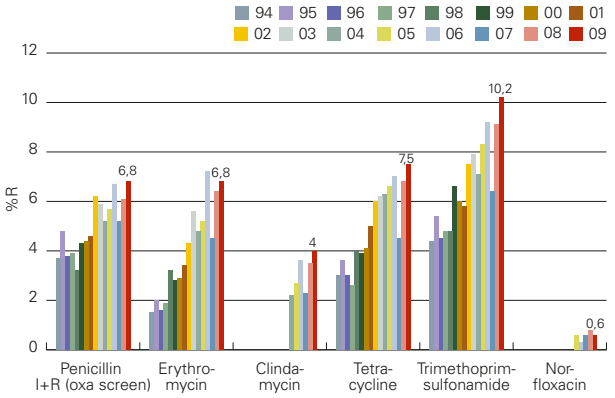

FIGURE 4.13. Resistance rates for *Streptococcus pneumoniae* 1994-2009 (data from the annual RSQC programme, approximately 3000 isolates per year).

Data on invasive isolates reported to EARSS

The Swedish data on susceptibility to penicillin and erythromycin among invasive isolates for 2001-2009 are given in Table 4.6. Levels of resistance were lower among invasive isolates than in the nasopharyngeal isolates from the RSQC programme. Also, there has been no increased resistance among invasive isolates, neither for penicillin nor erythromycin, contrary to the nasopharyngeal isolates. This might be explained by the fact that a substantial proportion of nasopharyngeal isolates are collected during contact tracing around resistant cases.

TABLE 4.6. Invasive isolates of *Streptococcus pneumoniae* reported to EARSS.

Penicillin * (I+R = PNSP)				
Year	**S%**	**I%**	**R%**	**Total**
2001	97.2	2.3	0.5	788
2002	97.5	2.4	0.1	783
2003	95.0	5.0	0	920
2004	96.8	2.8	0.4	955
2005	96.4	3.1	0.5	1017
2006	97.9	2.1	0	936
2007	97.1	2.9	0.1	1029
2008	98.0	1.6	0.4	1213
2009	97.2	2.8	0	1098
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

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

Tomas Söderblom, Barbro Olsson-Liljequist, Johan Struwe, Birgitta Henriques Normark, Gunnar Kahlmeter

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 immunosuppressed 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 also mandatory.

Notifications of VRE according to the Communicable Disease Act

From 2000 to 2006 low numbers of VRE cases were reported (18-35 per year), and in 2007 53 cases were notified. Beginning late autumn 2007, reports came from Stockholm county about an increase in the number of VRE cases. An increased dissemination of VRE was later reported from other counties and continued during the whole of 2008, adding up to a total of 618 cases. In 2009, the number of cases was 402, a reduction from the previous year with 35%. Reports on VRE came from 13 of the 21 Swedish counties, but the majority of cases (92%) were from the three counties with previously reported outbreaks, Stockholm (n=179), Västmanland (n=133) and Halland (n=59). An additional 31 cases were reported from the remaining 18 counties. The national incidence of VRE was 4.3 cases per 100 000 inhabitants. In the three affected counties the incidence had decreased in Stockholm from 21.1 to 8.8 and in Halland from 29.3 to 19.9, but increased in Västmanland from 33.2 to 53. Also Gotland, with five reported VRE cases, reached above the national incidence with 8.7 cases per 100 000 inhabitants. The mean age for all cases was 72 years with an even distribution between the sexes.

In 26 cases the VRE was acquired abroad and 16 different countries were stated. For 21 of these cases the acquisition was healthcare-related and for the remaining five cases information was missing.

During 2009, 394 cases had *Enterococcus faecium*. Of these, 326 carried the *van*B gene and 61 the *van*A gene. Information was missing for seven cases. In one case a double infection was reported with *Enterococcus faecium* with either *van*A or *van*B. *Enterococcus faecalis* was reported in six cases and all had the *van*A-gene. Three cases were reported with both *Enterococcus faecalis* and *Enterococcus faecium*.

According to the first laboratory notifications for each case the majority of isolates were from faeces (90%), whereas 2.5% each of the isolates were from rectum and urine. Invasive VRE infections, all from blood, were reported in 5 cases. Four of those were new cases and one case was known from previous years. The findings of VRE in faeces or rectum in more than 90% indicated that most of the cases were detected by screening.

Epidemiological typing

For enterococci PFGE was used as the standard typing method. All isolates from the counties of Halland and Västmanland with *van*B were analysed and found to have one variant each of the strain causing epidemic spread in these counties. Only a minor set of strains from Stockholm county was available for analysis, but exchange of information indicated that the majority of cases of *Enterococcus faecium* with the *van*B gene in Stockholm also belonged to this strain.

Comparisons with older isolates of *Enterococcus faecium* with the *van*B gene in the national strain collection and database indicated that this strain had not been detected before 2007. Several smaller outbreaks in Sweden during 2000-2006 were caused by strains of different PFGE-types.

Sporadic cases with *Enterococcus faecium* with the *van*A gene have been notified since 2000. PFGE analyses of those indicate that the majority are single cases with unique PFGE patterns.

Data on invasive isolates reported to EARSS

Enterococcus faecalis and *Enterococcus faecium* have been reported to EARSS 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%), and in 2004 three isolates were found (1.2%), Tables 4.7 and 4.8. Molecular typing of these vancomycin-resistant isolates indicated relatedness only between two of them from the same hospital. In 2006 two resistant blood isolates were found, in 2007 none, in 2008 six isolates of *Enterococcus faecium* with *van*B, and in 2009 two isolates. The six isolates from 2008 all showed the same PFGE pattern as the recent epidemic strain described in the highlighted section (page 34).

HLAR was more prevalent in *Enterococcus faecium* (27.4%) than in *Enterococcus faecalis* (19.6%) in 2009. 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* reported to EARSS 2001-200

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)

The nationwide outbreak of a vancomycin-resistant *Enterococcus faecium* with *van*B – an update

VANCOMYCIN-RESISTANT *Enterococcus faecium* and *Enterococcus faecalis* (VRE) in infection as well as colonization, have been mandatory notifiable according to the Swedish Communicable Diseases Act since year 2000. Mandatory contact tracing was implemented 2004. The basic epidemiological information of the notified cases has been given in chapter *Enterococcus faecalis* and *Enterococcus faecium*. In this highlighted area we describe the rise and present decline of this widespread dissemination in more detail.

The recognition of the outbreak situation in 2007 lead to intensive contact tracing and screening activities and also to other infection control measures. Since August 2007 until the end of 2009 altogether 1057 cases of VRE were found and reported from 17 counties. Of these, 11 counties reported 986 cases as acquired domestically, and a majority of these (95%, n=941) were healthcare-related. Among the domestic cases only 7% had clinical symptoms. 73% were identified through contact tracing, 13% by screening, and for 7% the indication for sampling was unknown. According to the first laboratory notifications of the domestic cases 88% (n=868) were isolated from faeces, 3.5% (n=35) from urine, 3.5% (n=34) from wounds, and 4 cases (0.4%) isolated from blood.

Typing and antibiotic resistance of the epidemic VRE

Verification by PCR of species and vancomycin resistance mechanism showed that 856 of the domestic cases were *E. faecium* with *van*B gene, 125 *E. faecium* with *van*A gene and in five cases the resistance gene was not reported. *E. faecalis* were reported for only 9 cases during the whole period, six with *van*A gene and in three cases the resistance gene was not reported. The species and resistance genotype distribution per county for the 941 domestic cases reported as healthcare-related are presented in Table 4.9.

TABLE 4.9. Species and resistance genotype for the domestic, healthcare-related VRE cases, August 1st 2007 to 31st December 2009.
Efm = *Enterococcus faecium*, Efs = *Enterococcus faecalis*. The numbers per county of species and resistance genotype do not always match exactly with the total number of cases due to double infections or missing information of resistance genotype.

County	No of cases	Efm, *van*A	Efm, *van*B	Efs, *van*A	Efs, *van*B
Stockholm	571	110	463	2	-
Västmanland	211	2	207	1	-
Halland	138	2	136	-	-
Uppsala	9	-	8	-	-
Gotland	4	-	3	1	-
Skåne	4	-	4	-	-
Västra Götaland	2	-	2	-	-
Värmland	1	-	1	-	-
Västerbotten	1	-	1	-	-

Epidemiological typing of the *E. faecium* isolates with *van*B gene was performed by PFGE. The results showed that all examined isolates from Västmanland and Halland, as well as the majority of the isolates from Stockholm county, had closely related PFGE patterns, suggesting dissemination of the same strain in these counties. Preliminary, but still incomplete, data indicate that this pattern has not been seen in VRE isolates reported before 2007 in Sweden. Moreover, this PFGE pattern could not be recognised in a large collection of recent VRE isolates from Germany (G Werner, personal communication).

The isolates of the epidemic strain were typically resistant to vancomycin (MICs 8-64 mg/L) but susceptible to teicoplanin (MICs 0.125-1 mg/L), and they were also resistant to ampicillin, imipenem, ciprofloxacin and macrolides but showed only low-level resistance to gentamicin.

The epidemic curve for the domestic, healthcare-related cases of *E. faecium* with *van*B (n=825) is presented in Figure 4.14.

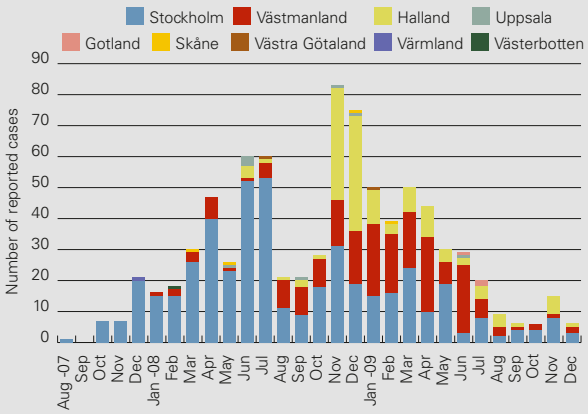

FIGURE 4.14. Epidemic curve for spread of healthcare-related domestic *Enterococcus faecium* with *van*B (n=825).

Conclusions

Intensive efforts have been made in the respective regions, with support from national authorities, to control the outbreaks and disseminations of VRE. Control measures and interventions have consisted of increased awareness of hand hygiene, not only for staff but also for patients, withdrawing of food buffets from the hospital wards, extensive cleaning of the patient environment, and use of probiotics (*Lactobacillus rhamnosus* GG). At the end of 2009 there was a dramatic decrease in the number of newly detected cases, but it is too early to state that this will be a permanent situation. A central field epidemiology group was recruited for an assessment of the management of the outbreaks. Based on its report and on expertise presented at a timely workshop in December 2008, a new nation-wide action-programme will soon be launched.

Barbro Olsson-Liljequist, Johan Struwe, Tomas Söderblom, Karin Tegmark-Wisell, Magnus Thore, Swedish Institute for Infectious Disease Control; Olov Aspevall, Karolinska University Hospital Huddinge; Mats Erntell, Communicable Disease Control, Halland; Karin Kidd-Ljunggren, Ingegerd Sjögren, Halmstad Hospital; Göran Hedin, Falun Hospital; Daniel Heimer, Västerås Hospital; Ingegerd Hökeberg, Communicable Disease Control, Stockholm; Åsa Melhus, Uppsala Akademiska University Hospital; Jan Smedjegård, Communicable Disease Control, Västmanland; Staffan Sylvan, Communicable Disease Control, Uppsala

TABLE 4.8. Resistance among invasive isolates of *Enterococcus faecium* reported to EARSS 2001-2009

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	0.8	27.4	311 (274)

Tomas Söderblom, Barbro Olsson-Liljequist, Karin Tegmark Wisell, Johan Struwe, Magnus Thore, Gunnar Kahlmeter

Streptococcus pyogenes

Annual Resistance Surveillance and Quality Control (RSQC) programme

Streptococcus pyogenes was not included in the RSQC programme in 2009.

Surveillance on invasive isolates additional to EARSS data

Data on consecutive blood isolates were obtained from 11 laboratories. One hundred and thirty-four isolates of 11.416 (1.2%) were *Streptococcus pyogenes* (GAS). This was in the same order of magnitude as in the previous two years with 1.8 and 1.2% GAS, respectively. All GAS isolates were susceptible to penicillin. Three isolates (2.2%) were resistant to erythromycin and clindamycin, indicating that they possessed *erm* genes (MLS_B type of resistance). This was an increase compared with 0.5% in 2008. Thirteen isolates (9.7%) were resistant to tetracycline which was a decrease from 2008 (14.6%). A majority of the isolates were retrieved from adults (> 50 years), and only 3% of the isolates were from children 0-9 years.

Streptococcus agalactiae

Surveillance on invasive isolates additional to EARSS data

131/11.416 (1.1%) of consecutive blood isolates from the participating 11 laboratories were *Streptococcus agalactiae* (GBS). This was in the same order of magnitude as the previous two years with 1.0 and 1.3% GBS, respectively. All GBS isolates were susceptible to penicillin/ampicillin. Nine of the isolates (6.9%) were resistant to erythromycin, but only five were 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 2009 (6.9%) was comparable to those from 2008 (6.5%) and 2007 (8.8%). A majority of the isolates were retrieved from adults (> 50 years), but 12 (9.2%) were isolated from children less than 2 months. 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 2009 as a follow-up to 2008 when a marked increase in rates of penicillin-resistant and trimethoprim-sulfamethoxazole-resistant isolates was seen (Figure 4.15).

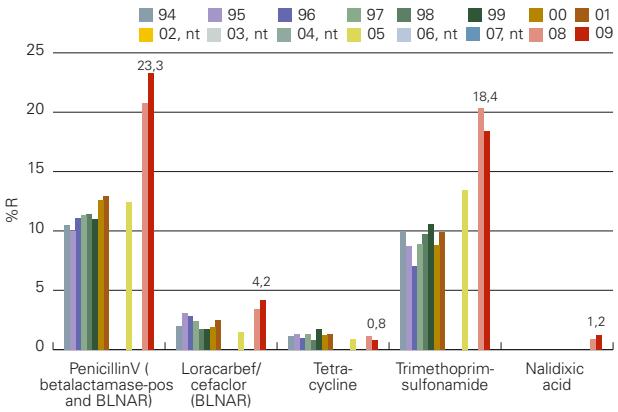

FIGURE 4.15. Resistance rates for *Haemophilus influenzae* 1994-2009 (data from the annual RSQC programme, approximately 3000 isolates per year), nt = not tested.

In 2009 the high rates of resistance remained for both types of antibiotics, with an even higher figure for penicillin V (23.3% compared to 20.8%) but a slightly lower for trimethoprim-sulfamethoxazole (18.4% compared to 20.3%). It should be noted that the figures for penicillin V represent both beta-lactamase-producing strains and strains with chromosomally mediated resistance (BLNAR = betalactamase-negative ampicillin-resistant). The frequency of BLNAR alone, as interpreted from the cefaclor screening disk, had increased from 3% to 4.2%.

Tetracycline resistance in *H. influenzae* was still rare (approximately 1%). A few isolates with fluoroquinolone resistance, detected by the nalidixic acid screening disk, were found.

Typing of betalactam resistant *Haemophilus influenzae*

From each of the clinical laboratories the first six betalactam-resistant isolates during the respective study periods in 2008 and 2009 were sent to SMI for further testing. A total of 242 isolates were collected, consisting of 177 betalactamase-positive (BLPAR) and 65 BLNAR isolates. They were analysed by disk diffusion and MIC testing, and were typed by PFGE to identify clusters of isolates which might explain the increased rate of resistance.

Resistance to trimethoprim-sulfamethoxazole was found in both groups but more frequently among BLNAR (36/65; 55%) than among BLPAR (55/177; 31%). Preliminary analysis of PFGE results showed at least 15 different patterns among BLPAR strains and 5-10 different patterns among BLNAR strains. Several of the patterns were restricted to 2-5 isolates each, which often originated from the same laboratory but sometimes from several laboratories. Only a few large clusters of betalactamase-producing isolates were identified, and they always originated from several laboratories.

In summary, in this selected material of betalactam resistant *H. influenzae* there was a wide variety of strains based both on their antibiotic susceptibility patterns and on their genetic relationship. The increased rates of *H. influenzae* with penicillin resistance which have been noted during the last couple of years could probably not be explained by the expansion of one single strain. Further analysis is needed in order to make a more precise statement.

Surveillance on invasive isolates additional to EARSS data

Of data on consecutive blood isolates from the participating 11 laboratories 49/11.416 (0.4%) were *Haemophilus influenzae*. Three of these isolates were from cerebrospinal fluid. Ten isolates (20.4%) were betalactamase-producing and ampicillin-resistant. This is comparable to 2008 when 25% of the isolates were resistant, and it corresponds to the increase seen in respiratory tract isolates (see above). None of the blood isolates had chromosomally mediated beta-lactam resistance (BLNAR). Seven isolates (14.3%) were resistant to trimethoprim-sulfamethoxazole, comparable to the results in 2008.

A majority of the isolates were retrieved from adults (> 50 years), but 3 were isolated from children 0-9 years.

Barbro Olsson-Liljequist, Henrik Hallin, Gunnar Kahlmeter

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, information on ESBL 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 of limiting ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in blood isolates to a maximum of 1% 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, also including plasmid-mediated AmpC variants and carbapenemases. All Swedish clinical microbiology laboratories were requested to report ESBL according to the new definition from January 2010. Already during 2009, a few cases were reported according to this new definition.

Notifications according to the Communicable Disease Act

A total of 3754 cases were notified during 2009. Reports came from all 21 counties of Sweden, corresponding to a national incidence of 40 cases per 100 000 inhabitants (Figure 4.16). In May and June 2008 a strike in the health-care sector may have affected the sampling frequency and the number of reported cases, thus comparisons of these periods or the entire years are difficult to make. When comparing the second half of the two years, a 27% increase of ESBL cases was noted for 2009.

Almost all Swedish counties had an increased incidence, the highest incidence found in Jönköping 2009. In Uppsala the incidence continued to decrease from 57 to 46 cases per 100 000 inhabitants in 2009. This was most probably due to the extensive infection control and screening programme launched to control the large ESBL outbreak that was discovered in 2005. It indicates that an outbreak situation with ESBL-producing *K. pneumoniae* may be reversed when a combination of control measures is undertaken.

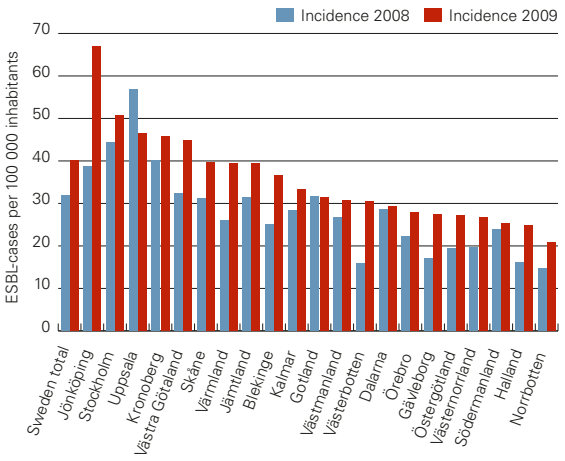

FIGURE 4.16. The incidence of ESBL in Swedish counties 2008-2009, arranged according to incidence 2009.

The most commonly reported species was *E. coli*, accounting for 82% of all cases, followed by *K. pneumoniae* with 7%, Table 4.10.

TABLE 4.10. Distribution of species among cases with ESBL-producing bacteria 2009.

Escherichia coli	3164
Klebsiella pneumoniae	290
Proteus mirabilis	29
Citrobacter species	28
Salmonella species	15
Other *Enterobacteriaceae*	105
Species not reported	243
Total number of reported species	3874*

* In 105 cases 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 69% of the cases according to the first laboratory notification. The second most common source was faecal samples with

12%. Isolates from rectum and wound samples constituted 4% each of the first notifications and blood isolates 3.5% of the first notifications. Invasive infections with ESBL-producing bacteria, all in blood, were notified in 186 cases during 2009. Among these, 168 were new cases for 2009 and 18 were known carriers of ESBL, notified during the previous year.

The incidence in age groups and gender differed between species and is shown in Figures 4.17 and 4.18. ESBL-producing *E. coli* were derived from women in 67% of cases. They had a median age of 54 years compared to 63 years for men. The *K. pneumoniae* ESBL cases were equally distributed between sexes, with median ages of 62 years for women and 58 years for men. Compared with 2008 the mean age had decreased with 9 years for men due to several cases among newborns.

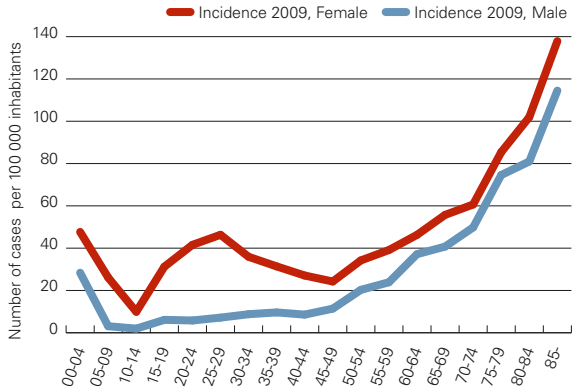

FIGURE 4.17. Age and gender distribution of *E. coli* ESBL cases 2009.

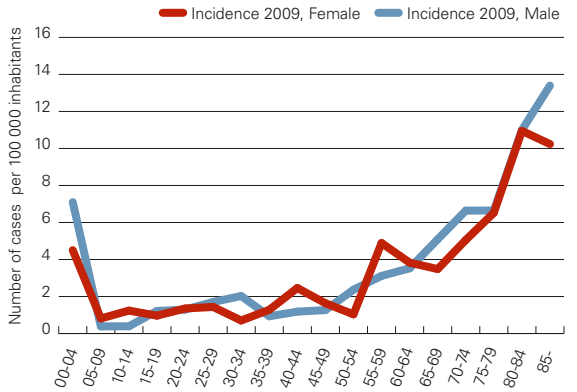

FIGURE 4.18. Age and gender distribution of *K. pneumoniae* ESBL cases 2009.

The nation-wide problem with ESBL-producing bacteria in Sweden has proven 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.

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. The average resistance rates to ampicillin have increased yearly, from 17 up to 30% (Figure 4.19). 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 exceeded 13% in 2009. Resistance to cephalosporins (cefadroxil tested), although much less prevalent than ampicillin resistance, has continued to increase and reached 3.5% in 2009. This mirrored the increasing incidence of ESBL-producing bacteria as seen from the notified cases (above) and reports to EARSS (below). Also for nitrofurantoin there was an increase, although from a much lower level than for the other antibiotics. Nitrofurantoin resistance is associated with some strains of ESBL-producing *E. coli*, thereby explaining the concomitant increasing resistance rates.

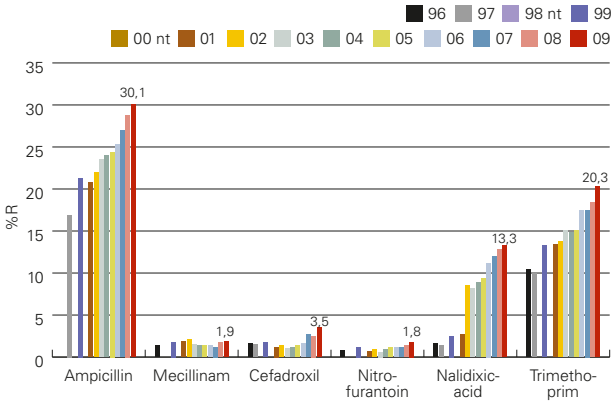

FIGURE 4.19. Resistance rates in *E. coli* 1996-2009. Between 1996-2001 fluoroquinolone resistance was detected with norfloxacin, from 2002 and onwards with nalidixic acid, nt = not tested.

In 2009 the RSQC programme was performed as usual, but a follow-up of the extended survey from 2007 was done in parallel. All laboratories were asked 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. A total of 370 *E. coli* and 20 *K. pneumoniae* were collected and tested with phenotypic and genotypic methods. Preliminary results for *E. coli* showed that among isolates with verified ESBL-activity (inhibition by clavulanic acid) the ESBLs of CTX-M subgroup 1 dominated (74%), followed by CTX-M subgroup 9 (22%). Nineteen isolates (7%) harboured plasmid-mediated AmpC-enzyme of the type CIT (originating from *Citrobacter* species). A majority of the ESBL-producing isolates were multiresistant as was also

Escherichia coli in blood and urine

CONSECUTIVE DATA on blood isolates are obtained from 20 laboratories taking part in the Swedish EARSS Network. These laboratories deliver data on seven pathogens, namely *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. From eleven of these 20 laboratories information is available on all their positive blood cultures (one isolate per patient), allowing for analysis on more microorganisms than the seven "EARSS"-bacteria. These sets of data are complete from 2005 and onwards and have been used to gather information on for instance *Streptococcus pyogenes* and *Streptococcus agalactiae* to previous SWEDRES reports.

However, the two most frequently found pathogens in blood cultures were *E. coli* and *S. aureus*, save for the commonly isolated coagulase negative staphylococci. We investigated the proportions of these two bacterial species in relation to the total numbers of positive cultures and also looked for trends.

The total numbers of blood cultures taken (pairs of bottles) increased every year in all of the eleven laboratories (Figure 4.9, page 30). This might indicate a general awareness of infectious diseases and an increased adherence to guidelines. However, the percentage of positive blood cultures did not change during these five years. It ranged between 7.6% and 7.9% in 2006-2009.

The proportions of *E. coli* (this chapter) were further analysed for geographical differences or changes over time. In Figure 4.20 is shown the percentage of *E. coli* of all positive blood cultures per laboratory and year. A rough estimate of the overall average was 20%.

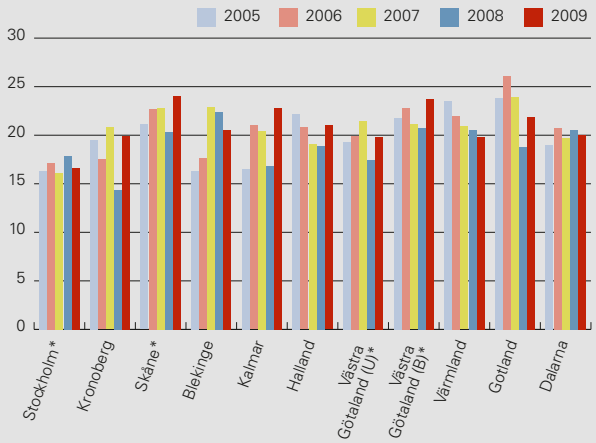

FIGURE 4.20. Proportions of *E. coli* among positive blood cultures from eleven counties 2005-2009.

There were only small differences between laboratories/counties as to their proportions of *E. coli* among invasive isolates. There were no obvious trends and no relation with either size or geographical location of the counties could be seen. In one county (Stockholm) the proportion seemed stable around 16%, and in others (Halland, Dalarna) it was stable around 20%.

Escherichia coli from UTI and consumption of UTI antibiotics

In three regions antimicrobial resistance in *E. coli* isolated from UTI in relation to age was analysed (Figure 4.21 a – d). For mecillinam (a) and nitrofurantoin (c) resistance was low in all age groups and in all three counties and appeared lowest in the really young (0–2 years). For nalidixic acid (b) as a marker for quinolone resistance and trimethoprim (d) resistance was high in all age groups although trimethoprim resistance appeared to be lower among the elderly.

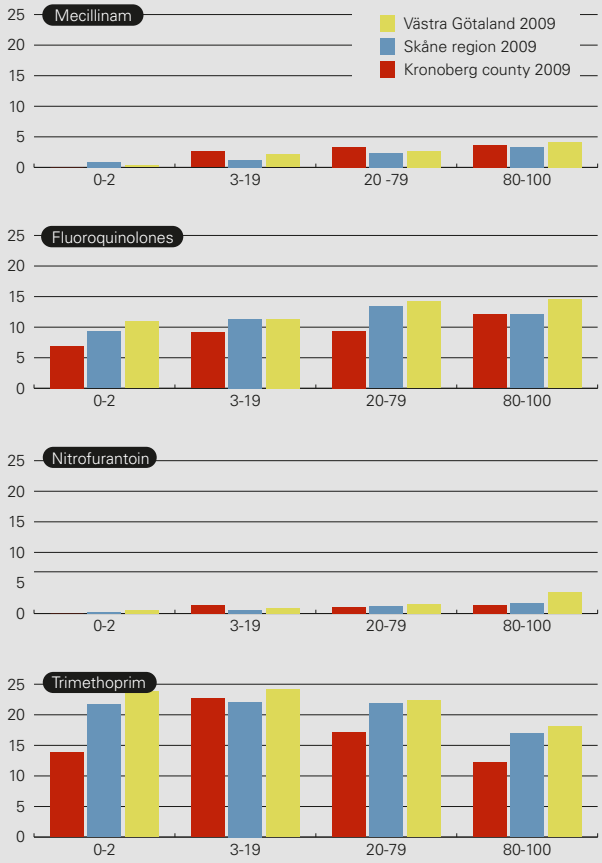

FIGURE 4.21. Resistance rates in different age groups to four antibiotics for treatment of urinary tract infections 2009; a) mecillinam, b) fluoroquinolones, c) nitrofurantoin, d) trimethoprim. Data collected from three regions in Sweden.

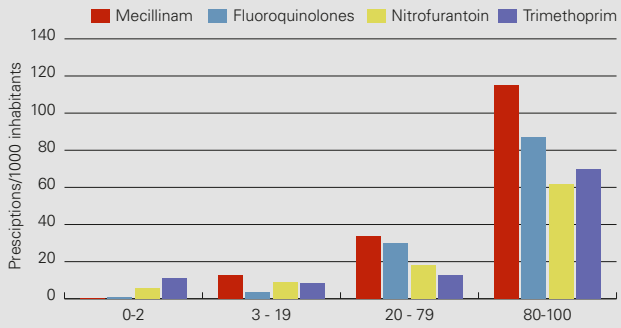

FIGURE 4.22. Prescriptions 2009 of four antibiotics for treatment of urinary tract infections to different age groups.

Gunnar Kahlmeter, Eva Melander, Christina Åhrén, Barbro Olsson-Liljeqvist

noted in the study from 2007. A complete report of all results from 2007 and 2009 will be presented and distributed to laboratories and other interested parties.

Data on invasive isolates reported to EARSS

Escherichia coli derived from invasive infections (blood isolates) have been part of the European Antimicrobial Resistance Surveillance System (EARSS) since 2001. The surveillance system has focused on resistance to beta-lactam antibiotics, especially ESBL, and on resistance to aminoglycosides and fluoroquinolones. Results for 2001-2009 are presented in Table 4.11.

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, 33% versus 30%. 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% in 2009, thus an increase from 2.3% in 2008. 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 3.7% in 2009. 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 from 5.5% in 2001 and reached 15.5% in 2009. These increasing trends of resistance in blood isolates were the same as those in urine isolates from the RSQC programme shown in Figure 4.19.

TABLE 4.11. *Escherichia coli* from blood cultures in Sweden 2001-2009, reported to EARSS/ECDC.

Year	Ampicillin-R (%) *	Cefotaxime-R (%; ESBL/other mechanism)	Aminoglycoside-R (%) **	Fluoro-quinolone-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

*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 since 2005.

As for *E. coli*, the RSQC 2009 programme for *K. pneumoniae* was mainly focused on urine samples, Figure 4.23. Resistance to commonly prescribed oral antibiotics for treatment of urinary tract infections was tested in 2009. The results indicated an increased resistance only to trimethoprim, whereas the rates of resistance to both cefadroxil and fluoroquinolones were the same or slightly lower than in 2008.

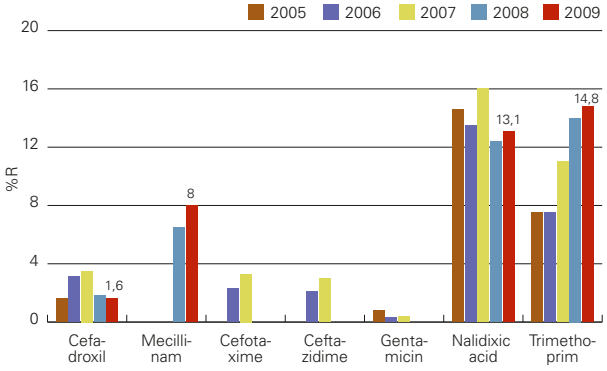

FIGURE 4.23. Resistance rates in *Klebsiella pneumoniae* isolates for four groups of antibiotics 2005-2009.

Also for *K. pneumoniae* the RSQC programme was performed as usual in 2009, but as for *E. coli* a follow-up of the extended survey from 2007 was done in parallel. All laboratories were asked to collect consecutive cefadroxil-resistant (R < 13 mm) isolates during a one-month period and send them to SMI for further analysis. A total of 20 *K. pneumoniae* were collected and tested with phenotypic and genotypic methods. Preliminary results for this small collection of *K. pneumoniae* showed that 16 isolates had verified ESBL-activity (inhibition by clavulanic acid) which most commonly was CTX-M subgroup 1. A majority of the ESBL-producing isolates were multiresistant. A complete report of all results from 2007 and 2009 will be presented and distributed to laboratories and other interested parties.

Data on invasive isolates reported to EARSS

Since July 2005, participants in the EARSS network have contributed with data on blood isolates of *K. pneumoniae*. In 2009 the number of isolates was lower than in 2008, 755 VS 826 as shown in Table 4.12. All cephalosporin resistance was caused by ESBLs of CTX-M type. The rate of fluoroquinolone resistance is slowly increasing.

TABLE 4.12. *Klebsiella pneumoniae* from blood cultures in Sweden 2005-2009, reported to EARSS.

Year	Cefotaxime-R (%; ESBL/other mechanism)	Aminoglycoside-R (%) *	Fluoroquinolone-I/R (%) **	Total number of isolates
2005 (half year)	0.7 / 0.7	1.4	9.8	281
2006	1.0 / 0.5	0.3	8.5	610
2007	1.1 / 0.3	1.1	10.8	649
2008	2.3 / 0	1.1	12.9	826
2009	1.8 / 0	1.0	12.2	755

*gentamicin or tobramycin, **ciprofloxacin
The data for 2005 represent six months from 20 laboratories. From 2006 and onwards the data represent the entire years from 20 laboratories.

Isolates with new resistance mechanisms

In 2007 the first isolate of *K. pneumoniae* with KPC-2 (*K. pneumoniae* carbapenemase) was detected in Sweden. In 2008 one isolate with a KPC-3 betalactamase was identified, and in 2009 there were reports of three isolates in Stockholm, one identified as KPC-2 and two as KPC-3. The cases were healthcare related and further investigations will elucidate the origin of the infections.

Barbro Olsson-Liljequist, Tomas Söderblom, Karin Tegmark Wisell, Petra Edquist, Christian Giske, Gunnar Kahlmeter, Johan Struwe

Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pseudomonas aeruginosa was re-entered 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 rates to all tested antibiotics showed similar or even lower levels of resistance compared to previous years, Figure 4.24.

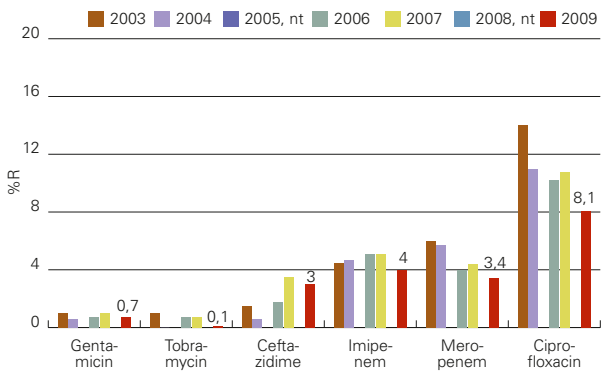

FIGURE 4.24. Resistance rates in *Pseudomonas aeruginosa* isolates for four groups of antibiotics 2003-2009, respiratory tract isolates excluded.

Data on invasive isolates reported to EARSS

Since July 2005, participants in the EARSS network have been asked to contribute with data on blood isolates of *P. aeruginosa*. From Sweden a total of 149 isolates from 20 laboratories were tested during the second half of 2005, and these data are compared to complete data sets for 2006-2009 in Table 4.13. The levels of resistance to beta-lactam antibiotics (ceftazidime and carbapenems) were in the range 3-7% for all four years. No change in resistance rates had occurred for either aminoglycosides (0%) or fluoroquinolones (10.1%).

TABLE 4.13. Resistance in *Pseudomonas aeruginosa* from blood cultures in Sweden 2005-2008, reported to EARSS.

Year	Ceftazidime-R (%)	Carbapenem-R (%) *	Aminoglycoside-R (%) **	Fluoroquinolone-I/R (%) ***	Total number of isolates
2005 (half year)	4.7	Insufficient data	0	9.0	149
2006	2.6	4.4	0.5	10.4	296
2007	4.5	7.0	0	10.4	342
2008	5.1	4.0	0	8.1	282
2009	3	7.5	0	10.1	352

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

Barbro Olsson-Liljequist, Gunnar Kahlmeter

Clostridium difficile

A national surveillance program for *Clostridium difficile* was initiated by SMI in 2009. The program included both a voluntary laboratory reporting system of all new cases and determination of resistance and epidemiological typing of collected isolates.

The laboratory reporting in SmiNet2 was launched in October and by the end of the year about half of the laboratories participated. The case definition for reporting of new cases was the detection of *C. difficile* cytotoxin B, regardless of method (direct positive by ELISA or ELISA-positive on a cultured isolate). At least 8 weeks was requested between positive samples from the same patient. During November-December these laboratories reported approximately 700 cases.

Isolates were collected and sent from 25 of the 28 Swedish laboratories during weeks 11 and 39. Susceptibility testing was performed by Etest for moxifloxacin, erythromycin, clindamycin, metronidazole and vancomycin. A total of 387 *C. difficile* isolates were typed by PCR ribotyping.

The most common types are presented in Figure 4.25. Type 014 was most frequent followed by types 020, 001, 023, 078 and 012. Type 014 consists of two subtypes according to the Swedish nomenclature, SE21 and SE21a, but these are not distinguished by the international type nomenclature. Increased numbers of types 078 and 023 were seen between weeks 11 and 39. These strains carry the so-called "binary toxin" and are commonly found in other European countries. One isolate of type 027 was detected, but this isolate was

susceptible to moxifloxacin – a typical marker for the virulent type 027 that has spread world-wide. For types 012, 017 and 046 geographical clusters were detected, Figure 4.26.

In summary, there was geographical clustering of certain *C. difficile* types that also were resistant to several antibiotics.

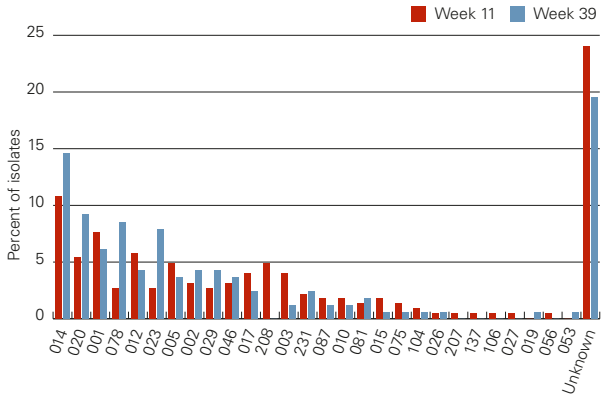

FIGURE 4.25. PCR ribotypes of *Clostridium difficile* in Sweden collected during two weeks 2009.

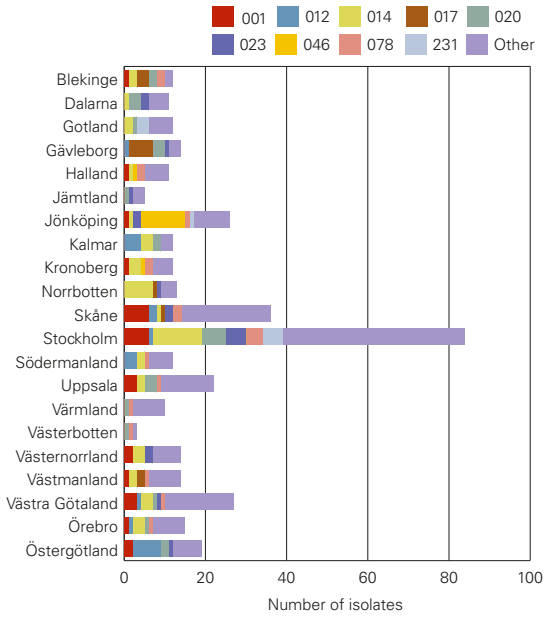

FIGURE 4.26. Distribution per county of the most common PCR ribotypes 2009.

Tomas Åkerlund, Tomas Söderblom, Karin Tegmark Wisell, Johan Struwe

Helicobacter pylori

Annual Resistance Surveillance and Quality Control (QCRS) programme

Helicobacter pylori derived from gastric biopsies was not included in the annual RSQC programme until 2001 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. Resistance to tetracycline is less than 1% and resistance to amoxicillin has only been described in a few strains and only outside Scandinavia. Frequencies of resistance to clarithromycin and metronidazole in clinical isolates from southwest of Sweden, representing a population of approximately 300 000, are presented in Table 4.13.

TABLE 4.13. *Helicobacter pylori* University Hospital MAS, Malmö, Sweden1996-2009, %R, nt = not tested.

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

* Molecular biology technique from 2005

Mats Walder

Salmonella and *Shigella* spp.

Annual Resistance Surveillance and Quality Control (QCRS) 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. Noteworthy is that fluoroquinolone resistance was high, 20-25%, among *Salmonella* strains, and 15-20% among *Shigella* spp.

Antibiotic resistance in domestic Salmonella spp 2009

To get a more comprehensive picture of the situation in Sweden we analysed the antibiotic susceptibility of a selection of domestic *Salmonella* spp. The isolates were chosen from the collection of domestic isolates sent to SMI in 2009 (n=593). More than 80 different serotypes were represented in this collection, but the ten most common were Typhimurium (n=172), Enteritidis (n=93), subspecies I (n=68), Agona (n=17), Infantis (n=13), Java (n=12), Stanley (n=12), Poona (n=11), Thompson (n=11) and Virchow (n=10). Together they consti-

tuted more than 70% of the total number. Susceptibility testing by disk diffusion was performed according to recently developed European guidelines (EUCAST) on 200 faecal isolates, chosen to represent the ten most common serotypes but also with regard to geographical location of patients and time of isolation. 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. We included ampicillin, cefotaxime, nalidixic acid, ciprofloxacin, gentamicin, streptomycin, chloramphenicol, tetracycline, trimethoprim and sulphonamides.

In summary we showed that 56% of the selected isolates were susceptible to all tested antibiotics. 88 isolates were resistant to one or several antibiotics and multiresistance (resistance to three or more antibiotic classes) was found in 61 of those. The most common resistance pattern was ampicillin/streptomycin/sulphonamides/tetracycline (n=26) and this pattern combined with quinolone resistance in an additional 21 isolates. Two isolates were resistant to cefotaxime and were comfirmed to have ESBLs of the type plasmid-mediated AmpC. The disk diffusion method for tetracycline was sensitive enough to separate resistant isolates of S. Typhimurium DT104 (inhibition zones 9-12 mm) from other resistant isolates (6 mm) (Figure 4. 27), and to show the almost complete correlation between nalidixic acid resistance (6 mm) and reduced zones for ciprofloxacin (25-33 mm) (Figure 4.28).

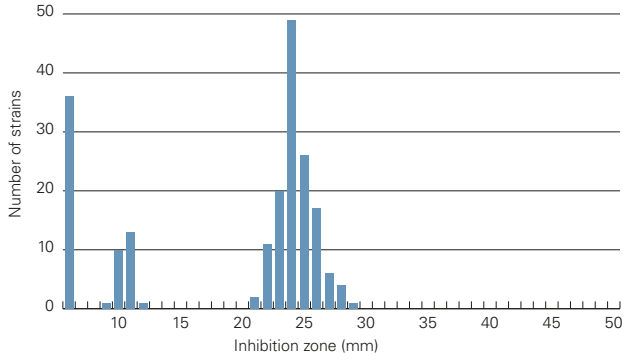

FIGURE 4.27. Inhibition zones of tetracycline 30 ug disk on 200 isolates of *Salmonella* spp.

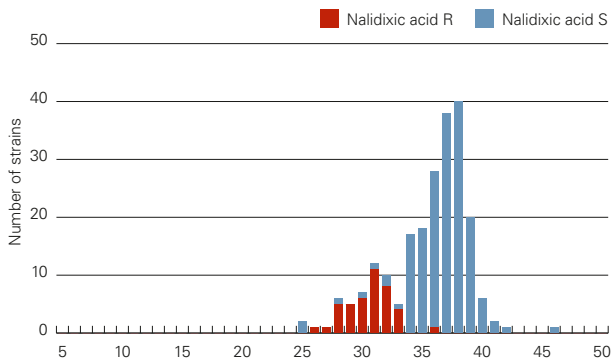

FIGURE 4.28. Inhibition zones of ciprofloxacin 5 ug disk on 200 isolates of *Salmonella* spp. and correlation to susceptibility (S) or resistance (R) to nalidixic acid.

Barbro Olsson-Liljequist, Cecilia Svensson, Mats Walder

Campylobacter spp

Annual Resistance Surveillance and Quality Control (QCRS) 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 note 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, this 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 4.14.

TABLE 4.14. *Campylobacter jejuni/coli* University Hospital MAS, Malmö, Sweden1995-2009 %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

Mats Walder

Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable disease/infection and in 2009, 611 cases 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 Malmoe, 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; the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm; and

TABLE 4.15. Antibiotic resistance rates (%) and β-lactamase production of Swedish Neisseria gonorrhoeae strains from 2003 to 2009.

	2003 (n=130)*	2004 (n=149)*	2005 (n=497)*	2006 (n=352)*	2007 (n=406)*	2008 (n=447)*	2009 (n=384)*
β-lactamase pos.	22	26	23	30	30	28	44
Ampicillin	22	26	23	30	30	28	44
Cefixime**	0	<1	0	0	<1	1	5
Ceftriaxone	0	0	0	0	0	<1	0
Azithromycin**	<1	0	<1	5	7	13	6
Ciprofloxacin	56	51	49	61	70	63	75
Spectinomycin	0	0	0	0	0	0	0

* From 2003 to 2004, only data from the Swedish Reference Laboratory for Pathogenic Neisseria, Örebro University Hospital, Örebro, Sweden were reported. From 2005 to 2008, also data from the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden were reported. In 2009, in addition data from Department of Clinical Microbiology, Malmö University Hospital, Malmö, Sweden are included.

** For cefixime and azithromycin, new SIR breakpoints were introduced in 2009 and the results from previous years have been recalculated.

the Department of Clinical Microbiology, Malmö University Hospital, Malmö, Sweden.

In 2009, isolates from 387 of the notified clinical cases were completely characterised at these laboratories, representing 63% of the notified cases. In total, 384 different *N. gonorrhoeae* strains were cultured from these cases (n=387).

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). Production of beta-lactamase was examined by using Nitrocefin discs. Results for 2009 are compared with those from 2003 to 2008 in Table 4.15. Notably, the levels of resistance to all antimicrobials used in the traditional gonorrhoea treatment are exceedingly high. The levels of resistance to azithromycin and cefixime have substantially increased in 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 2009 65 clinical cases of the disease were reported. A total of 45 clinical isolates from blood or cerebrospinal fluid were analysed at 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.

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

None of the isolates produced beta-lactamase. Eight isolates (17%) had reduced susceptibility to bensylpenicillin (MIC>0.064 mg/L). All isolates had MICs of cefotaxime ≤ 0.008 mg/L except one with 0.032, and all had MICs of ciprofloxacin ≤ 0.008 mg/L. MICs of meropenem varied between 0.002 and 0.064 mg/L. MICs of chloramphenicol varied between 0.25 and 1 mg/L, and MICs of rifampicin were ≤ 0.032 mg/L.

Per Olcén

Mycobacterium tuberculosis

During 2009 a total number of 642 new cases of tuberculosis (TB) were diagnosed in Sweden compared to 554 cases in 2008, an increase of 16%. The number and proportion of culture confirmed cases were 515 (80%) in 2009 compared to 436 (79%) in 2008. *Mycobacterium tuberculosis* was identified in 509 cases, *Mycobacterium africanum* in one patient and *Mycobacterium bovis* in five patients. The numbers of cases diagnosed with isoniazid resistant TB in 2009 were 38/515 (7.4%) and with MDR-TB 13/515 (2.5%).

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 52 patients corresponding to 10% of the 510 with culture confirmed TB, see Table 4.16. The five isolates of *M. bovis* were not included since these strains are naturally resistant to pyrazinamid. As always, resistance to isoniazid was most commonly found. Among the patients born in Sweden 5/89 (5.6%) had resistant TB and they were all resistant to isoniazid only. In the largest group of patients with TB in Sweden, immigrants from Somalia, 17/159 (10.7%) had some kind of resistant TB, four of which had MDR-TB (2.5%). Among patients born in the rest of the world 36/262 (13.7%) had TB with some kind of resistance, nine of which had MDR-TB (3.4%).

Of the 510 culture confirmed cases, 31 (6%) had a history of previous treatment for TB after 1949, the time when effective medication was made available. Of these 31 cases, 7 (23%) had strains resistant to one or more of the first line drugs including 4 with MDR-TB. The corresponding figures for cases with no reported previous treatment were 51/479 (11%), nine of which (2%) with MDR-TB. None of the 13 cases with MDR-TB were born in Sweden. They had all lived in Sweden

for less than 6 years and 7 of them came to Sweden during 2009. In total 7 of the 13 cases had pulmonary manifestations but only two were smear positive.

Genetic typing with RFLP (restriction fragment length polymorphism) was performed on 50 of the 58 resistant strains so far. Typing of the remaining eight is ongoing. This is done to detect clusters which could indicate ongoing spread of resistant strains. Sixteen of the 50 examined strains belong to 12 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. Several of the clustered 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 1990ies to 9% in the period 2000–2006 and then to 12.7% in 2007. In 2009 the proportion was slightly lower(51/510, 10%). In parallel the annual proportion of MDR-TB increased from 0,8% in 2006 to 4% in 2007 and dropped to 2,5% (13/510) in 2009. We have seen a marked increase in the number of cases from Somalia but the proportion of resistant TB in this group has been smaller than among immigrants from the rest of the world during 2009. This was not the case in 2008 when resistant TB was more common among Somalis as compared with other immigrants.

Sven Hoffner, Jerker Jonsson

TABLE 4.16. Drug resistant tuberculosis in Sweden, 2001-2009.

Year of diagnosis	2001		2002		2003		2004		2005		2006		2007		2008		2009	
Culture confirmed *M. tuberculosis* or *M. africanum*	354		346		345		368		448		395		361		434		510	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Any resistance	38	10.7	36	10.4	32	9.3	43	11.7	52	11.6	43	10.9	49	13.6	57	13.1	58	11.4
Isoniazid	31	8.8	34	9.8	26	7.5	35	9.5	46	10.3	38	9.6	46	12.7	51	11.8	51	10.0
Rifampicin	6	1.7	4	1.2	10	2.9	6	1.6	5	1.1	6	1.5	15	4.2	15	3.5	14	2.7
Ethambutol	3	0.8	1	0.3	5	1.4	3	0.8	3	0.7	1	0.3	7	1.9	6	1.4	7	1.4
Pyrazinamid	6	1.7	4	1.2	7	2.0	12	3.3	6	1.3	6	1.5	11	3.0	18	4.1	15	2.9
Isoniazid + rifampicin (MDR)	4	1.1	4	1.2	8	2.3	5	1.4	4	0.9	3	0.8	15	4.2	14	3.2	13	2.5

Appendix 1. Abbreviations

ABU	Asymptomatic bacteriuria
AST	Antibiotic susceptibility testing
ATC	The Anatomical Therapeutic Chemical classification system
BLNAR	Betalactamase negative ampicillin resistant
BLPAR	Betalactamase positive ampicillin resistant
CDCDC	County Department for Communicable Disease Control
DDD	Defined daily dose
DST	Drug susceptibility testing
EARSS	European Antimicrobial Resistance Surveillance System
ESBL	Extended spectrum beta-lactamase
GAS	Group A streptococci or *Streptococcus pyogenes*
GBS	Group B streptococci or *Streptococcus agalactiae*
ICU	Intensive care unit
KPC	*Klebsiella pneumoniae* carbapenemase
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 infections
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
TB	Tuberculosis
UTI	Urinary tract infection
VRE	Vancomycin-resistant enterococci

Appendix 2. Demographics and denominator data

TABLE APP 2.1. Population by county and age group, December 31st 2008.

	0-6 years	7-19 years	20-59 years	60-79 years	+80 years	All ages
Stockholm	182 229	300 712	109 0681	322 732	84 909	198 1263
Uppsala	26 915	52 300	174 505	58 550	14 918	327 188
Södermanland	20 650	43 282	131 119	57 362	15 111	267 524
Östergötland	32 449	67 253	217 530	82 396	23 541	423 169
Jönköping	26 712	56 013	167 395	65 259	19 867	335 246
Kronoberg	14 118	28 792	91 911	36 395	110 08	182 224
Kalmar	15 715	36 440	113 456	52 704	150 82	233 397
Gotland	3 755	9 112	28 325	12 501	3 311	57 004
Blekinge	11 345	22 893	75 015	33 730	9 276	152 259
Skåne	98 238	185 204	635 007	230 639	65 670	1 214 758
Halland	23 942	48 779	145 348	59 137	16 366	293 572
Västra Götaland	123 505	243 969	817 719	290 304	82 633	1 558 130
Värmland	18 702	42 445	135 132	59 929	17 166	273 374
Örebro	20 980	44 273	139 641	56 585	16 253	277 732
Västmanland	18 645	39 806	125 332	52 240	13 951	249 974
Dalarna	19 478	43 746	134 100	61 105	17 438	275 867
Gävleborg	19 450	42 753	135 349	61 517	16 839	275 908
Västernorrland	18 018	37 080	118 577	54 828	14 869	243 372
Jämtland	9 333	19 384	62 813	27 215	8 152	126 897
Västerbotten	19 070	40 470	133 585	51 016	13 671	257 812
Norrbotten	17 060	38 795	125 057	55 683	13 082	249 677
Sweden	740 309	1 443 501	4 797 597	1 781 827	493113	9 256 347

TABLE APP 2.2. Population in Sweden 2000-2009. Numbers represent the population by December 31st the previous year.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Population	8 861 265	8 882 831	8 909 322	8 940 744	8 975 669	9 011 391	9 047 803	9 113 297	9 182 923	9 256 347

TABLE APP 2.3. Number of admissions and patient-days in somatic medical care, 2008. Numbers represent production by hospitals in the counties.

	Patient-days	Admissions
Stockholm	1 108 000	261 162
Uppsala	312 621	59 091
Södermanland	200 899	37 712
Östergötland	285 391	62 987
Jönköping	246 566	52 769
Kronoberg	142 195	25 003
Kalmar	170 728	38 269
Gotland	41 774	9 455
Blekinge	120151	20 951
Skåne	925 417	186 580
Halland	218 536	44 309
Västra Götaland	1 233 362	245 484
Värmland	191 085	38 807
Örebro	229 033	49 197
Västmanland	201 154	38 738
Dalarna	210 814	47 587
Gävleborg	198 161	41 774
Västernorrland	194 053	39 645
Jämtland	97 736	18 674
Västerbotten	277 850	49 716
Norrbotten	185 225	38 348
Sweden	679 0751	1 406 258

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

	Number of analyses 2009									Number of positive cultures 2009				
Laboratory	**Blood (pair of bottles)**	**Cerebro-spinal fluid (CSF)**	**Nasopharynx**	**Throat**	**General culture**	**Screen MRB**	**Urine**	**Faeces SSYC**	**Faeces *Clostridium difficile* (toxin)**	***Staphylococcus aureus***	***Streptococcus pneumoniae***	***Streptococcus pyogenes***	***Escherichia coli***	***Clostridium difficile* (toxinpositive)**
Borås	14 344	201	2 823	4 305	10 885	1 391	26 892	6 628	1 874	4 489	682	779	7491	151
Eskilstuna (Unilabs)	8906	142	5 897	4 354	8 279	950	24 629	3 793	1 978	3 728	665	903	678	241
Falun	15 404	391	3 069	1 722	10 217	3 816	26 836	3 816	1 829	4 355	550	602	7 184	331
Gävle	11 212	187	2 071	1 152	9 450	2 048	23 183	3 470	2 191	3 701	342	329	7 046	485
Göteborg	28 473	1 055	3 263	4 022	16 444	38 762	70 712	11 906	4 772	13 058	799	1 065	17 892	NA
Halmstad	10 023	132	2190	2 169	8 826	33 081	24 050	4 435	1 836	3 442	468	527	6 586	187
HS Stockholm	33 579	576	12 306	5 338	36 728	104 300	81 199	11 623	6 212	13 449	1713	1 823	20 691	792
KS Stockholm	30 856	2 050	18 587	6 017	38 624	64 351	71 793	10 284	7 011	13 224	2 089	1 490	18 688	263
Jönköping	16 211	185	3 689	3 616	14 370	16 667	36 558	7 080	2 950	6 040	1110	650	9 610	530
Kalmar	9 458	148	3 391	2 461	7 853	2 185	25 677	3 966	1 471	4 032	517	524	7 185	224
Karlskrona	5 330	115	1 148	1 858	5 220	1 240	15 435	2 671	1 558	1 854	214	356	4 207	361
Karlstad	15 476	208	1 409	2 621	12 280	5 992	32 287	4 328	1 940	5 661	286	812	8 049	143
Linköping	17 093	911	5 633	3 428	18 620	5 580	37 325	7 060	3 769	6 484	788	812	9 540	822
Lund*	38 380	1 467	16 093	11 730	34 294	20 480	98 766	18 670	6 587	16 470	3 015	2 402	25 451	710
Malmö	22 270	348	5 613	6 280	12 817	47 410	60 537	11 364	4 109	8 422	1 656	1 399	15 670	589
Aleris Medilab	NP	NP	9 656	4 536	8 755	9 547	35 878	8 168	940	3 811	1 043	1 055	8 178	42
St:Göran (Unilabs)	7 599	125	5 577	8 512	13 779	32 713	31 343	7 415	2 946	5 388	560	946	9 840	168
Skövde (Unilabs)	9 402	189	6 784	4 170	10 203	3 953	39 735	5 016	3 336	4 252	421	573	8 870	249
Sunderby, Luleå	8 196	142	1 694	2 993	8 084	1 734	26 530	3 292	1 421	3 116	329	563	7 581	292
Sundsvall	9 969	127	2 357	1 722	7 784	6 204	26 414	3 839	1 796	3 265	458	458	6 879	241
NÄL Trollhättan**	14 886	155	1 720	2 550	8 515	5 390	33 970	4 700	1 500	4 630	420	510	9 880	170
Umeå	12 074	538	3 177	3 595	11 795	4 430	32 886	4 380	1 710	4 082	459	614	9 102	114
Uppsala	17 682	723	4 977	2 331	14 374	7 403	31 379	5 441	3 074	5 250	691	553	8 736	605
Visby	3 457	4	2 514	570	2 578	NP	6 786	1 087	746	1 183	330	110	2 157	108
Västerås	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Växjö	6 404	77	2 211	2018	6 300	4 700	19 950	3 810	1 387	3 100	336	440	4944	192
Örebro	15 013	256	8 611	1 648	14 669	6 189	31 439	5 040	2 556	5 865	1 125	562	7 785	563
Östersund	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	381 697	10 452	136 460	95718	351 743	430 516	972 189	163 282	71 499	152 351	21 066	20 857	249 920	8 573

* Included is data from the Kristianstad laboratory which closed in May 2009.
** Former Uddevalla laboratory.
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 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 2009 is not available. Therefore, data from 2008 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.

Information about the incidence of mastoiditis and pneumonia is obtained from the register of inpatient diseases held by the National Board of Health and Welfare.

Data on antibiotic consumption in Swedish ICUs were obtained from Apotekens Service AB and expressed as defined daily doses (DDD) per 1000 occupied bed day (DDD1000). We used the annually updated DDD calculated by the WHO Collaborating Centre for Drug Statistics Methodology as the average maintenance dose per day in adults for the main indication of the drug. Data were analysed using the non-parametric test for trend across ordered groups and Spearman's rank correlation using STATA/SE 9.2(StataCorp LP, College Station, TX, USA) and SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). Statistical significance was assumed if $P < 0.05$.

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 ad Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Since data for 2009 is not available until August denominator data from 2008 and sales data

from 2009 are used in some figures in this report. The number of admissions and patient-days in Swedish medical care 2008 is shown in Appendix 2, Table App 2.3. The Swedish Association of Local Authorities and Regions keeps a searchable database at the web, http://www.skl.se/artikel.asp?A=3768&C=1801.

Appendix 4. Antibiotic susceptibility testing

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

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

Phenotypic methods (disk diffusion or MIC) are performed on a basic medium for AST, ISA (IsoSensitest Agar) from Oxoid Ltd, UK. For this medium and the corresponding antibiotic paper disks, interpretive criteria for SIR-categorization are provided by the SRGA-M. The criteria are regularly updated and available through the web-site www.srga.org .

Internal and external quality assurance and quality control of susceptibility testing is performed by each laboratory. Internal quality control includes using international QC strains regularly (every day, once a week) and analysing data in relation to national guidelines. Validation of susceptibility testing can also be done by histogram analysis of consecutive clinical isolates (see www.srga.org) External quality control is often done by participation in UK-NEQAS and/or other international programs, whereas quality assurance is one of the features of the Swedish "100-strains or RSQC programme".

Appendix 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 *Eenterobacteriaceae*, both the clinician caring for a patient with a notifiable disease (clinical notification) and the laboratory diagnosing the pathogen causing the disease (laboratory notification) are obliged to notify. This double notification significantly enhances the sensitivity of the surveillance system.

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

Infections (or carriage) with different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with Penicillin G MIC > 0.5 mg/L (PNSP) have been notifiable since 1996. Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE) have been notifiable since 2000.

Since 1st February 2007 ESBL-producing *Enterobacteriaceae* were made notifiable by laboratory notifications. All notifications are entered into the national computerized surveillance system, 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 strains are sent to SMI for epidemiological typing using pulsed-field gel electrophoresis (PFGE). For MRSA from 1 July 2006 spa-typing replaced PFGE as the primary typing method.

Tuberculosis (TB) is a notifiable disease, irrespective of drug resistance. On a voluntary basis the TB laboratories are reporting all drug-resistant isolates of *Mycobacterium tuberculosis* and *bovis* to SMI. All resistant isolates are sent to SMI for epidemiological typing, using restriction fragment length polymorphism (RFLP).

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

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

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

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

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100-200 consecutive clinical isolates of a number of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. 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 data from the laboratories and, following approval of registered data by one of two web administrators, instantly displayed it in the form of resistance frequencies on the geographical areas on maps of Sweden. Behind each resistance frequency the distribution of zone diameters or MICs together with the relevant demographic data are directly accessible. The software will accept both MIC and zone distributions of well-characterized data sets. The graphs presenting the data are designed to include all necessary information in order for the graphs to be used on their own (in presentations etc). A recently introduced feature enables each laboratory to view all its own data and also to link this information to a website of its own local health care system. The ResNet software also has the feature of displaying aggregated, quantitative data of invasive isolates which form the Swedish part of the EARSS network (see below).

EARSS

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

Participation in EARSS was initially intended for member states of the European Union, also including Norway and Iceland, but in year 2000 six countries in eastern Europe were

included, and by 2003 28 countries provide susceptibility data regularly. Information about EARSS, as well as a database yielding information about the susceptibility results for each country, year and pathogen, is available through a web-site (www.earss.rivm.nl). During 2009 a transition of EARSS from RIVM in the Netherlands to ECDC in Stockholm is prepared and will be effective by 1st January 2010.

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

Although not perfect, the EARSS network of networks form a solid base for surveillance of resistance and is constantly extended and improved.

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

Surveillance of invasive isolates additional to EARSS data

Data on invasive isolates on all positive blood cultures were obtained from eleven laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is 3.7 millions, thus representing more than 40% of the Swedish population. From these laboratories data for the pathogens specified by the EARSS network are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In the SWEDRES 2007-2009 data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* are presented.

Sentinel surveillance

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

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

Appendix 6. Recent publications (2007-2009)

3. Use of antibiotics

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