SWEDRES | 2008

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

SMITTSKYDDSINSTITUTET
Swedish Institute for Infectious Disease Control

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.

Publishers:
Strama, The Swedish Strategic Programme against Antibiotic Resistance, and the Swedish Institute for Infectious Disease Control

Editors:
Johan Struwe 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.ki.se
www.smittskyddsinstitutet.se
www.strama.se

Layout:
Björn Lundquist AB, Malmö

Print:
Edita Västra Aros AB

ISSN 1400–3473
SMI-tryck 168-2009

Content

1. Preface

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

Data in this and previous reports indicate that the Swedish strategies in human and veterinary medicine still are comparatively successful in containing resistance. In human medicine, resistance continued to increase in many bacteria, although at a slower pace than in many parts of the world. Resistance emerging in one country can rapidly spread to others through trade and travel, which underlines the need for international collaboration in all fields. For example, studies in Swedish charter tourists have shown that on average one third acquire enterobacteria with ESBL in their stools during a trip. The need for continued collective efforts in all sectors was iterated in the European Union's Council Conclusions on Antimicrobial Resistance (10 June 2008).

In SWEDRES 2008 we have highlighted a couple of areas needing particular attention and further investigation. One of these areas is the high antibiotic pressure and poor compliance to guidelines for the diagnosis and antibiotic treatment of the elderly. Another is an outbreak of vancomycinresistant enterococci detected 2007 in Stockholm county which continued to spread to several other counties in 2008 causing large local outbreaks.

Good news was that transmission of MRSA in the healthcare sector seems to have stabilised, probably due to extensive case-finding and promotion of compliance to basal hygiene principles. Furthermore, after a slow increase in antibiotic use three years in a row, the figures again decreased slightly. Most notably, the consumption of fluoroquinolones and cephalosporins continued to decrease. This is in accordance with guidelines for treatment of lower urinary tract infections in women and for treatment of mild and moderately severe community acquired pneumonia. The reduction in fluoroquinolones and cephalosporins is also recommended in the antibiotic policy in order to reduce the risk for selection and spread of ESBL-containing bacteria in the hospitals.

In Sweden, the strategic programme against antimicrobial resistance is co-ordinated by Strama. A secretariat to support a network with a specific remit to address issues related to animals and food, Strama VL, was initiated at SVA during 2008.

Our hope is that the information in SWEDRES and SVARM is translated into further investigations and action in order to preserve our increasingly threatened, but still favourable, situation.

2.1 Summary

Use of antibiotics

Sales of antibiotics in Sweden 2008 were 1.6% lower than the previous year. This decrease follows a series of years with rising use. In 2008, media attention has been drawn towards healthcare issues related to the use of antibiotics in both primary health care and hospital care.

Together with tetracyclines, different kinds of penicillins are the most common classes of antibiotics in primary health care. The prescribing of penicillins shows great variance within Sweden, both in terms of number of prescriptions and in choice of drug. Penicillins with an extended spectrum constitute 20% of the prescriptions to children aged 0 to 6 years in the counties with the lowest use and 40% in the high-prescribing counties. One third of all children aged 0 to 6 years were treated with at least one course of antibiotics in 2008.

The treatment of lower urinry tract infections in women has been the subject of information campaigns for several years. This is clearly reflected in the sales of antibiotics commonly used against this condition in women aged 18 to 79 years: Pivmecillinam and nitrofurantoin, the recommended first-line antibiotics, represent more than 60% of the prescriptions. However, the use of fluoroquinolones is still high in the elderly.

The use of antibiotics in hospital care has continuously increased since the end of the 1990s. A difficulty in the interpretation of these data is that the way nursing homes buy their antibiotics has changed over the years and also differ between the counties. The change in nursing homes from personal prescriptions to dispensing antibiotics from store rooms can probably explain some of the increase within hospital care. When measuring the use of antibiotics only in hospitals, in relation to patient admissions and patient-days, there is no increase at all during the last three years. This analysis has been possible this year by collecting local data from each county.

The distribution of antibiotics used within hospital care has changed in a desirable way towards less broad spectrum and more narrow spectrum antibiotics. Various types of penicillin have increased and the use of cephalosporins and fluoroquinolones is decreasing. When analysing data per quarter, betalactamase-sensitive penicillins increase and cephalosporins decrease to the same level by the end of 2008 (DDD/1000/year). This is a remarkable shift since Sweden has a long tradition of an extensive use of cephalosporins. Strama's point prevalence studies, performed in 2003, 2004, 2006 and 2008, confirm that the use of cephalosporins for the treatment of uncomplicated community acquired pneumonia has decreased considerably.

Use of antifungals in Sweden 2008

While the total use of systemic antifungals in hospital care remained constant, a significant increase in the utilization of amphotericin B and a decrease in the use of fluconazole stand out during 2008. Amphotericin B, a macrolide with excellent activity against most fungi that cause human disease, has many serious side effects. The development and marketing in recent years of lipid-based formulations of amphotericin B have made a safer administration of this drug possible. The in-patient use of fluconazole, a triazol compound widely indicated for the prophylaxis and treatment of *Candida* and *Cryptococcus* infections, declined during 2008 after several years of steep increases. Fluconazole still represents 80% of the total antifungal used in hospitalized patients. Fluconazole shows reduced or lack of activity against *Candida* species that account for every fifth episode of candidemia in Sweden. Equinocandin antifungals such as caspofungin and the newly introduced anidulafungin and micafungin, have good activity against azole-resistant *Candida* species and are increasingly being used for the treatment of invasive candidiasis. As in previous years, more than 95% of all antifungal prescriptions took place in community care.

Antibiotic resistance

While a few forms of antibiotic resistance is 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 1307 cases of MRSA were notified in 2008, a 16% increase compared with 1128 cases in 2007. More than half of the reported cases (665 cases) had acquired MRSA in Sweden, and one-third (450 cases) had acquired the infection abroad. Six of the Swedish counties had an incidence of notified MRSA cases above the average country incidence of 14.1 cases/100 000 inhabitants, and four of them had the highest incidences also in 2006 or 2007.

Invasive isolates of MRSA were as few in 2008 (n=16, 0.7%) 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 to the European surveillance network EARSS.

Epidemiological typing of all MRSA isolates has been performed by spa-typing since 2006. The five most commonly encountered spa-types in 2008 were t002 (n=132), t008 (n=113), t044 (n=107), t019 (n=54), t032 (n=51). The prevalence of MRSA with PVL toxin was slowly increasing and was

present in all or a majority of isolates with the common spa-types t008, t044, and t019.

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

Streptococcus pneumoniae: In 2008 there were 565 notifications of PNSP (*Streptococcus pneumoniae* with MIC of penicillin > 0.5 mg/L) in Sweden. PNSP have decreased in annual incidence rate per 100 000 population from around 10 in 1997 to values between 6 and 8 since 2000. Most cases were identified through nasopharyngeal culture. The majority of PNSP cases, independent of year observed, were found in the age group 0–4 years. In 19 cases (3.4%) 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 common serotypes/groups found were 19F, 9V, 14, 6B, and 23F.

For all four antibiotics tested on *Streptococcus pneumoniae* in the RSQC programme 2008 the rates of resistance were back to the levels noted in 2006.

Rates of non-susceptibility to penicillins in *Streptococcus pneumoniae* (=PNSP) were lower among invasive isolates than in the nasopharyngeal isolates from the RSQC programme. Resistance to macrolide antibiotics was 5–6% in both types of isolates.

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 up til now been rare in Sweden. In 2008 there were 618 notified cases of VRE, almost 12 times more cases than 2007. This high notification rate was attributable to the spread of *vanB*-carrying *Enterococcus faecium* not only in the Stockholm county, but also in the counties of Halland and Västmanland, which led to intensive infection control efforts of screening and contact tracing. The strain of *Enterococcus faecium* with the *vanB* gene, affecting all three counties, was new according to epidemiological typing using PFGE.

This new epidemic strain also appeared in blood cultures, giving a rate of vancomycin resistance of 1.5% as reported to EARSS. A more common feature among invasive isolates of both *Enterococcus faecalis* and *Enterococcus faecium* was high-level aminoglycoside resistance (HLAGR) with 20% and 25%, respectively.

Streptococcus pyogenes: Data were obtained on 196 invasive isolates in 2008 (data derived from eleven laboratories). Only one of the isolates (0.5%) was resistant to erythromycin and none was resistant to clindamycin. Twenty-six isolates (15%) were resistant to tetracycline, and this was a marked increase compared with 2007 when 8% of the isolates were resistant.

Streptococcus agalactiae: Data were obtained from eleven laboratories on 107 invasive isolates in 2008. Seven isolates (6.5%) were resistant to erythromycin and clindamycin, a figure that was similar to those from 2006 and 2007.

Haemophilus influenzae: Data were obtained in the RSQC programme in 2008 after three years without reporting. A marked increase was seen in rates of penicillin-resistant and trimethoprim-sulfamethoxazole-resistant isolates. Against both types of antibiotics the resistance rates were > 20%, compared with stable results for many years of 10–13% resistance. One third of the patients with betalactamase-producing isolates was children 0–9 years, and the remaining isolates were evenly distributed among all other age groups.

Haemophilus influenzae was rarely found among blood isolates, only 63 cases in 2008 according to data derived from eleven laboratories. Sixteen of these (25%) were betalactamase-producing, a marked increase compared with 2007 when only three resistant isolates were found in the corresponding small material.

Enterobacteriaceae producing extended spectrum betalactamases (ESBL) were made notifiable by the laboratories from February 2007. A total of 2957 cases were notified during 2008. Reports came from all 21 counties of Sweden, corresponding to an average national incidence of 32 cases per 100,000 inhabitants. When comparing the second halfs of 2007 and 2008, respectively, a 28% increase of ESBL cases was noted for 2008. Most ESBLs were found in urine samples (70%) and the most commonly reported species was *E. coli* (84%). 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 betalactamase (most often of TEM-type) was increasingly found in both blood isolates and urine isolates (32% and 29%) in 2008. The level of resistance to third generation cefalosporins had increased to 2.2% among blood isolates, and in the majority of these cases the resistance was caused by plasmid-mediated ESBLs of CTX-M type. This resistance was often accompanied by resistance to many other antibiotics, e.g. aminoglycosides and fluoroquinolones. Resistance to fluoroquinolones has increased every year and was almost the same in urine as in blood isolates (13 vs. 14%) in 2008.

Other gram-negative bacteria that have been monitored in the RSQC programme and also through the EARSS network are *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The levels of resistance for the antibiotics tested were comparable between the two surveillance programmes for each of the microorganisms. Approximately 2% of *Klebsiella pneumoniae* were cephalosporin resistant and ESBL-producing. In 2007 the first isolate of *Klebsiella pneumoniae* with KPC-2 was detected in Sweden. In 2008 at least one more isolate with a KPC betalactamase has been identified, and also one isolate with a metallo-betalactamase of VIM-type. In all these cases a history of hospital care in the south of Europe was reported.

In *Pseudomonas aeruginosa*, the prevalence of carbapenem

resistance was approximately 5% and of fluoroquinolone resistance 10%.

Helicobacter pylori has been monitored locally by a few laboratories. Resistance to clarithromycin (and erythromycin) has been steadily increasing but a marked decrease was noted since 2007 according to tests performed in one laboratory. In *Campylobacter jejuni/coli* high levels of resistance were seen against fluoroquinolones (> 60%), tetracyclines (> 30%) and lower but increasing levels against erythromycin (7%) in 2008.

Neisseria gonorrhoeae. Gonorrhoeae is a notifiable disease, and in 2008 724 clinical cases of the disease were reported. Isolates from 447 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 62% of the notified cases. In 2008 28% of these isolates were betalactamase-producing and ampicillin resistant, and 63% were resistant to ciprofloxacin.

Mycobacterium tuberculosis. The total number of new cases of TB diagnosed in Sweden 2008 was 554. Resistance against at least isoniazid and rifampicin (MDR-TB) was diagnosed in 3.2% of all foreign born patients with culture confirmed TB (14/359), 6.4% of those coming from Somalia (7/110) and 2.8% from other countries (7/249).

Genetic typing with RFLP (restriction fragment length polymorphism) was performed in 49 of the 57 resistant strains of *Mycobacterium tuberculosis* or *M. africanum*. Twentynine of the 49 examined isolates were identified to belong to 16 different clusters with two or more patients in each cluster.

2.2 Sammanfattning

Antibiotikaförbrukning

Efter flera år med ökande användning av antibiotika sjönk försäljningen något år 2008. Den minskade försäljningen omfattar de flesta preparat, län och åldersgrupper. Flera hälso- och sjukvårdsfrågor med anknytning till antibiotikaanvändning och resistens har fått uppmärksamhet i media under året. Som exempel kan nämnas vårdvalsmodeller i primärvården och utbrott av resistenta bakterier på flera sjukhus.

Tillsammans med tetracykliner är olika slags penicilliner de preparat som oftast förskrivs på recept. Användningen av penicilliner varierar mycket inom Sverige, både vad gäller antalet recept och val av preparat. Penicilliner med brett spektrum utgör 20 procent av recepten till barn mellan 0 och 6 år i de län som har lägst totalförskrivning av penicilliner till denna åldersgrupp. I län med hög förskrivning är motsvarande siffra 40 procent. En tredjedel av barnen mellan 0 och 6 år fick minst en antibiotikakur under 2008.

Behandlingen av nedre urinvägsinfektioner hos kvinnor har varit föremål för informationsinsatser under flera år. Detta märks tydligt i förskrivningen av preparat mot detta tillstånd till kvinnor mellan 18 och 79 år: Pivmecillinam och nitrofurantoin, de rekommenderade förstahandspreparaten, utgör tillsammans mer än 60 procent av förskrivningen.

Antibiotikaanvändningen inom slutenvård har ökat stadigt sedan slutet av 1990-talet. En svårighet i analysen av data är att sjukhem och särskilda boenden i varierande utsträckning har börjat beställa läkemedel på rekvisition istället för att använda recept till enskilda patienter. Läkemedel som rekvireras blir därmed en del av slutenvårdsstatistiken. Andelen antibiotika som köps på detta vis varierar över tid och mellan länen. För att bättre belysa slutenvårdsstatistiken redovisas i årets rapport data över försäljningen av antibiotika till enbart sjukhus. Dessa data visar inte någon ökning av antibiotikaförsäljningen till svenska sjukhus under de senaste tre åren.

Fördelningen mellan olika antibiotikaklasser i slutenvården har förändrats i önskvärd riktning. Användningen av preparat med smalt antibakteriellt spektrum, såsom penicilliner, ökar medan preparaten med brett spektrum, exempelvis cefalosporiner och fluorokinoloner, minskar. Under det sista kvartalet 2008 passerar penicilliner med smalt spektrum cefalosporinerna som största grupp. Detta är anmärkningsvärt, eftersom Sverige har haft en tradition av utbredd använding av cefalosporiner. Stramas punktprevalensstudier som genomförts 2003, 2004, 2006 och 2008 bekräftar att användningen av cefalosporiner i behandlingen av okomplicerad samhällsförvärvad pneumoni har minskat.

Förhållandet mellan cefalosporiner och penicilliner med smalt spektrum varierar mycket mellan länen. Karbapenemer och piperacillin/tazobactam är preparatgrupper som fortfarande utgör en liten del av den totala användningen i slutenvård, men som ökat stadigt under de senaste åren. Även här är användningen mycket varierande mellan länen.

Förbrukning av medel mot svampinfektioner

Liksom tidigare år utfördes drygt 95% av alla ordinationer av svampmedel i öppenvården. I jämförelse med föregående år förblev den sammanlagda användningen av antimykotika för systemisk bruk oförändrad. Under 2008 sågs en

avsevärd ökning i förbrukningen av amphotericin B och en minskning av flukonazol. Amphotericin B är en antimykotikum med hög aktivitet mot de flesta svamparter av klinisk betydelse. Allvarliga biverkningar är emellertid vanliga vid amphotericin B-behandling. Utvecklingen och marknadsföringen av nya lipidbaserade sammansättningar av amphotericin B har under senare år möjliggjort en säkrare användning av läkemedlet. Förbrukningen av flukonazol, en triazol som indikeras för profylax och behandling av *Candida*- och *Cryptococcus*-infektioner, sjönk under 2008 efter flera år av kraftiga ökningar. Trots nedgången utgör flukonazol 80% av den totala antimykotikakonsumtion i landets slutenvård. Medlet har nedsatt effekt, eller saknar aktivitet, mot *Candida*-arter som ger upphov till 20–25% av candidemifallen i Sverige. Caspofungin såsom de nyligen godkända anidulafungin och micafungin tillhör echinocandinerna, en ny klass av svampmedel. Equinocandiner har hög aktivitet mot azol-resistenta *Candida*-arter och används i ökad utsträckning för behandlingen av invasiv candidos.

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 2008 och analyseras tillsammans med föregående års data.

Staphylococcus aureus: Totalt 1307 fall av MRSA anmäldes 2008, en ökning med 16 procent från 2007 då 1128 fall noterades. Mer än hälften av fallen hade blivit smittade i Sverige (665 fall), och en tredjedel (450 fall) hade blivit smittade utomlands. Jämfört med övriga länder i Europa är förekomsten av MRSA låg i Sverige. I sex län/regioner var incidensen av MRSA-fall högre än riksgenomsnittet (14.1 fall per 100 000 invånare). Fyra av dessa hade också haft högre incidens än genomsnittet under 2006 eller 2007. Antalet invasiva isolat av MRSA var lika få 2008 (n=16) som föregående år, vilket innebär 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 epidemiologiska typningsmetoden. De fem vanligast förekommande spa-typerna var t002 (n=132), t008 (n=113), t044 (n=107), t019 (n=54) och t032 (n=51). Förekomsten av MRSA med PVL-toxin ökade långsamt och toxinet förekom hos alla eller hos majoriteten av de vanliga spa-typerna t008, t044 och t019, men dessutom hos ett flertal andra spatyper. *Staphylococcus aureus* i sårinfektioner (data från ResNet) var i mer än 95 procent av fallen känsliga för antibiotika med undantag för fusidinsyra. Nivån var lägre än föregående år, men fortfarande var mer än 5 procent av isolaten resistenta.
Streptococcus pneumoniae: Under 2008 noterades 565 fall med nedsatt känslighet för penicillin (MIC av penicillin > 0.5 mg/L, definierade som PNSP). Incidensen PNSP/ 100 000 invånare har minskat från 10,1 1997 till 6–8 sedan år 2000. De flesta fallen identifierades genom nasofarynxodling. Majoriteten av PNSP-fallen var i åldersgruppen 0–4 år. I 19 fall (3,4 procent) påvisades PNSP från blod och/eller spinalvätska. Multiresistens (resistens mot penicillin och minst två ytterligare antibiotika) var vanlig hos PNSP. De vanligast förekommande serotyperna/grupperna var 19F, 9V, 14, 6B och 23F. Enligt data rapporterade i ResNet var resistens mot testade antibiotika åter tillbaka till 2006 års nivå, och den minskning som sågs 2007 var sannolikt tillfällig. Frekvensen PNSP var lägre hos invasiva isolat än hos nasofarynx-isolat medan däremot frekvensen av makrolidresistens var densamma i båda kategorierna (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 drabbat riskpatienter. De har hittills varit ovanliga i Sverige, men 2007 sågs en mindre ökning. Under 2008 rapporterades 618 fall vilket var nästan tolv gånger så många som 2007. Det stora antalet fall kunde tillskrivas förekomst och spridning av en *vanB*-innehållande *Enterococcus faecium* som uppträdde inte enbart i Stockholm utan också i Halland och Västmanland. Intensiva vårdhygieniska åtgärder, kontaktspårning och screening har vidtagits. Genom epidemiologisk typning med PFGE framkom att den aktuella VRE-stammen sannolikt inte hade förekommit i Sverige före 2007. Bland invasiva enterokock-isolat rapporterade till EARSS 2008 förekom den nya stammen i ett par fall vilket gav 1,5 procent resistens. Hos invasiva isolat av både *Enterococcus faecalis* och *Enterococcus faecium* förekom också höggradig aminoglykosidresistens (HLAGR), i 20 respektive 25 procent av isolaten.

Streptococcus pyogenes: Data för 196 invasiva isolat, erhållna från elva laboratorier under 2008, visade minskad förekomst av makrolid-resistens, 0,5 procent jämfört med 2,5 procent 2007, men högre frekvens tetracyklin-resistens, 15 procent jämfört med 8 procent 2007.

Streptococcus agalactiae: Data för 107 invasiva isolat, erhållna från elva laboratorier under 2008, visade att 6,5 procent var makrolid-resistenta, vilket var en liten minskning jämfört med 2007.

Haemophilus influenzae: Data från övervakningen i ResNet, som genomfördes 2008 efter ett uppehåll på tre år, visade på en kraftigt ökad förekomst av betalaktamas-producerande (ampicillin-resistenta) isolat och också av trimetoprim-sulfaresistenta isolat. Siffrorna var nu > 20 procent jämfört med tidigare års genomsnitt på 10–13 procent. En tredjedel var 0–9 år, medan övriga var jämnt fördelade mellan åldersgrupperna. *Haemophilus influenzae* var ett sällsynt fynd bland invasiva isolat, och endast 63 fall fanns registrerade från de elva

laboratorier som rapporterade blododlingar 2008. Sexton av dessa var betalaktamas-producerande (25 procent), vilket var en ökning jämfört med 2007 då endast tre sådana isolat fanns.

Enterobacteriaceae som producerar betalaktamaser med utvidgat spektrum, så kallade ESBL, blev anmälningspliktiga i februari 2007. Totalt 2 957 fall rapporterades under 2008. Samtliga landsting rapporterade fall, och den genomsnittliga incidensen i Sverige var 32 fall per 100 000 invånare. Vid jämförelse mellan andra halvåret 2008 och samma period 2007 noterades en 28-procentig ökning av fallen 2008. De flesta isolaten återfanns i urinprover (70 procent) och var *Escherichia coli* (84 procent), och de hade oftast ESBL av CTX-M-typ. Multiresistens var vanlig 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 2008 (32 procent respektive 29 procent). Frekvensen blodisolat med resistens mot 3:e generationens cefalosporiner var 2,2 procent, och hos majoriteten av dessa var resistensen orsakad av plasmidmedierade ESBL av CTX-M-typ. De cefalosporin-resistenta stammarna var ofta resistenta mot andra antibiotikagrupper som aminoglykosider och kinoloner. Resistens mot kinoloner har ökat årligen och var hos både blodisolat och urinisolat 13–14 procent 2008.

Andra gram-negativa bakterier som övervakats är *Klebsiella pneumoniae* och *Pseudomonas aeruginosa*. Resistensnivåerna hos desssa var oförändrade 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, och under 2008 har ytterligare ett KPC-producerande isolat påträffats, och även ett isolat med metallo-betalaktamas av VIM-typ. I samtliga dessa fall fanns en bakomliggande historia med sjukvård i södra Europa. Hos *P. aeruginosa* var karbapenemresistensen 5 procent och kinolonresistensen 10 procent.

Helicobacter pylori har övervakats regelbundet vid ett laboratorium. Resistens mot klaritromycin har ökat stadigt under flera år men från 2007 har en minskning skett.

Hos *Campylobacter jejuni/coli* var kinolonresistensen >60 procent och tetracyklinresistensen >30 procent, medan erytromycinresistensen var mycket lägre men ändå ökande upp till 7 procent 2008.

Neisseria gonorrhoeae: Gonorré är en anmälningspliktig sjukdom och 2008 rapporterades 724 kliniska fall. Isolat från 447 (62 procent) av dessa har undersökts. Tjugoåtta procent av isolaten var beta-laktamasproducerande och därmed ampicillinresistenta, och 63 procent var resistenta mot kinoloner (ciprofloxacin testat).

Mycobacterium tuberculosis: Antalet anmälda nya fall av tuberkulos var 554 under 2008. *Mycobacterium tuberculosis* med resistens mot minst två antibiotika (MDR-TB) rapporterades hos 3,2 procent av alla utlandsfödda patienter med odlingsverifierad TB (14/359 fall). Epidemiologisk typning med RFLP av alla resistenta TB-isolat visade att de tillhörde 16 olika kluster med två eller fler patienter i varje.

2.3 Contributors to chapters 3 and 4

Otto Cars, Strama
otto.cars@strama.se

Ulrica Dohnhammar, Strama
ulrica.dohnhammar@strama.se

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

Victor Fernandez, Department of Parasitology, Mycologoy and Environmental Microbiology, Swedish Institute for Infectious Disease Control
victor.fernandez@smi.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

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 Disease Control
sven.hoffner@smi.se

Sara Hæggman, Department of Bacteriology, Swedish Institute for Infectious Disease Control
sara.haeggman@smi.se

Gunnar Kahlmeter, National Reference Laboratory for Antibiotic Resistance, Department of Clinical Microbiology, Växjö Hospital
gunnar.kahlmeter@ltkronoberg.se

Bengt Lindeskog, Medical Products Agency
bengt.lindeskog@mpa.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

Victoria Romanus, Department of Epidemiology, Swedish Institute for Infectious Disease Control
victoria.romanus@smi.se

Gunilla Skoog, Strama
gunilla.skoog@strama.se

Johan Struwe, Department of Epidemiology, Swedish Institute for Infectious Disease Control and Strama
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

Michael Toepfer, Department of Clinical Microbiology, Ryhov's Hospital Jönköping
michael.toepfer@lj.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

The Strama group for analysis of antibiotic sales: **Ingrid Brännström, Jonatan Dahlqvist, Örjan Ericsson, Mats Erntell, Maria Grünewald** and **Mikael Hoffmann**.

Acknowledgements

The national surveillance of antibiotic resistance would not have been possible without the active support of all the Swedish clinical microbiology laboratories. Completing of epidemiological information on clinical notifications has been performed by the local County Department for Communicable Disease Control.

Data on antibiotic use in hospital have kindly been provided by pharmacists in local Strama-groups.

Andrejs Leimanis, The National Board on Health and Welfare, has kindly provided individually based data on the use of antibiotics.

3. Use of antimicrobials

3.1. Use of antibiotics

Statistics on antibiotic sales have been obtained from The National Corporation of Swedish Pharmacies. Sales data are expressed either as defined daily doses per 1000 inhabitants and day (DDD/1000 inhabitants/day) or as prescriptions per 1000 inhabitants and year (prescriptions/1000 inhabitants/year).

Data on all drugs prescribed in primary health care are also included in the Swedish Prescribed Drug Register, which is administered by the Swedish National Board of Health and Welfare. Since this register is based upon individuals rather than products, it is possible to investigate the actual number of people treated during a certain period of time. The number of individuals treated with at least one course of antibiotics is expressed as users per 1000 inhabitants and year.

Sales of antibiotics in hospital care are related to either inhabitants, number of admissions to hospitals or number of patient-days. The latter are obtained from the Swedish Association for Local Authorities and Regions.

Denominator data are found in Appendix 2.

Total sales of antibiotics

Sales of antibiotics in Sweden 2008 were 1.6% lower than the previous year, Table 3.1.1. This decrease follows a series of years with rising use. In 2008, some media attention has been drawn towards healthcare issues related to the use of antibiotics in both primary health care and hospital care. Several outbreaks of resistant bacteria in hospitals and patients' free choice of caregiver in primary healthcare are examples of debated topics.

TABLE 3.1.1. Total sales of antibacterial drugs for systemic use in Sweden 2000-2008, DDD/1000 inhabitants/day. Methenamine is an antiseptic and therefore of no interest regarding antibiotic resistance.

	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01 excl methenamine	15.2	15.3	14.8	14.6	14.3	14.8	15.2	15.6	15.4
Methenamine	1.6	1.5	1.6	1.7	1.9	1.9	1.9	1.8	1.6
Total J01	16.8	16.8	16.4	16.3	16.2	16.6	17.1	17.4	17.0

Primary health care

After three years of increase, the sales of antibiotics in primary health care decreased in 2008. Moreover, the seasonal variation seems to be less pronounced than in the years before. This could be seen as an indicator of good quality in prescribing, Figure 3.1.1. The decrease in sales encompasses almost all classes of antibiotics, all age groups and all counties, as will be shown in the further analysis.

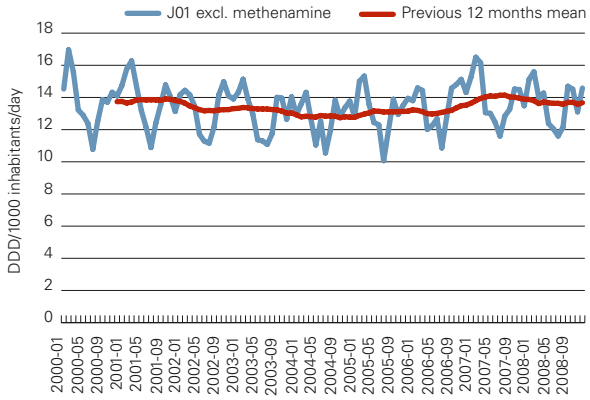

FIGURE 3.1.1. Antibiotics in primary health care 2000–2008, DDD/1000 inhabitants/day. Monthly sales and 12 months mean.

Betalactamase-sensitive penicillins and tetracyclines are still the largest classes of antibiotics in primary health care in Sweden but these classes, as well as the vast majority of other antibiotics are decreasing in sales. Pivmecillinam, an antibiotic used in treatment of lower urinary tract infections in women, and the betalactamase-resistant penicillins are the only classes showing a slight increase, Figure 3.1.2.

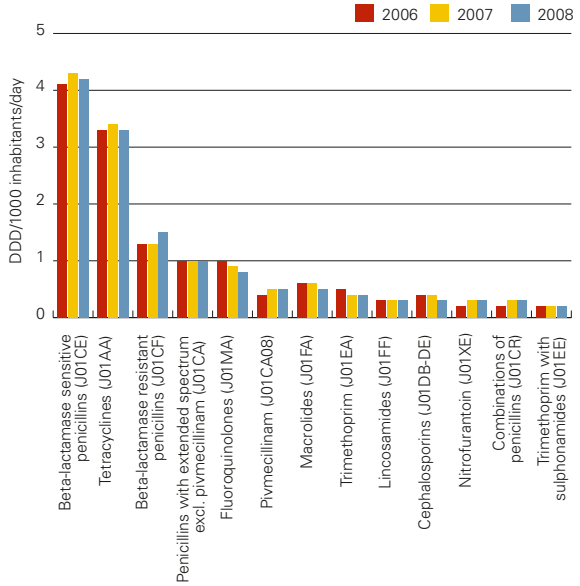

FIGURE 3.1.2. Antibiotics in primary health care 2006–2008, DDD/1000 inhabitants/day.

A shift towards higher doses of betalactamase-resistant penicillins is evident, since the number of DDDs increase by around 15% in all age groups except young children, while the number of prescriptions remains stable, Table 3.1.2. This change is expected and desirable since the Swedish Reference Group for Antibiotics has promoted the dosing of penicillins

TABLE 3.1.2. Antibiotics in primary health care, classes of antibiotics and age groups. DDD/1000 inhabitants/day and prescriptions/1000 inhabitants/year. 2004-2008. Users/1000 inhabitants/year. 2006-2008.

Age group (years)	DDD/1000 inhabitants/day					Prescriptions/1000 inhabitants/year					Users/1000 inhabitants/year		
	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008	2006	2007	2008
Tetracyclines (J01AA)													
0-6	0.00	0.00	0.00	0.00	0.00	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.0
7-19	2.36	2.71	3.12	3.23	3.26	25.4	28.9	32.7	33.9	32.0	20.4	21.5	19.6
20-59	3.36	3.52	3.56	3.68	3.50	62.9	67.2	66.3	68.3	61.3	51.8	53.4	47.6
60-79	3.90	4.15	4.11	4.29	4.05	91.7	99.7	96.3	99.3	90.1	71.6	74.4	67.2
80 -	2.83	3.04	2.89	2.93	2.78	75.8	82.6	76.4	77.8	71.7	60.1	62.0	56.8
All age groups	3.06	3.26	3.33	3.44	3.29	58.6	63.2	62.6	64.3	58.3	46.9	48.6	43.7
Penicillins with extended spectrum (J01CA) excl. pivmecillinam													
0-6	1.25	1.41	1.59	1.74	1.71	84.7	85.0	86.9	95.2	90.8	64.6	70.5	66.7
7-19	0.32	0.38	0.45	0.46	0.43	10.8	12.5	14.1	14.5	13.6	12.4	12.8	11.5
20-59	0.64	0.72	0.72	0.77	0.75	16.8	18.3	18.4	19.4	18.7	16.0	16.7	15.1
60-79	1.43	1.56	1.59	1.62	1.63	39.3	41.2	41.4	42.0	41.3	32.3	32.9	29.9
80 -	1.65	1.80	1.81	1.79	1.83	45.3	47.5	47.3	46.8	46.5	38.3	38.0	32.9
All age groups	0.84	0.94	0.98	1.02	1.02	27.4	29.0	29.6	31.0	30.5	23.4	24.5	22.5
Pivmecillinam (J01CA08)													
0-6	0.01	0.01	0.01	0.01	0.01	0.3	0.4	0.5	0.5	0.7	0.4	0.5	0.6
7-19	0.14	0.15	0.17	0.19	0.24	7.4	8.7	10.7	12.4	15.5	9.6	11.0	13.6
20-59	0.32	0.31	0.34	0.36	0.43	15.4	16.9	20.1	22.2	26.9	17.3	19.0	22.5
60-79	0.72	0.70	0.71	0.74	0.84	33.4	36.2	40.3	43.0	49.5	31.2	33.1	37.3
80 -	2.05	1.90	1.84	1.84	1.95	97.4	100.0	106.7	109.3	116.6	80.1	81.8	85.1
All age groups	0.43	0.42	0.43	0.46	0.53	20.5	22.3	25.5	27.6	32.2	20.7	22.3	25.6
Betalactamase-sensitive penicillins (J01CE)													
0-6	3.32	3.35	3.59	4.03	4.14	307.9	310.5	327.3	350.7	343.7	230.8	244.3	235.9
7-19	2.92	3.01	3.38	3.68	3.64	120.6	121.5	135.0	142.5	135.0	113.1	117.3	110.2
20-59	4.16	4.18	4.28	4.49	4.42	105.5	105.2	107.9	112.8	108.4	91.6	95.2	90.9
60-79	4.33	4.27	4.46	4.57	4.51	104.8	102.9	107.0	109.0	106.1	88.0	89.4	87.0
80 -	3.32	3.39	3.33	3.36	3.51	86.8	87.1	84.2	84.2	85.7	71.4	72.2	72.4
All age groups	3.90	3.92	4.09	4.30	4.26	122.6	122.5	128.1	134.3	130.0	104.0	108.1	103.7
Betalactamase-resistant penicillins (J01CF)													
0-6	0.33	0.31	0.35	0.33	0.33	34.3	32.2	35.6	32.9	32.8	26.7	25.2	24.8
7-19	0.67	0.65	0.70	0.69	0.80	32.0	30.7	33.6	31.9	31.9	27.5	26.4	26.2
20-59	0.88	0.88	0.95	0.96	1.14	31.7	31.7	33.5	33.3	33.2	26.9	26.7	26.5
60-79	1.94	1.91	2.04	2.04	2.37	54.5	54.4	57.4	56.3	56.9	37.7	37.1	37.3
80 -	4.47	4.38	4.44	4.40	5.01	124.2	122.0	123.4	122.6	122.1	68.7	67.9	66.8
All age groups	1.18	1.18	1.25	1.25	1.46	40.9	40.5	42.9	42.2	42.3	31.2	30.7	30.5
Combinations of penicillins (J01CR)													
0-6	0.68	0.73	0.73	0.75	0.67	48.5	51.8	51.2	52.7	46.4	34.4	35.2	30.9
7-19	0.17	0.20	0.22	0.21	0.20	5.1	6.0	6.4	6.4	6.0	5.1	4.9	4.5
20-59	0.15	0.17	0.18	0.20	0.21	3.3	3.8	3.9	4.4	4.6	3.5	3.9	4.0
60-79	0.17	0.20	0.22	0.25	0.27	3.5	4.2	4.5	5.1	5.5	3.6	4.1	4.4
80 -	0.11	0.15	0.15	0.17	0.20	2.4	3.0	3.0	3.4	4.1	2.3	2.7	3.2
All age groups	0.19	0.22	0.24	0.26	0.26	6.9	7.8	8.0	8.5	8.3	6.1	6.5	6.3
Cephalosporins (J01DB-DE)													
0-6	0.53	0.50	0.52	0.52	0.46	49.7	46.4	49.0	49.7	43.6	37.6	38.0	33.9
7-19	0.30	0.29	0.30	0.29	0.27	20.9	19.6	20.6	20.2	18.4	17.4	17.2	15.7
20-59	0.30	0.30	0.29	0.28	0.25	16.9	16.6	16.8	16.2	14.5	14.2	13.7	12.2
60-79	0.48	0.47	0.46	0.40	0.36	23.6	23.1	22.6	20.2	17.7	17.1	15.5	13.5
80 -	0.79	0.77	0.73	0.65	0.54	42.6	42.3	40.5	35.4	29.4	30.9	27.4	22.9
All age groups	0.40	0.38	0.37	0.35	0.31	23.4	22.5	22.5	21.5	19.0	17.9	17.2	15.3

Age group (years)	DDD/1000 inhabitants/day					Prescriptions/1000 inhabitants/year					Users/1000 inhabitants/year		
	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008	2006	2007	2008
Trimethoprim (J01EA)													
0-6	0.12	0.11	0.12	0.12	0.10	15.6	14.8	16.0	15.4	14.0	11.1	10.6	9.8
7-19	0.21	0.20	0.21	0.18	0.15	12.4	11.9	12.4	10.9	8.9	10.8	9.5	7.8
20-59	0.36	0.33	0.33	0.29	0.24	18.7	17.3	17.4	14.6	11.8	14.7	12.4	9.9
60-79	0.92	0.86	0.84	0.76	0.64	44.6	41.7	40.7	35.2	29.2	29.7	25.6	21.0
80 -	2.48	2.28	2.19	1.91	1.58	136.0	125.6	120.1	104.5	84.7	73.3	61.6	49.1
All age groups	0.53	0.49	0.49	0.43	0.36	28.2	26.4	26.3	22.8	18.8	19.8	16.9	13.8
Trimethoprim with sulphonamides (J01EE)													
0-6	0.15	0.15	0.16	0.16	0.14	18.4	18.1	18.1	18.8	16.7	13.2	13.5	12.0
7-19	0.09	0.10	0.10	0.10	0.11	4.0	4.1	4.0	4.1	4.2	2.7	2.6	2.7
20-59	0.12	0.12	0.13	0.14	0.14	2.7	2.8	2.9	3.0	3.1	1.9	1.9	2.0
60-79	0.33	0.34	0.36	0.39	0.44	8.2	8.4	8.8	9.2	10.1	5.8	6.1	6.8
80 -	0.35	0.34	0.36	0.39	0.43	11.8	11.5	11.7	12.2	13.1	8.8	9.1	9.9
All age groups	0.18	0.18	0.19	0.20	0.21	6.2	6.2	6.3	6.4	6.5	4.0	4.1	4.3
Macrolides (J01FA)													
0-6	0.73	0.80	0.80	0.85	0.68	34.5	37.4	37.3	38.1	29.9	29.6	30.4	23.3
7-19	0.62	0.72	0.76	0.74	0.54	18.1	21.0	22.1	21.7	15.4	17.9	17.2	11.8
20-59	0.54	0.56	0.54	0.55	0.49	16.3	16.8	16.3	16.5	14.3	13.0	13.2	11.3
60-79	0.49	0.51	0.50	0.50	0.47	14.1	14.8	14.5	14.6	13.0	11.0	11.0	9.6
80 -	0.31	0.34	0.34	0.32	0.30	9.7	9.8	9.3	8.7	8.4	7.2	6.8	6.4
All age groups	0.55	0.59	0.58	0.59	0.50	17.3	18.4	18.2	18.4	15.3	14.4	14.4	11.7
Lincosamides (J01FF)													
0-6	0.02	0.02	0.02	0.03	0.02	4.1	4.5	5.0	5.3	5.0	3.6	3.9	3.7
7-19	0.09	0.10	0.11	0.12	0.12	6.5	6.9	7.8	8.3	8.4	6.2	6.7	6.9
20-59	0.24	0.25	0.28	0.29	0.30	12.6	13.0	14.3	15.6	15.6	11.1	12.2	12.2
60-79	0.51	0.53	0.55	0.55	0.57	21.1	22.1	23.7	24.4	24.6	15.3	15.9	16.3
80 -	0.71	0.77	0.75	0.74	0.76	30.0	32.2	32.6	32.8	33.2	18.1	18.6	19.2
All age groups	0.27	0.29	0.31	0.32	0.33	13.5	14.1	15.4	16.3	16.4	10.9	11.7	11.9
Fluoroquinolones (J01MA)													
0-6	0.01	0.02	0.01	0.01	0.01	0.4	0.8	0.8	0.8	0.7	0.4	0.4	0.4
7-19	0.12	0.12	0.12	0.13	0.12	5.5	5.5	5.5	5.5	4.8	4.7	4.4	3.9
20-59	0.81	0.81	0.80	0.76	0.69	33.1	31.9	30.2	27.8	23.8	22.0	20.3	17.3
60-79	2.07	2.08	2.05	1.93	1.75	88.0	84.6	80.2	73.7	63.9	52.7	48.7	42.7
80 -	3.14	3.13	3.00	2.74	2.41	158.4	149.4	136.8	119.7	98.5	92.5	81.5	68.1
All age groups	0.98	0.99	0.98	0.93	0.84	42.5	41.0	39.0	35.7	30.6	27.0	24.9	21.5
Nitrofurantoin (J01XE)													
0-6	0.07	0.07	0.07	0.07	0.06	6.9	6.4	6.3	6.3	6.2	4.2	4.2	4.2
7-19	0.11	0.12	0.12	0.14	0.13	4.9	5.3	5.2	6.7	6.6	4.4	5.8	5.8
20-59	0.17	0.19	0.20	0.24	0.23	7.4	8.5	8.5	11.0	10.6	7.0	9.1	8.8
60-79	0.29	0.34	0.36	0.46	0.47	11.7	14.1	14.6	19.4	20.6	10.7	14.3	15.2
80 -	0.68	0.78	0.78	0.97	0.95	31.0	36.5	37.2	46.7	47.7	24.0	30.3	31.2
All age groups	0.20	0.23	0.24	0.30	0.29	9.0	10.3	10.5	13.5	13.6	8.0	10.3	10.4
All agents (J01 excl. methenamine)													
0-6	7.23	7.49	7.98	8.62	8.34	605.9	608.8	634.7	666.8	630.8	335.6	348.5	330.3
7-19	8.13	8.76	9.79	10.18	10.02	274.1	283.4	311.1	319.8	301.4	204.5	208.1	195.8
20-59	12.09	12.37	12.63	13.04	12.82	344.2	350.9	357.6	366.1	348.0	223.9	228.7	217.8
60-79	17.66	18.02	18.34	18.58	18.46	541.0	550.0	554.5	553.7	531.0	288.8	289.6	279.0
80 -	23.01	23.20	22.74	22.33	22.37	856.3	854.2	833.3	807.9	765.1	379.4	372.5	356.2
All age groups	12.77	13.13	13.51	13.87	13.70	418.2	425.6	436.1	443.8	423.1	249.8	254.1	242.5

three instead of two times daily in the treatment of several common infections in primary care. Notably, the number of macrolide prescriptions to the age groups 0–6 years and 7–19 years was 25% lower in 2008 than in 2007. Young children and the elderly have the highest consumption of antibiotics and variation in sales is often most evident in these groups.

The shift in sales of antibiotics commonly used in the treatment of lower urinary tract infections in women continues and is even more pronounced in 2008, Figure 3.1.3. Pivmecillinam is the most common substance and accounts with nitrofurantoin, the other recommended first-line drug, for over 60% in women aged 10–79 years. Unfortunately, there was a shortage of nitrofurantoin in the summer of 2008.

Treatment of lower urinary tract infections in women has been the subject of campaigns and educational activities for several years. The new recommendations launched by Strama and The Swedish Medicinal Products Agency in 2007 seem to have added to the shift. Pivmecillinam and nitrofurantoin are recommended over trimethoprim, and prescribers are encouraged to minimize the use of fluoroquiolones.

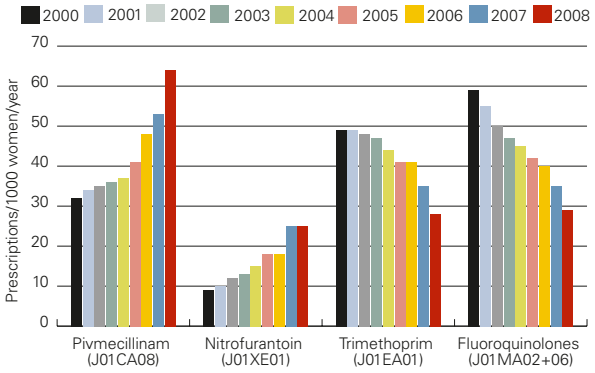

FIGURE 3.1.3. Antibiotics commonly used to treat lower urinary tract infections in women, 2000–2008, prescriptions/1000 women/year.

The fraction of people treated with any kind of antibiotic (users per 1000 inhabitants) is about the same as in previous years. However, antibiotic use varies within Sweden. 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.

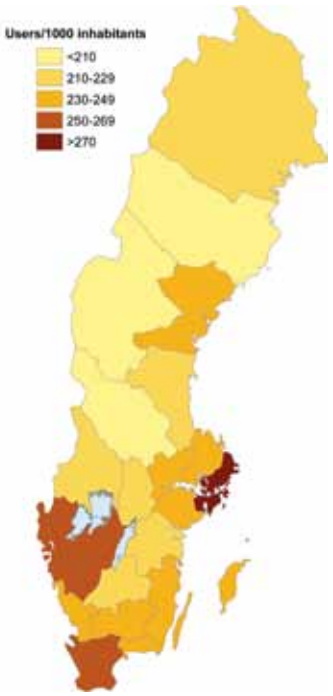

FIGURE 3.1.4. Fraction of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2008, users/1000 inhabitants. Age and gender standardized data.

Concerning the fraction of children that had at least one course of antibiotics in 2008, Stockholm county was again the highest with 384 users per 1000 children whereas Västerbotten county was the lowest with 249 users per 1000 children, Figure 3.1.5. Taken together, the fraction of children treated with antibiotics was 330 users per 1000 children, which is 5% lower than in 2007.

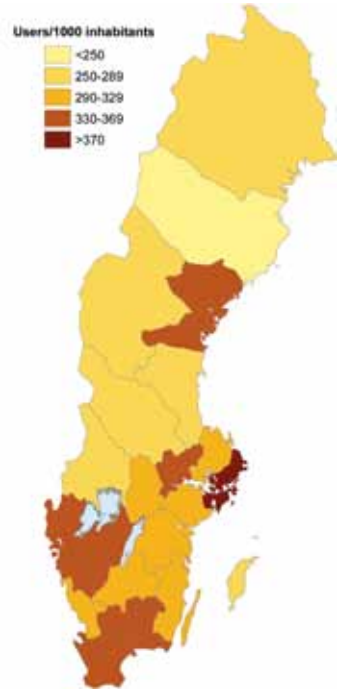

FIGURE 3.1.5. Fraction of children aged 0 to 6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2008, users /1000 children.

As seen in Table 3.1.2., different kinds of penicillins are the most commonly prescribed antibiotics to children in Sweden. However, there are large differences between the counties. The number of prescriptions range from nearly 600 per 1000 children in Stockholm county to 300 in Västerbotten county, Figure 3.1.6. The diversity seems mostly relate to the use of penicillins with an extended spectrum, i.e. amoxicillin and amoxicillin with clavulanate. The use of these substances varies from over 200 prescriptions per 1000 children to less than 80 per 1000 children. Penicillins with an extended spectrum are prescribed to a much greater extent in counties that also have a high level of prescription of narrow spectrum penicillins, hence the big difference between counties.

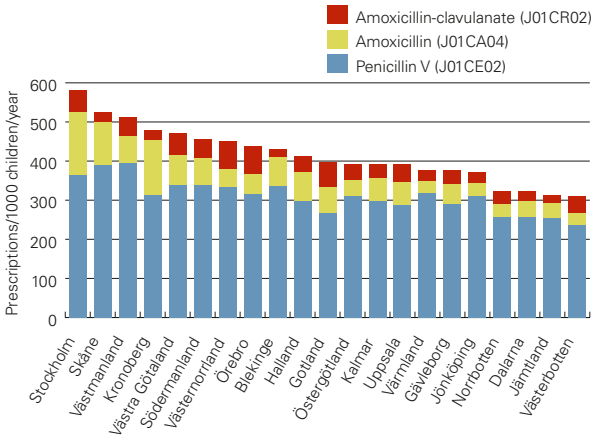

FIGURE 3.1.6. Penicillins to children aged 0–6 years, per county. Prescriptions/1000 children/year.

Ulrica Dohnhammar, Gunilla Skoog

Hospital care

Hospital care includes data from all Swedish hospitals as well as data from those nursing homes that order their antibiotics through requisitions. Patients in some nursing homes get their antibiotics through prescriptions and in those cases data are included in primary health care data, presented in the previous section. The analysis of hospital care data is thus complicated as the number of nursing homes using requisitions vary over the years and between counties.

In this section we also present data from local data sources of antibiotic treatment in hospitals, i.e. nursing homes excluded.

The use of antibiotics in hospital care has continuously increased since the end of the 1990s. This trend was broken 2008. About 10% of the total antibiotic use is within hospital care. In Table 3.1.3. the antibiotic use within hospital care, with and without methenamine, is listed.

TABLE 3.1.3. Antibiotic use in hospital care 2000-2008, DDD/1000 inhabitants/day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01 excl methenamine	1.26	1.26	1.27	1.33	1.37	1.43	1.50	1.55	1.52
Methenamine	0.03	0.03	0.03	0.05	0.07	0.07	0.07	0.07	0.05
Total J01	1.30	1.29	1.30	1.38	1.44	1.50	1.57	1.62	1.57

Figure 3.1.7. shows all classes of antibiotics used in hospital care during the last three years. The most pronounced increases are seen in the various types of penicillin. Broad spectrum antibiotics, such as cephalosporins and fluoroquinolones are decreasing. This change towards less broad spectrum and more narrow spectrum antibiotics is desirable and has been promoted by the Strama hospital care group.

Moreover, new recommendations for the treatment of uncomplicated community acquired pneumonia were published by the Swedish Society of Infectious Diseases a few years ago. Betalactamase-sensitive penicillins were suggested as first choice and the use of cephalosporins should be reduced. These are possible explanations of the decrease in cephalosporins and increase in betalactamase-sensitive penicillins. Stramas point prevalence studies, performed in 2003, 2004, 2006 and 2008, confirm that the use of cephalosporins for the treatment of uncomplicated community acquired pneumonia has decreased considerably.

Cephalosporins have traditionally been used extensively within Swedish hospital care, in particular cefuroxime. In 2007 cephalosporins represented 15% of total DDD per 1000 inhabitants and in 2008 this proportion had decreased to 13%. The decrease in DDD is partially a result of the shift from cefuroxime to cefotaxime since the prescribed daily doses, PDD, in Sweden do not correspond to the WHO definition of DDD. The most commonly used PDD in Sweden for cefuroxime is 4.5g (WHO 3g) and for cefotaxime 3g (WHO 4g).

The increased use of tetracyclines was commented in Swedres 2007. The high use in 2007 seems to have diminished but the reason for this is unclear.

The increased use of betalactamase-resistant penicillins could be a result of changed dosage recommendations, from twice to three times daily.

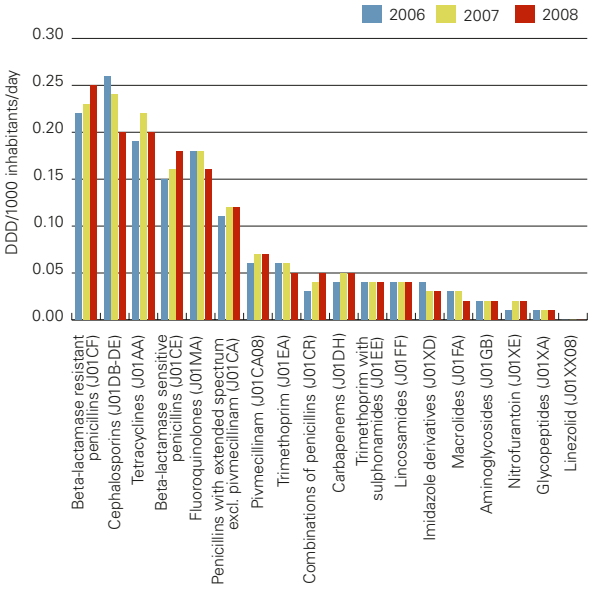

FIGURE 3.1.7. Antibiotics in hospital care 2006–2008, DDD/1000/day.

An increasing number of infections involving ESBL-producing bacteria may be another reason for the lower use of cephalosporins. Strama's proposed action plan "ESBL resistance in enteric bacteria" recommends a reduction in cephalosporins in favour of penicillins (http://en.strama.se/dyn//,95,15.html). Figure 3.1.8. shows the use of cephalosporins and the possible alternatives such as narrow spectrum penicillin, carbapenems, piperacillin/tazobactam and aminoglycosides. There has been an obvious reduction in the use of cephalosporins during the last two years. Meanwhile the use of betalactamase-sensitive penicillins and piperacillin/tazobactam has increased. Part of the increase of the former may be a result of changed dosage recommendations. Also the use of carbapenems seems to have increased over the last years.

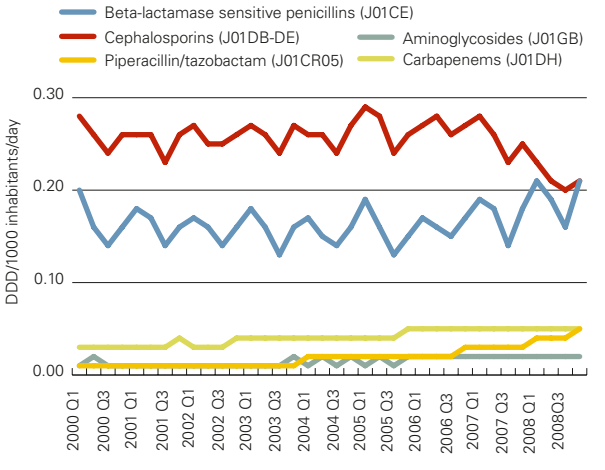

FIGURE 3.1.8. The use of some antibiotic groups within hospital care, per quarter 2000–2008, DDD/1000/day.

The use in all counties of cephalosporins and possible alternatives is shown in Figure 3.1.9. These data represent only hospital use, nursing homes are excluded. The proportion between cephalosporins and betalactamase-sensitive penicillins varies considerably within Sweden. Perhaps this is an effect of campaigns and activities in certain counties, conducted by local Strama-groups and drug committees. Carbapenems and piperacillin/tazobactam still comprise a small portion of the total antibiotic use in hospital care in most counties.

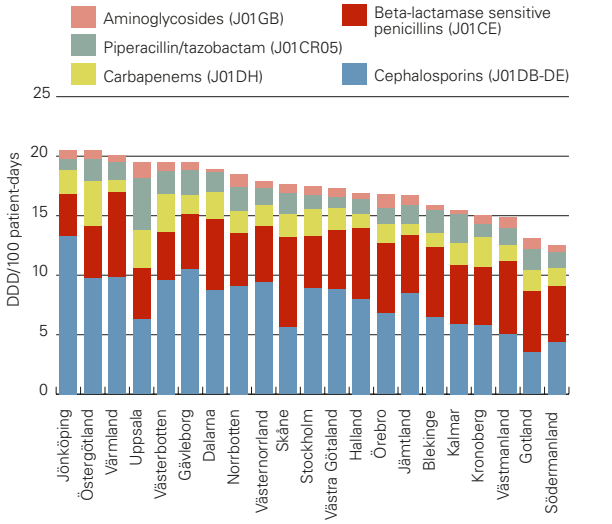

FIGURE 3.1.9. The use of some antibiotic groups within Swedish hospitals, all counties 2008 (denominator data from 2007), DDD/100-patient days.

Table 3.1.4. and 3.1.5. show antibiotic use in relation to number of admissions and number of patient days in hospital somatic care during 2006–2008. Please note that comparable tables in previous Swedres reports also partly include data from nursing homes.

TABLE 3.1.4. Antibiotics in Swedish hospitals 2006-2008, DDD/100 admissions within somatic care.

	2006	2007	2008*
Tetracyclines (J01AA)	28.8	29.9	26.5
Penicillins with extended spectrum (J01CA)	26.2	27.1	28.3
Betalactamase-sensitive penicillins (J01CE)	24.2	25.2	30.1
Betalactamase-resistant penicillins (J01CF)	40.3	41.8	46.5
Combinations of penicillins (J01CR)	6.7	8.2	11.0
Cephalosporins (J01DB-DE)	57.2	53.9	45.9
Carbapenems (J01DH)	10.6	10.8	11.3
Trimethoprim (J01EA)	6.7	6.3	5.8
Trimethoprim with sulphonamides (J01EE)	7.7	8.3	9.1
Macrolides (J01FA)	5.4	5.3	4.7
Lincosamides (J01FF)	7.8	8.0	8.2
Aminoglycosides (J01GB)	3.8	3.8	4.3
Fluoroquinolones (J01MA)	33.9	32.5	29.5
Glycopeptides (J01XA)	3.4	3.4	3.4
Imidazole derivatives (J01XD)	8.4	7.9	7.5
Methenamine (J01XX05)	4.7	4.5	3.8
Linezolid (J01XX08)	0.3	0.3	0.3
All agents (J01)	278.4	279.8	278.9

*Denominator data from 2007.

TABLE 3.1.5. Antibiotics in Swedish hospitals 2006-2008, DDD/100 patient-days within somatic care.

	2006	2007	2008*
Tetracyclines (J01AA)	5.5	5.7	5.1
Penicillins with extended spectrum (J01CA)	5.0	5.2	5.4
Betalactamase-sensitive penicillins (J01CE)	4.6	4.8	5.8
Betalactamase-resistant penicillins (J01CF)	7.7	8.0	8.9
Combinations of penicillins (J01CR)	1.3	1.6	2.1
Cephalosporins (J01DB-DE)	10.9	10.4	8.8
Carbapenems (J01DH)	2.0	2.1	2.2
Trimethoprim (J01EA)	1.3	1.2	1.1
Trimethoprim with sulphonamides (J01EE)	1.5	1.6	1.8
Macrolides (J01FA)	1.0	1.0	0.9
Lincosamides (J01FF)	1.5	1.5	1.6
Aminoglycosides (J01GB)	0.7	0.7	0.8
Fluoroquinolones (J01MA)	6.5	6.3	5.7
Glycopeptides (J01XA)	0.6	0.6	0.7
Imidazole derivatives (J01XD)	1.6	1.5	1.4
Methenamine (J01XX05)	0.9	0.9	0.7
Linezolid (J01XX08)	0.1	0.1	0.1
All agents (J01)	53.2	53.8	53.6

*Denominator data from 2007.

Gunilla Skoog, Ulrica Dohnhammar

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 (Läkemedelsverket). The reports originate from health care professionals. The antibiotic related adverse reactions in the last five years (2004–2008) 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=485), hepatobiliary disorders (n=204), gastrointestinal disorders (n=200), general disorders (n=151), musculoskeletal disorders (n=143), blood disorders (n=129), and neurological reactions (n=125). 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 3.1.6. A newcomer in this top-ten-list is cefuroxime.

TABLE 3.1.6. Most reported antibiotic agents to the Swedish Medical Products Agency 2004–2008

Antibiotic	Total number of ADR reports 2004 to 2008	Number of 'serious' reports	Number of fatal cases (causal relationship possible)
Ciprofloxacin	210	111	3
Flucloxacillin	114	76	3
Nitrofurantoin	105	53	1
Clindamycin	86	36	1
Fenoxymethylpenicillin	82	37	0
Trimethoprim	81	35	0
Doxycylin	71	26	3
Sulphamethoxaxol + trimethoprim	66	41	2
Cefuroxime	55	30	1
Norfloxacin	45	20	2

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 the data are based on spontaneous reporting, no clear conclusions can be made regarding these trends, Table 3.1.7.

TABLE 3.1.7. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2004–2008

	2004	2005	2006	2007	2008	2004-2008
Fluoroquinolones						
Total no of reports	69	56	45	55	35	260
Number of reactions						
Musculoskeletal	34	24	19	22	9	108
tendinitis	15	13	11	10	2	51
tendon rupture	12	5	3	6	5	31
Skin- and subcutaneous tissue	7	11	6	17	4	45
Psychiatric disorders	4	10	8	4	2	28
Nitrofurantoin						
Total no of reports	24	15	20	22	24	105
Number of reactions						
Respiratory system	10	8	12	3	7	40
dyspnoea	3	2	4	0	1	10
interstitial pneumonia	2	2	2	2	2	10
pulmonary fibrosis	1	0	2	0	0	3
Skin- and subcutaneous tissue	7	1	7	8	7	30
General disorders	11	7	8	7	6	39
fever	6	6	4	3	4	23

Charlotta Edlund, Bengt Lindeskog

3.2. Use of antifungals

Hospital care

The total use of antifungals administered systemically in hospital care remained basically unchanged from 2007 to 2008 (from 52.2 to 52.8 DDD/106/day). However, somewhat of a trend shift in the use of systemic antimycotics in Sweden, namely an increase in the utilization of amphotericin B and a decrease in fluconazole, was seen during 2008, Figure 3.2.1. The use of amphotericin B, that steadily decreased from 8.3 to 2.2 DDD/106/day in the period 2001–2007, showed a 35% increase in 2008. Amphotericin B is a macrolide polyene with excellent antifungal activity against most fungi that cause human disease. It is primarily indicated for the treatment of aspergillosis and other invasive mold infections, cryptococcal meningitis, and infections caused by endemic dimorphic fungi. Adverse effects of amphotericin B are many and often severe. Nephrotoxicity, electrolyte imbalance and hepatotoxicity are most common. Lipid-based formulations of amphotericin B such as liposome conjugates have been developed to reduce systemic toxicity and improve tolerability to higher doses. With a superior safety profile, the second-generation triazole voriconazole has increasingly being used as the first choice drug for the treatment of invasive aspergillosis since 2002, when its efficacy was established. Other approved indications for voriconazole include severe infections caused by *Scedosporium* spp., *Fusarium* spp. and fluconazole-resistant *Candida* spp. Recent recognition of frequent clinical *Candida glabrata* isolates with decreased susceptibility to voriconazole and the widespread occurrence of cross-resistance between triazoles nevertheless argue against the use of voriconazole for the treatment of infections caused by *Candida* species with innate resistance to azole compounds. After peaking in 2005–2006, the total use of voriconazole has decreased by 23% in the last two years.

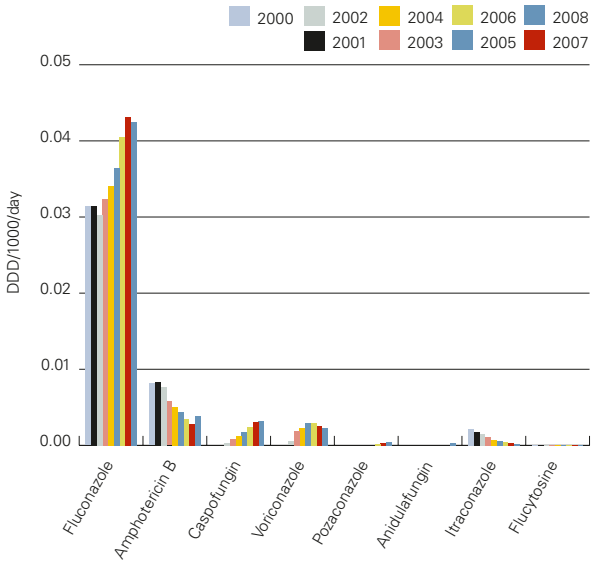

FIGURE 3.2.1. Use of antifungals in hospital care, 2000–2008.

The reduction of the in-patient use of fluconazole during 2008 was fairly small (2%) but stands in contrast to the steep increase observed in the period 2002–2007, Figure 3.2.1. Despite this trend shift, fluconazole still accounted for 80% of the total use of antifungals in hospitalized patients during 2008. Fluconazole is a fungistatic agent indicated for the treatment of candidosis in non-neutropenic patients as well as cryptococcal meningitis, and prophylactically against invasive Candida infections. In later years, awareness has increased in regards to the risks associated with the use of fluconazole to treat C. non-albicans infections, in particular those caused by azole-resistant species such as *C. glabrata* and *C. krusei* that in Sweden represent 20–25% of all candidemia episodes. The echinocandin antifungal caspofungin is increasingly being used, since its introduction in 2002, for the treatment of invasive candidiasis and as salvage therapy for invasive aspergillosis. Caspofungin, as other echinocandins, disrupt glucan synthesis in the fungal cell wall by inhibiting the enzyme β(1,3)-D-glucan synthase. It has a well demonstrated activity against azole-resistant Candida species and a relatively benign safety profile. Two new echinocandin drugs, anidulafungin and micafungin, have recently been licensed in Sweden. These developments underscore the need for continued surveillance of antifungal resistance and for diagnostic methods that make possible the early application of pathogen-specific antifungal therapy.

Primary health care

In 2008, as in previous years, more than 95% of all antifungal prescriptions took place in primary health care. Formulations of two agents, miconazole and fluconazole, accounted for nearly half of the total. The imidazole miconazole combined with hydrocortisone is indicated for topical use against dermatophyte infections, Trychophyton-, Epidermophyton- and Microsporum-species, and for application on mucosal membranes against oral and vaginal thrush caused by Candida spp. Fluconazole, administered orally, is indicated against vaginal and other mucocutaneal Candida infections. Measured as DDD/1000/day, the antifungal most sold over-the-counter was ketoconazole, an imidazol available in shampoo formulations used for body wash against seborrhoeic dermatitis caused by Malassezia yeasts. Azole agents for gynecological use constitute the antifungal group most commonly sold (46% of total sales) over-the-counter.

Victor Fernandez

4. Antimicrobial resistance

IN SWEDEN, testing of clinical isolates for antibiotic susceptibility is routinely performed using standardized methods (Appendix 4). 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 *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 laboratory as well as clinical notification, whereas ESBL require laboratory notification only.

In addition to these mandatory notifications a national programme for the surveillance of resistance was initiated in 1994 (Appendix 5). Well-characterised data on resistance in many bacterial pathogens are available since several years both at regional and national level.

Twenty-one of the Swedish laboratories, covering approximately 75% of the population, report susceptibility data on invasive isolates of seven defined bacterial species to the European Antimicrobial Resistance Surveillance system, EARSS. Eleven of these laboratories also deliver data from all positive blood cultures, in total 11.115 isolates in 2008. (Appendix 5).

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. The annual numbers of samples specifically registered to be analysed for screening for (multi-) resistant bacteria, MRB, is shown in Figure 4.1. Even if the screening programmes and criteria for registering analyses under this heading may vary between laboratories, they are fairly constant within each laboratory. In 2008 27 of 31 laboratories provided data on MRB-screening.

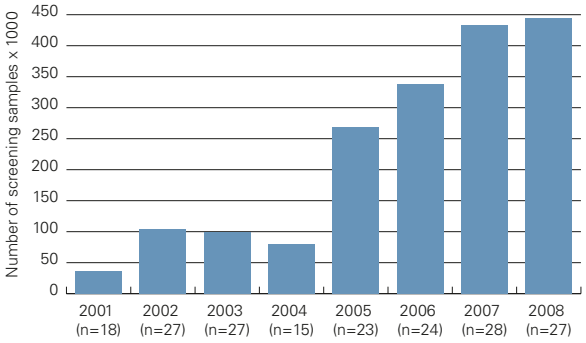

FIGURE 4.1. Annual number of recorded screening samples for multiresistant bacteria, 2001–2008. n refers to the number of participating laboratories

Staphylococcus aureus

Background

Following an extensive outbreak in Western Sweden and increasing alertness responding to the situation seen in other European countries MRSA was made mandatory notifiable in the year 2000. Compared to many other European countries, where the proportion of MRSA exceeds 25% of invasive *S. aureus* isolates, the prevalence of MRSA among such isolates is still below 1% in Sweden (see details on EARSS data in the following text). Infection control programmes have been developed and implemented locally under supervision by the County Department for Communicable Disease Control (CDCDC) and infection control teams. These programmes are based on early case-finding through extensive screening of patients with risk factors and contact tracing combined with infection control measures such as isolation of MRSA positive cases and intensive campaigns on basic hygiene precautions.

Notifications of MRSA according to the Communicable Disease Act

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 three years an active effort has been made to improve the quality of the 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 CDCDCs. A total of 1307 cases of MRSA were notified in 2008, an increase with 16% compared with the 1128 cases 2007, Figure 4.2.

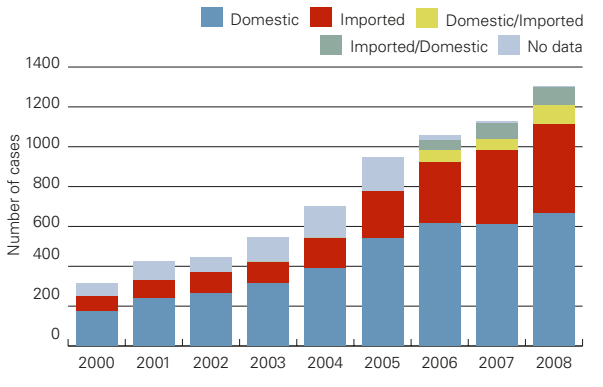

FIGURE 4.2. Number of MRSA notified annually by country of infection, Sweden 2000–2008. "Domestic/Imported" and "Imported/Domestic" indicate several mentioned countries of infection with the most likely mentioned first.

In 2008, six of the Swedish counties had a higher incidence than the total national incidence of 14.1 cases/100 000 inhabitants, Table 4.1.

TABLE 4.1. MRSA notified in 2000-2008 by county according to the Communicable Disease Act

	2000		2001		2002		2003		2004		2005		2006		2007		2008	
County	**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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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

* = Incidence (cases/100 000 inhabitants)

During 2008, 51% (n=665) of all reported MRSA cases were domestically acquired and 34% (n=450) were acquired abroad. Thailand (39 cases), Iraq (31 cases), the Philippines (29 cases), India (28 cases) and USA (20 cases) made up the five most common countries for imported MRSA infection during 2008. In 14% Sweden and at least one more country was mentioned as possible countries for acquisition of MRSA. These cases were divided between "domestic/imported or "imported/domestic" depending on the order of listing the countries in the clinical notification. The country for acquisition was reported as "unknown" in seven cases and in three cases no country of acquisition was listed.

The increase in the number of domestic cases in recent years has mainly occurred in the age groups below 50 years of age. Since mandatory reporting of MRSA started, the proportion of cases below the age of 50 has almost doubled, Figure 4.3.

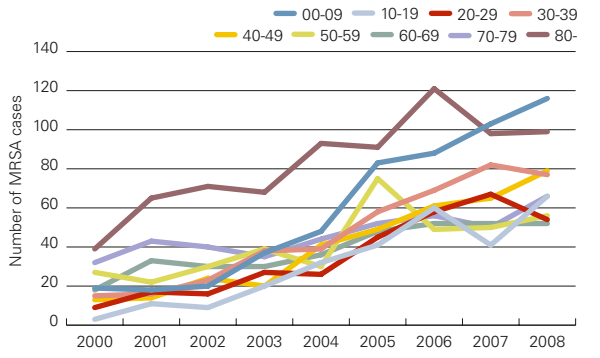

FIGURE 4.3. Age distribution of notified domestic cases of MRSA, Sweden 2000–2008.

Figure 4.4. shows that in 2008, 54% of the domestic and 64% of the imported cases were identified in targeted screening or contact tracing and 46% of the domestic and 35% of the imported cases presented with clinical symptoms. Fifteen newly discovered cases had invasive MRSA infection.

Even if aggregated data on the total number of clinical cultures are not available at present, it is reasonable to assume that the number of cultures have increased as culturing even of furuncula and minor blisters is widely encouraged in community care. Thus, wider indications for culturing in combination with spread of PVL (Panton-Valentine Leucocidin)-positive MRSA in the community may explain the increase in the proportion of clinical isolates during recent years.

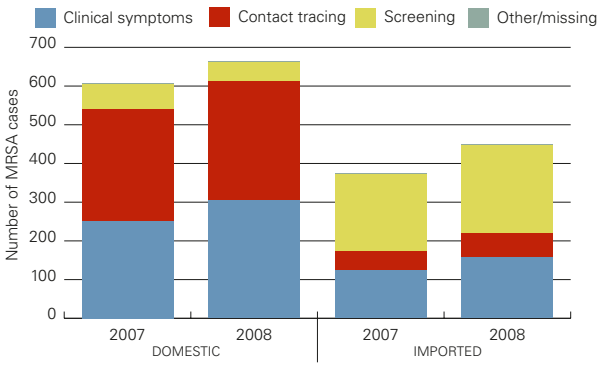

FIGURE 4.4. The reason for detection of domestic and imported MRSA cases in Sweden 2007–2008.

Epidemiological classification of the acquisition of MRSA is based on information in the clinical notifications and subsequent investigations at the local level, Figure 4.5.

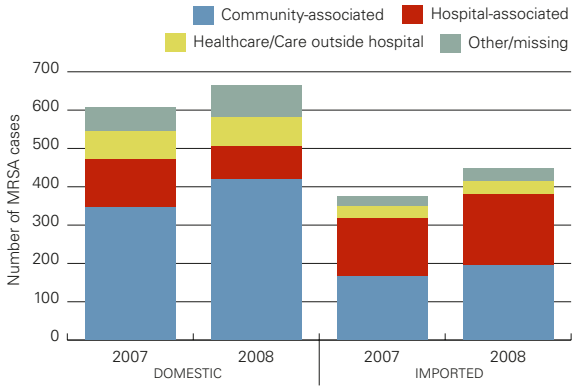

FIGURE 4.5. Epidemiological classification of the acquisition of domestic and imported MRSA, Sweden 2007–2008

Community associated infections dominated among domestic cases 2008 and comprised 63% (n=420) of all cases. This is an increase from 2007 and shows that MRSA in Sweden today is acquired primarily in the community. Also among the imported MRSA cases the proportion of community associated infections increased during 2008, representing 43% (n=194) of all cases.

Hospital associated MRSA was relatively more common in imported cases, 41% (n=186) as compared with 13% (n=85) among domestic cases. Among imported cases a similar proportion of hospital association was seen in 2007 and 2008, but for domestic cases the proportion of hospital associated MRSA in 2008 was lower than the 20% registered during 2006–2007.

In 14% of all 1307 notified MRSA cases several countries were mentioned (2–7 countries), and acquisition of MRSA in the community was stated for 70% of these cases.

During 2008 only minor outbreaks were reported from the Swedish healthcare system or from long-term care facilities for the elderly. These small outbreaks were reported from several counties. Despite the steady increase in domestic MRSA cases and reports of patients identified during hospitalisation, there is presently no Swedish region reporting secondary spread of MRSA in the hospitals. The diversity in MRSA types reported (see below) and the low numbers of multiresistant MRSA further suggest primarily community acquisition of MRSA in Sweden.

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 during 2006 which 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 during 2008 were t002 (n=132), t008 (n=113), t044 (n=107), t019 (n=54), t032 (n=51), t127 (n=38), t437 (n=37), t024 (n=32), t015 (n=31), and t037 (n=30). Nine of these ten types were also found among the top-ten in 2007, the only change being that t690 had been replaced by t127 in 2008. The five most common of these types comprised more than one third, and all ten most common types comprised 50% of all cases. Spa-types found in connection with small hospital outbreaks were t002, t015 and t172.

In 2008 focus was 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 2008). In humans in Sweden 2008 only two cases of MRSA with spa-type t011 and one with t034 were found, both spa-types belonging to CC398.

As in 2007, isolates with spa-types t032, t037 and t015 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, 445 (35%) of all tested isolates from 2008 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 t044 were still most frequently found, followed in decreasing order by t008, t019, t437, t024, t002, t355 and t657.

Antibiotic resistance in MRSA

All MRSA isolates were investigated with regard to resistance to antibiotics other than betalactam antibiotics, Table 4.2. In 2008 concomitant resistance to erythromycin, clin-

TABLE 4.2. Numbers and rates of resistance to indicated antibiotics among MRSA isolates 2000-2008

Year/Antibiotic	Erythromycin	Clindamycin	Ciprofloxacin	Fusidic acid	Gentamicin	Mupirocin	Rifampicin
2000	179 (55.9)	nt	187 (58.4)	74 (23.1)	76 (23.8)	8 (2.5)	42 (13.1)
2001	208 (50.5)	nt	252 (61.2)	89 (21.6)	87 (21.1)	30 (7.3)	44 (10.7)
2002	220 (50.3)	nt	280 (64.1)	128 (29.3)	80 (18.3)	48 (11)	27 (6.2)
2003	220 (40.4)	nt	278 (51.1)	156 (28.7)	91 (16.7)	47 (8.6)	25 (4.6)
2004	229 (33.3)	nt	270 (39.3)	135 (19.7)	97 (14.1)	24 (3.5)	24 (3.5)
2005	374 (39.2)	326 (34.1)	318 (33.3)	155 (16.2)	183 (19.2)	21 (2.2)	34 (3.6)
2006	371 (37.1)	308 (30.8)	322 (32.2)	162 (16.2)	140 (14.0)	20 (2.0)	40 (4.0)
2007	433 (39.6)	343 (31.4)	401 (36.7)	159 (14.6)	207 (19.0)	20 (1.8)	47 (4.3)
2008	425 (33.7)	317 (25.2)	338 (26.8)	155 (12.3)	152 (12.1)	18 (1.4)	20 (1.6)

damycin and ciprofloxaxin was still most frequently found, but the frequencies have slowly been decreasing since 2004. Approximately 75% of the macrolide resistant isolates had the MLS_B type of resistance, indicated by simultaneous resistance to clindamycin (inducibly or constitutively expressed *erm* genes). Resistance to fusidic acid, which is typical for t044 isolates but also found in other types, became less frequent (<20%) since 2004. Aminoglycoside resistance (gentamicin tested) was found in 15–20% of isolates through the years but was less frequent in 2008. Resistance to mupirocin or rifampicin was found in less than 4% of isolates during the last five years.

The decrease in the proportion of concomitant antibiotic resistance in MRSA probably reflects the transition from hospital-acquired to community acquired strains.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Staphylococcus aureus from wound infections was included in the annual RSQC programme 2001 (Appendix 5). Twenty-nine 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.

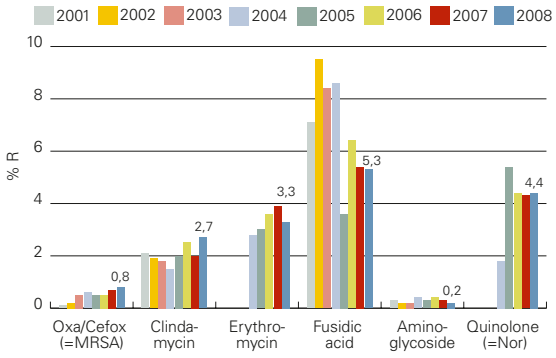

FIGURE 4.6. Resistance rates for *Staphylococcus aureus* 2001–2008 (data from the annual RSQC programme, approximately 3000 isolates per year). In 2005 resistance rates were recorded in *S.aureus* isolated from wounds and secretions from elderly (> 65 years) people only,

The frequency of MRSA in wound infections (cefoxitin used as test compound) increased in 2008 but the level remained below 1%. The resistance rate for erythromycin (3.3%) was only slightly higher than that for clindamycin (2.7%). This situation was different from previous years and indicated a shift with an increased prevalence of *erm* genes (constitutively or inducibly expressed) among the clinical isolates. The level of fusidic acid resistance was stable around 5%. The lower level of resistance in 2005 indicates that the epidemic fusidic acid resistant strain causing impetigo in children was not as prevalent in the elderly population. Almost no resistance to aminoglycosides was seen in bacteria from wound infections. Fluoroquinolone resistance was stable at 4–5%.

Data on invasive isolates reported to EARSS

In 2008, only 0.7% of the invasive *S. aureus* isolates were MRSA (identified by the cefoxitin screen disk test and confirmed by detection of the *mecA* gene). This low level has remained during the eight years of mandatory reporting, indicating that infection control measures to prevent MRSA from spreading in the hospital environment have been successful. Twelve spa-types were identified among the 16 newly discovered invasive MRSA isolates in 2008.

TABLE 4.3. *Staphylococcus aureus* susceptibility results (number of strains and percentage) in blood isolates by the disk diffusion method and by confirmation of the *mecA* gene. Data reported from SMI to EARSS.

Year	S	I	R
2001	1618 (99.1%)	0	14 (0.9%)
2002	1830 (99.4%)	0	12 (0.6%)
2003	1839 (99.1%)	0	16 (0.9%)
2004	1891 (99.3%)	0	14 (0.7%)
2005	1756 (99%)	0	18 (1.0%)
2006	1849 (99.1%)	0	16 (0.9%)
2007	2162 (99.5%)	0	11 (0.5%)
2008	2408 (99.3%)	0	16 (0.7%)

Tomas Söderblom, Johan Struwe, Sara Hæggman, 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 after reports of increasing resistance in southern Sweden. In addition invasive infections with *S. pneumoniae*, regardless of resistance, became notifiable in 2004.

Notifications according to the Communicable Disease Act

In 2008 there were 565 notifications of PNSP in Sweden, Figure 4.7, a decrease with 16% compared with 2007. Sixty-four percent of the cases were reported to be infected domestically and 12% in a foreign country. In the remaining 135 cases no country for acquisition was given.

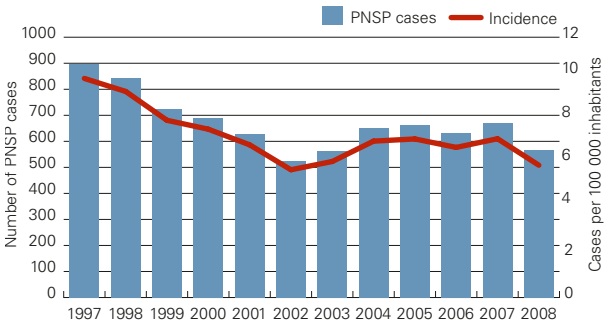

FIGURE 4.7. Number of cases of *S. pneumoniae* with reduced susceptibility to penicillin, MIC ≥0.5 mg/L (PNSP in Sweden 1997–2008.

The PNSP incidence in Sweden was 6.1 cases per 100 000 inhabitants 2008. Previous analysis has indicated that the declining incidence from 1997 to 2002 was related to a concurrent decrease in nasopharyngeal culturing propensity. The majority of PNSP cases, independent of year observed, are found in the age group 0–4 years, Figure 4.8. Compared with 2007 the decrease in number of reported cases primarily is in this age-group. There is no difference in the proportion of the reported cases with regard to sex.

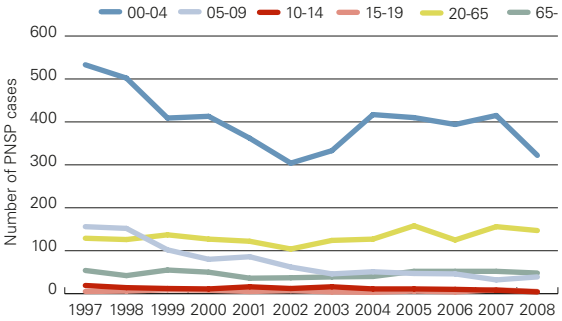

FIGURE 4.8. Age-group distribution among all cases reported with PNSP in Sweden 1997–2008.

PNSP were reported from all 21 counties with Stockholm (184 cases) and Skåne (216 cases) accounting for 71% of all notifications. Remaining counties report 1–32 cases each. Due to regional differences in general culturing propensity, case finding intensity as well as presence of targeted screening programme comparison of regional incidence rates is difficult.

The majority, 82% of all notifications of the PNSP, are found in cultures from nasopharynx. 19 cases in 2008 were reported to have invasive PNSP infections, 18 cases in blood and one in cerebrospinal fluid. For four of these cases the serotype were reported, two had serotype 19, one serotype 14 and one serotype 9. The most commonly found serotypes among all PNSP were, in decreasing order, 19F, 9V, 14, 6B, and 23F.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pneumococci have been included since 1994 in the surveys by Swedish laboratories. These isolates 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 ug screen disk), erythromycin, tetracycline, and trimethoprim-sulfamethoxazol, using the disk diffusion method. The national summary of the results is shown in Figure 4.9. For all four tested antibiotics the rates of resistance are back to the levels noted in 2006, and the decrease seen in 2007 seems to have been only temporary.

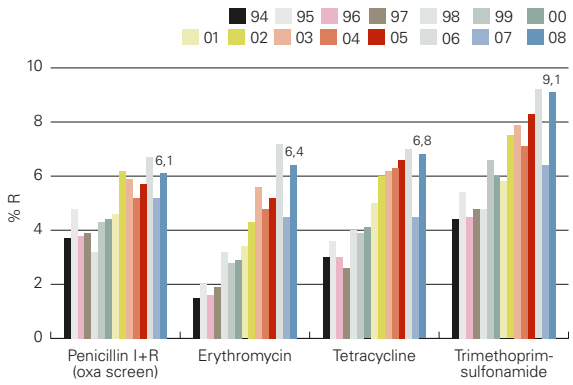

FIGURE 4.9. Resistance rates for *Streptococcus pneumoniae* 1994–2008 (data from the annual RSQC programme, approximately 3000 isolates per year).

Data on invasive isolates reported to EARSS

The Swedish data on susceptibility to penicillin and erythromycin for 2001–2008 are given in Table 4.4. Levels of resistance are lower among invasive isolates than in the nasopharyngeal isolates from the RSQC programme. Also, there has been no trend of increasing resistance among invasive isolates, neither for penicillin nor erythromycin, contrary to the nasopharyngeal isolates.

TABLE 4.4. Invasive isolates of *Streptococcus pneumoniae* reported to EARSS.

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

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

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

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

There were 618 notified cases of VRE during 2008, almost 12 times more cases compared with 2007. From 2000 to 2007 the numbers of reported cases of VRE have been 20, 18, 19, 47, 21, 35, 24 and 53 respectively. Reports on VRE came from 12 out of 21 Swedish counties but the majority of cases were from Stockholm (n=418), Halland (n=86), Västmanland (n=83), and Uppsala (n=13). Another 18 cases were reported from eight other counties. The national incidence for VRE was 6.7 cases per 100 000 inhabitants whereas the incidence figures in the affected counties were 21.1 in Stockholm, 29.3 in Halland, 33.2 in Västmanland, and 4.0 in Uppsala. The average age for all cases was 70 years, and there was an even distribution between the sexes.

In 13 cases the VRE was acquired abroad and 10 different countries were stated. For eight of the cases the acquisition was health-care related and for the remaining five cases information was missing.

During 2008, 610 notified cases had *Enterococcus faecium*. Of these 505 carried the *vanB* gene and 96 the *vanA* gene. Information was missing for four cases. In five cases a double infection was reported with *Enterococcus faecium -vanA* and *Enterococcus faecium -vanB*. *Enterococcus faecalis* was reported in only four cases. One isolate was reported as *vanA*-positive, information was missing for the other three. Two cases were reported with both *Enterococcus faecalis* and *Enterococcus faecium*.

According to the first laboratory notification for each case the majority were isolated from faeces (84%), whereas 5% each of the isolates were from wounds and urine. Invasive VRE infections were reported for 11 cases, all in blood.

A more detailed description is presented in Highlighted areas, section 5.4.

Annual Resistance Surveillance and Quality Control (RSQC) programme

Enterococcus faecalis was not included in the RSQC programme on antibiotic resistance 2008.

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 aminoglycoside antibiotics.

In 2003 the first four Swedish vancomycin-resistant invasive isolates of *Enterococcus faecium* were reported (2.2% of all), and in 2004 three isolates were found (1.2%), Tables 4.5 and 4.6. 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, and in 2008 six isolates of *Enterococcus faecium* with *vanB*. These latter isolates all showed the same PFGE pattern as the epidemic strain.

High-level aminoglycoside resistance (HLAGR) was more prevalent in *Enterococcus faecium* (25%) than in *Enterococcus faecalis* (20%) in 2008. From 2006 and onwards all laboratories who reported HLAGR used gentamicin (GEN) as test disk for detection.

TABLE 4.5. Resistance among invasive isolates of *Enterococcus faecalis* reported to EARSS 2001-2008

Year	Vancomycin-R (%)	HLAGR (%)	Total number (number tested for HLAGR by GEN)
2001	0	12.7	395 (212)
2002	0	17	430 (235)
2003	0	17.5	593 (440)
2004	0	15.4	592 (533)
2005	0	18.7	567 (492)
2006	0.4	19.9	579 (563)
2007	0	16.1	651 (632)
2008	0	20.1	720 (703)

TABLE 4.6. Resistance among invasive isolates of *Enterococcus faecium* reported to EARSS 2001-2008

Year	Vancomycin-R (%)	HLAGR (%)	Total number (number tested for HLAGR by GEN)
2001	0	9.1	169 (99)
2002	0	6.3	181 (96)
2003	2.2	11.2	231 (170)
2004	1.2	7	260 (227)
2005	0	4.3	253 (211)
2006	0.3	14	286 (286)
2007	1.1	14.4	279 (263)
2008	1.5	24.8	333 (331)

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

Streptococcus pyogenes

Annual Resistance Surveillance and Quality Control (RSQC) programme

Streptococcus pyogenes was not included in the RSQC programme in 2008.

Surveillance of invasive isolates in addition to EARSS

Of data on consecutive blood isolates from the participating 11 laboratories 196/11.115 (1.8%) were *Streptococcus pyogenes* (GAS). This represented a small increase compared with 2007 when 1.2% of the blood isolates were identified as GAS.

Only one of the isolates (0.5%) was resistant to erythromycin and none was resistant to clindamycin. Twenty-six isolates (14.6%) were resistant to tetracycline, and this was an increase compared with 2007 when 8% of the isolates were resistant. A majority of the isolates were retrieved from adults (> 50 years), and only 5% were from children 0–9 years.

Streptococcus agalactiae

Surveillance on invasive isolates additional to EARSS data

107/11.115 (1.0%) of the blood isolates collected from the 11 laboratories were *Streptococcus agalactiae* (GBS), which was in the same order as in 2007 when 1.3% were GBS. Seven of the isolates (6.5%) were resistant to erythromycin and clindamycin, which is comparable to 2007 (8.8%) and 2006 (4.4%). A majority of the isolates were retrieved from adults (> 50 years), but 16 (15%) were isolated from children less than 2 months. A seasonal tendency was observed with peaks in December-January and June-July. Five (30%) of the 16 infant findings occurred in June.

Haemophilus influenzae

Annual Resistance Surveillance and Quality Control (RSQC) programme

Haemophilus influenzae was re-entered in the RSQC programme in 2008 after a period of three years. A marked increase in rates of penicillin-resistant and trimethoprim-sulfamethoxazole-resistant isolates was seen, which is further discussed in section 5.5. For both types of antibiotics the rates were > 20%, compared with stable results for many years of 10–13% resistance as a national average. The increased rates of resistance were seen in all counties. Also the rate of chromosomally mediated (BLNAR = betalactamase-negative ampicillin-resistant) had increased from 2 to 3%. The shift in 2008 from loracarbef back to cefaclor as screening disk might account for some of this increase and this needs to be confirmed by comparative testing. Tetracycline resistance in *H. influenzae* was still rare (approximately 1%).

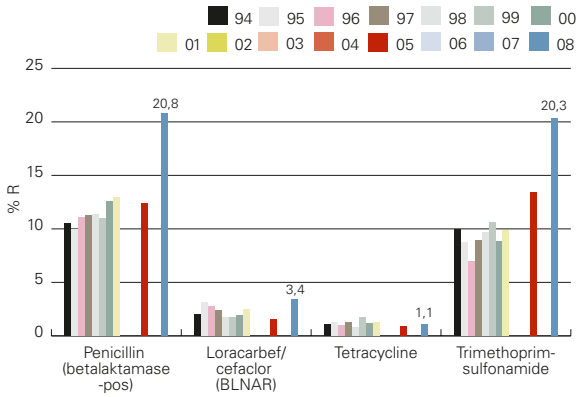

FIGURE 4.10. Resistance rates (resistant isolates in percent of all *Haemophilus influenzae* isolates) for four groups of antibiotics 1994–2008. No data available for 2002–2004 and 2006–2007.

Surveillance on invasive isolates additional to EARSS data

Only 63 of the 11.115 blood isolates (0.6%) were *Haemophilus influenzae*. Three of the isolates were from CSF and were obtained during late summer and early autumn.

Sixteen isolates (25%) were betalactamase-producing and ampicillin-resistant. This was a marked increase compared with 2007 when only three ampicillin-resistant isolates were found, and the increase corresponded to the increase seen in respiratory tract isolates (RSQC survey, see above). One isolate with chromosomally mediated beta-lactam resistance (BLNAR) was detected. Nine isolates were resistant to trimethoprim-sulfamethoxazole in 2008, also an increase as compared with one isolate in 2007. A majority of the isolates were retrieved from adults (> 50 years), but 4 were from children 0–9 years.

Barbro Olsson-Liljequist, Michael Toepfer, Gunnar Kahlmeter

Extended spectrum betalactamase-producing *Enterobacteriaceae* (ESBL)

Background

Increasing numbers of findings at Swedish clinical laboratories and increasing numbers of reported outbreaks with bacteria producing betalactamases with an extended spectrum (ESBL), both nationally and internationally, were the reasons for ESBL-producing *Enterobacteriaceae* being notifiable according to the Communicable disease act from February 1st 2007. Notifications of ESBL 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.

Notifications according to the Communicable Disease Act

A total of 2957 cases were notified during 2008. Reports came from all 21 counties of Sweden, corresponding to an average national incidence of 32 cases per 100,000 inhabitants, see Figure 4.11.

In Uppsala county the incidence decreased from 73 cases per 100 00 inhabitants (during 11 months of mandatory notification 2007) to 57 cases per 100 00 inhabitants for 2008. This was a result of an extensive infection control and screening program launched to control a large ESBL outbreak that was discovered in 2005. This shows that an outbreak situation with ESBL-producing *Klebsiella* may be reversed with an intensive effort and a combination of control measures.

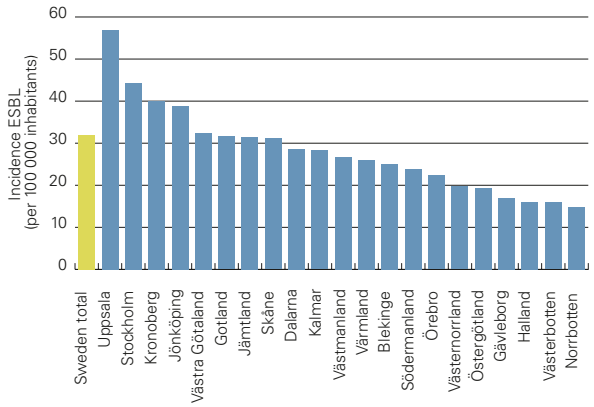

FIGURE 4.11. The incidence of ESBL in Swedish counties 2008.

When comparing the second half of the two years, a 28% increase of ESBL cases was noted for 2008, Figure 4.12. During the first month of 2007 the routine for notification system was under development which may have resulted in underreporting of cases. 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.

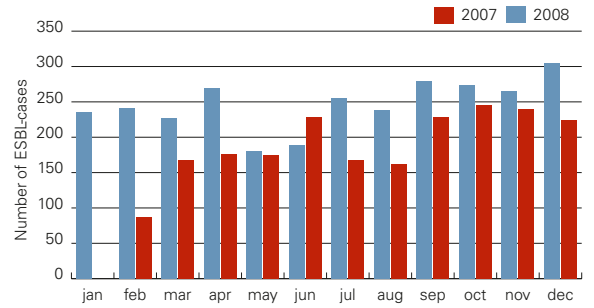

FIGURE 4.12. The number of reported ESBL cases per month, for 2007 and 2008.

The most commonly reported species were *Escherichia coli*, accounting for 83% of all cases, followed by *Klebsiella pneumoniae* with 9%, Table 4.7.

TABLE 4.7. Distribution of species among cases with ESBL-producing bacteria 2008.

Escherichia coli	2 512
Klebsiella pneumoniae	269
Proteus mirabilis	16
Citrobacter species	16
Salmonella species	5
Other *Enterobacteriaceae*	57
Species not reported	161
Total number of reported species	3 036*

* In 65 cases two different ESBL-producing species were reported and 7 cases had notifications with three different species resulting in a higher number of isolates than number of cases reported.

Bacteria were cultured from urine in 70% of the cases according to the first laboratory notification. The second most common source for ESBL-producing *Enterobacteriaceae* was faecal samples with 13%. Samplings from blood and wounds constituted 4% each of the first notifications. One-hundred and fifty cases with invasive ESBL infections were notified during 2008, all in blood. Among these, 138 were new cases for 2008 and 12 were known carriers of ESBL notified the previous year.

The distribution of gender and age differed between species. The incidence in age groups and gender for the ESBL-cases with *E. coli* and *K. pneumoniae* is shown in Figure 4.13 and 4.14. Of ESBL-producing *E. coli* 69% were derived from women with an average age of 53 years. This was six years less than the average age for men. The *K. pneumoniae* ESBL cases were almost equally distributed between sexes (48% women), with mean ages of 56 years for women and 59 years for men. Compared with 2007 the mean age had decreased with 12 years for women and eight years for men. The reason for this was an increased number of cases of *K. pneumoniae* which were isolated from young patients during outbreaks in paediatric surgery and neonatal care.

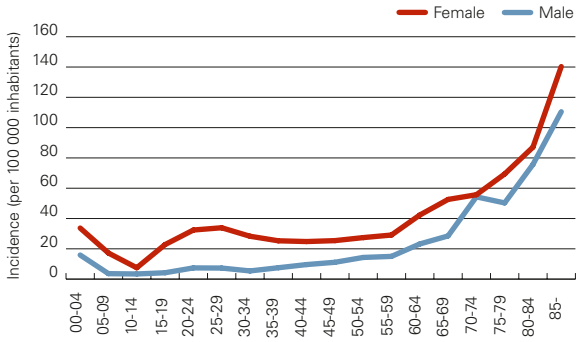

FIGURE 4.13. Age and gender distribution of *E. coli* ESBL cases 2008.

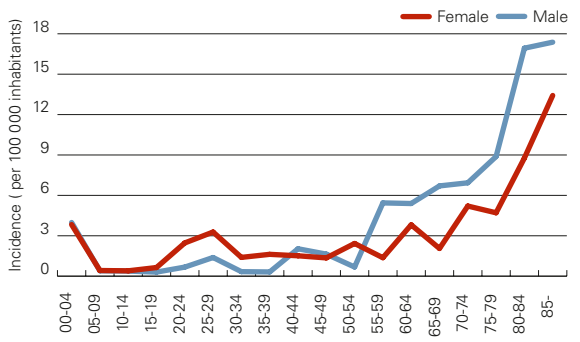

FIGURE 4.14. Age- and gender distribution of *K. pneumoniae* ESBL cases 2008.

The first full year of mandatory notification showed that 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 average resistance rates to ampicillin have increased yearly, from 17 up to 29%, Figure 4.15. A similar trend has been seen for trimethoprim with an increase from 10 to 18%. Fluoroquinolone resistance, detected by the nalidixic acid screening disk since 2002, has also increased during this period and reached an average of almost 13% in 2008. Resistance to cephalosporins (cefadroxil tested), although much less prevalent than ampicillin resistance, has doubled during the last two years and reached 2.5%. This mirrored the increasing incidence of ESBL-producing bacteria as seen from the notified cases and reports to EARSS (below).

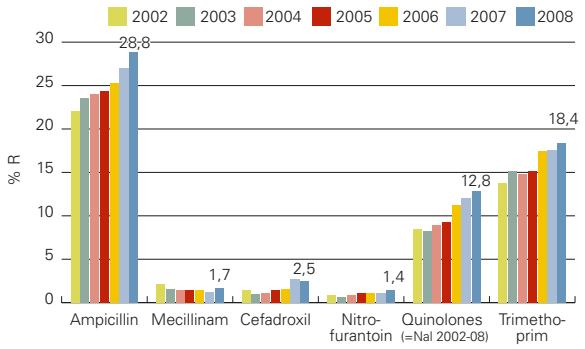

FIGURE 4.15. Resistance rates (resistant isolates in percent of all *Escherichia coli* isolates) for six antibiotics 2002–2008. Fluoroquinolone resistance was detected with nalidixic acid.

In 2007 the RSQC programme was extended to last for three months, February – April, and included not only urine isolates but *Escherichia coli* from all types of samples. Apart from the regular UTI antibiotics, the isolates were also tested for susceptibility to cefotaxime, ceftazidime, and a carbapenem. Resistance rates to cefotaxime, ceftazidime, and carbapenem were 2.4%, 2.2% and 0%, respectively. Isolates with verified ESBL-activity were collected and analysed further (n=240). In the collection 74% of the isolates harbored ESBL-genes belonging to the CTX-M-1 subgroup and 22% the CTX-M-9 subgroup. In two isolates genes belonging to both subgroup CTX-M-1 and CTX-M-9 were detected. The remaining 4% were CTX-M-negative but harboured ESBL-genes of SHV-type. A majority of these ESBL-producing isolates were multiresistant.

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 2001–2008 are presented in Table 4.8.

Ampicillin resistance, caused by production of plasmid-mediated betalactamase (most often of TEM-type) was slightly higher in blood isolates than in the urine isolates tested in the RSQC programme, 32% VS. 29%. However, data on blood isolates were incomplete since one third of participating laboratories do 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 2.3% in 2008. In the majority of the cefotaxime-R isolates (1.9%) resistance was attributed to the presence of ESBLs of CTX-M type.

Aminoglycoside resistance in *Escherichia coli* has shown an increasing trend for the last couple of years but remained at 2.2% in 2008.

Reduced susceptibility and resistance to fluoroquinolones (I+R) has varied between 5.5% and 13% since 2001 but reached 14% in 2008. These increasing trends of resistance in blood isolates were the same as those in urine isolates from the RSQC programme, as can be seen in Figure 4.16.

TABLE 4.8. *Escherichia coli* from blood cultures in Sweden 2001-2008, reported to EARSS.

Year	Ampi-cillin-R (%) *	Cefotaxi-me-R (%; ESBL / other mecha-nism)	Amin-oglyco-side-R (%) **	Fluoro-quinolo-ne-I/R (%) ***	Total number of iso-lates
2001	26.5	0.5	1	5.5	2 627
2002	24.9	0.5	0.6	7.1	3 062
2003	28.5	0.4	1	8.3	3 300
2004	23	0.5 / 0.6	1.5	11.1	3 336
2005	26	0.9 / 0.4	1.5	8.9	3 212
2006	28.1	1.3 / 0.1	1.7	8.7	3 514
2007	32.9	1.6 / 0.6	2.3	13.3	3 745
2008	31.9	1.9 / 0.4	2.2	14.3	4 028

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

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

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 EARSS since 2005.

As for *Escherichia coli*, the RSQC 2008 programme for *Klebsiella pneumoniae* was mainly focused on urine samples,

Figure 4.16. Resistance to commonly prescribed oral antibiotics for treatment of UTI was tested in 2008. Data for 2008 indicated an increase in resistance only to trimethoprim, whereas the rates of resistance to both cefadroxil and fluoroquinolones were slightly lower than in 2007.

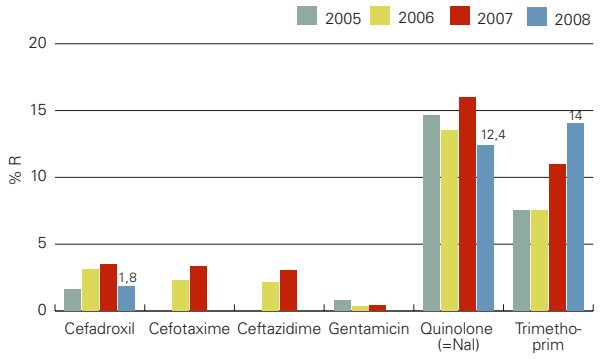

FIGURE 4.16. Resistance rates (resistant isolates in percent of all *Klebsiella pneumoniae* Isolates) for four groups of antibiotics 2005–2008.

In 2007 the RSQC programme was extended to last for three months, February – April, and included not only urine isolates but *Klebsiella pneumoniae* from all sample types. Apart from the regular UTI antibiotics, the isolates were also tested for susceptibility to cefotaxime, ceftazidime, and a carbapenem. From the results in Figure 4.16 it can be seen that cefadroxil resistance had more than doubled between 2005 and 2007 and reached 3.5% (> 3 500 isolates tested). Resistance rates to cefotaxime, ceftazidime, and carbapenem were 3.3%, 3% and 0%, respectively. Isolates with verified ESBL-activity were collected and analysed further (n=48). In the collection 73% of the isolates harbored ESBL-genes belonging to the CTX-M-1 subgroup and 10% the CTX-M-9 subgroup. Among the remaining there were ESBL-genes of SHV-type. A majority of these ESBL-producing isolates were multiresistant.

Data on invasive isolates reported to EARSS

From 1 July 2005, participants in the EARSS network have contributed with data on blood isolates of *Klebsiella pneumoniae*. In 2008 the number of isolates had increased to 826 as shown in Table 4.9. All cephalosporin resistance was caused by ESBLs of CTX-M type. The rate of fluoroquinolone resistance is slowly increasing.

TABLE 4.9. *Klebsiella pneumoniae* from blood cultures in Sweden 2005-2008, reported to EARSS.

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

*gentamicin or tobramycin, ** ciprofloxacin

The data for 2005 represent six months from 20 laboratories. From 2006 and onwards the data represent the whole years from 20 laboratories.

Isolates with new resistance mechanisms

In 2007 the first isolate of *Klebsiella pneumoniae* with KPC-2 (*K.pneumoniae* carbapenemase) was detected in Sweden. In 2008 at least one more isolate with a KPC betalactamase has been identified, and also one isolate with a metallo-betalactamase of VIM-type. In all these cases hospital care in the south of Europe were reported.

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

Pseudomonas aeruginosa

Annual Resistance Surveillance and Quality Control (RSQC) programme

Pseudomonas aeruginosa was not included in the RSQC programme in 2008 but will be re-entered in 2009.

Data on invasive isolates reported to EARSS

From 1 July 2005, participants in the EARSS network have been asked to contribute with data on blood isolates of *Pseudomonas aeruginosa*. From Sweden a total of 149 isolates from 20 laboratories were tested during the second half of 2005, and these data are compared with complete data sets for 2006, 2007 and 2008 in Table 4.10. The levels of resistance to beta-lactam antibiotics (ceftazidime and carbapenems) were in the range 3–7% for all three years. No change in resistance rates had occurred for either aminoglycosides or fluoroquinolones .

TABLE 4.10. *Pseudomonas aeruginosa* from blood cultures in Sweden 2005–2008, reported to EARSS.

Year	Ceftazi-dime-R (%)	Carba-penem-R (%) *	Amino-glycoside-R (%) **	Fluoroqui-nolone-I/R (%) ***	Total number of isolates
2005 (half year)	4.7	Insuf-ficient 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	5.2	4.0	0.3	7.6	315

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

Barbro Olsson-Liljequist, Gunnar Kahlmeter

Clostridium difficile

A screening study aimed at identifying the internationally well established strain of moxifloxacin-resistant *C. difficile* correlated with high morbidity and mortality (PCR ribotype 027) was conducted in cooperation with 20 of the 29 Swedish microbiological laboratories. In total 581 strains were analysed with PCR ribotyping. One isolate was confirmed as PCR ribotype 027.

The frequency of moxifloxacin-resistant *C. difficile* varied geographically, from 2% to 34%. Among the resistant strains two types dominated, designated SE17 and SE37, Figure 4.17. Type SE17 (PCR ribotype 012 according to the international nomenclature), was common in the counties of Södermanland, Västra Götaland, Örebro and Östergötland, Figure 4.18. Type SE19c was frequent in counties of

Jönköping and Östergötland. In Gävleborg county all but one isolate belonged to type SE28 (international nomenclature PCR ribotype 017). SE37 dominated among the moxifloxacinresistant isolates analysed from Stockholm county. This type has until this study been reported only rarely and the international nomenclature is not known. Only one case of the international well established PCR ribotype 027 was identified. We therefore conclude that Sweden, contrary to many other European countries, does not have this strain established yet.

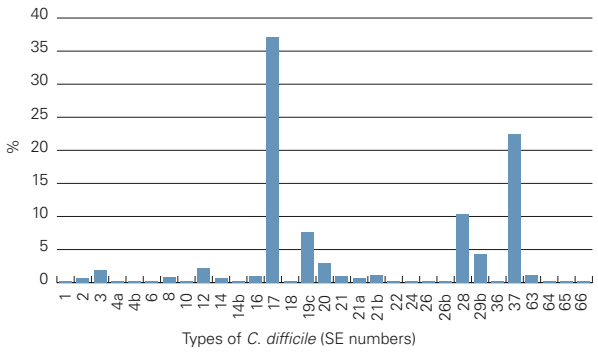

FIGURE 4.17. Moxifloxacinresistant *C. difficile* according to PCR ribotype.

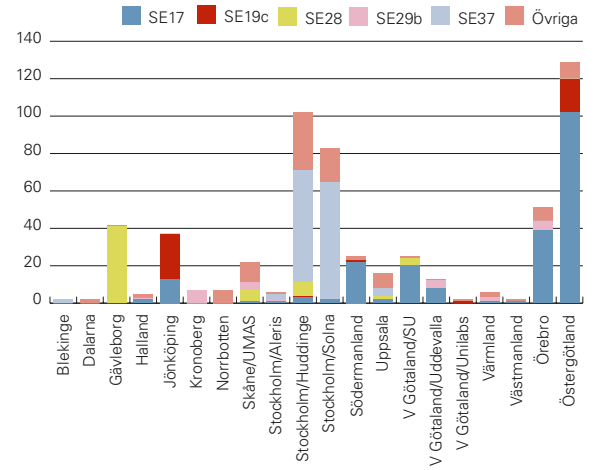

FIGURE 4.18. Distribution per county of the most common PCR ribotypes.

Tomas Åkerlund, Karin Tegmark-Wisell, Johan Struwe

Helicobacter pylori

Annual Resistance Surveillance and Quality Control (QCRS) programme

Helicobacter pylori derived from gastric biopsies has not until 2001 been included in the annual RSQC programme but has been monitored locally at a few laboratories. In vitro resistance to metronidazole has been reported in 10–40% of Scandinavian isolates. Resistance to clarithromycin was less common but has increased and has locally, at one laboratory, reached up to 16% in 2006, but then again during the last two years decreased dramatically. Frequencies of resistance to clarithromycin and metronidazole in clinical isolates from southwest of Sweden are presented, representing a population of approximately 300 000.

TABLE 4.11. *Helicobacter pylori* University Hospital MAS, Malmö, Sweden1996-2008, %R

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

* 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 was included in the annual RSQC programme from 2002 but have been monitored only 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 their geographical origin. Too few strains are included in the Swedish survey to obtain conclusive results. However fluoroquinolone resistance is high, between 20–25%, among *Salmonella* strains, and among *Shigella* spp isolates producing ESBL have been detected.

Mats Walder

Campylobacter spp

Annual Resistance Surveillance and Quality Control (QCRS) programme

Campylobacter spp. derived from patients with diarrhoea was included in the annual RSQC programme from 2001 but has been monitored only by a few laboratories. Approximately 50% of *Campylobacter* strains are imported. Since resistance to fluoroquinolones is of major concern worldwide it is interesting to notice that the small decline in quinolone resistance among *Campylobacter* isolates noticed a few years ago has now regained the former level of about 50%. When screening for fluoroquinolone resistance using nalidixic acid disks was introduced in Sweden in 2001, it was expected to influence the resistance rates dramatically. The data for nalidixic acid and ciprofloxacin in parallel show, however, that the two disks are equally able to detect quinolone resistance in *Campylobacter* spp.

TABLE 4.12. *Campylobacter jejuni/coli* University Hospital MAS, Malmö, Sweden1995-2008

Year	Nalidixic acid %R	Ciproflox-acin %R	Tetra-cycline %R	Erythro-mycin %R
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	69	36	7

Mats Walder

Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable disease/infection and in 2008, 725 cases were reported. Most of the cases were identified in the three largest counties of Sweden, which comprise the cities Stockholm, Gothenburg, and Malmö, respectively. Clinical isolates were characterised at the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Swedish Institute for Infectious Disease Control), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital and at the Division of Clinical Bacteriology, Department of Laboratory Medicine, Karolinska University Hospital Huddinge.

In 2008, isolates from 447 of the notified clinical cases were completely characterised at these laboratories, representing 62% of the notified cases. In total, 447 different N. gonorrhoeae strains were cultured from these cases (n=447). Susceptibility testing was performed according to standardized methodology using Etest for MIC determination of ampicillin, cefixime, ceftriaxone, azithromycin, ciprofloxacin, and spectinomycin. SIR-breakpoints have been determined by the Swedish Reference Group for Antibiotics, SRGA. Production of ß-lactamase was examined by Nitrocefin discs.

Results for 2008 are compared with those from 2002 to 2007 in Table 4.12. Notable, even if the levels of resistance to azithromycin (3%) and especially cefixime (0%) remain low, the proportions of intermediate susceptibility to these antimicrobials have rapidly increased, i.e. to 10% and 4%, respectively.

Magnus Unemo, Hans Fredlund

TABLE 4.13. Antibiotic resistance rates (%) and ß-lactamase production of Swedish *Neisseria gonorrhoeae* strains from 2002 to 2008.

	2002 (n=120)	2003 (n=130)	2004 (n=149)	2005 (n=497)*	2006 (n=352)*	2007 (n=406)*	2008 (n=447)*
ß-lactamase pos.	39	22	26	23	30	30	28
Penicillin G	48	-	-	-	-	-	-
Ampicillin	39	22	26	23	30	30	28
Cefuroxime	4	-	-	-	-	-	-
Cefixime	0	0	0**	0	0	0	0
Ceftriaxone	0	0	0	0	0	0	<1
Azithromycin	0	<1	0**	0	1	1	3
Tetracycline	54	-	-	-	-	-	-
Ciprofloxacin	58	56	51	49	61	70	63
Spectinomycin	0	0	0	0	0	0	0

(- = not analysed)

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

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

TABLE 4.14. Drug resistant tuberculosis in Sweden. Resistance among initial isolates of *Mycobacterium tuberculosis* or *africanum* against at least one of the four drugs: isoniazid. rifampicin, ethambutol or pyrazinamid.

Year of diagnosis	2000		2001		2002		2003		2004		2005		2006		2007		2008	
Culture confirmed *M. tuberculosis* or *M.africanum* (N=)	366		354		346		345		368		448		395		361		434	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No	%	No	%
Any resistance Total (%)	45	12.3	38	10.7	36	10.4	32	9.3	43	11.7	52	11.6	43	10.9	49	13.6	57	13.1
Isoniazid	37	10.1	31	8.8	34	9.8	26	7.5	35	9.5	46	10.3	38	9.6	46	12.7	51	11.8
Rifampicin	5	1.4	6	1.7	4	1.2	10	2.9	6	1.6	5	1.1	6	1.5	15	4.2	15	3.5
Ethambutol	2	0.5	3	0.8	1	0.3	5	1.4	3	0.8	3	0.7	1	0.3	7	1.9	6	1.4
Pyrazinamid	11	3.0	6	1.7	4	1.2	7	2.0	12	3.3	6	1.3	6	1.5	11	3.0	18	4.1
Isoniazid + rifampicin (MDR)	5	1.4	4	1.1	4	1.2	8	2.3	5	1.4	4	0.9	3	0.8	15	4.2	14	3.2

Neisseria meningitidis

Notifications according to the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease. In 2008 49 clinical cases were reported. A total of 38 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), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital.

Susceptibility testing was performed according to standardized methodology using Etest on Müller Hinton II agar medium with 5% defibrinated horse blood for determination of MIC for bensylpenicillin (pcG), fenoxymethylpenicillin (pcV), cefotaxime, ciprofloxacin, chloramphenicol and rifampicin. Production of betalactamase was examined by Nitrocefin discs.

None of the isolates produced betalactamase. Eleven isolates (29%) had reduced susceptibility to pcG (MIC>0.064 mg/L). The MIC for pcV is normally 5–10 times higher. All the isolates had cefotaxime-MIC ≤0.008, except three with MIC 0.012 and two with MIC 0.016, and ciprofloxacin-MIC ≤0.006 mg/L. Chloramphenicol-MIC varied between 0.19 and 1.0 and rifampicin was not higher than 0.023 mg/L. The intervals for MIC within the SIR-system, as determined by SRGA, are for pcG 0.06/0.25 (e.g. sensitive ≤0.06 mg/L and resistant >0.25 mg/L), cefotaxime 0.12/0.12, ciprofloxacin 0.03/0.06, chloramphenicol 2/4, and rifampicin 0.25/0.25.

Per Olcén

Mycobacterium tuberculosis

Drug resistant tuberculosis in Sweden during 2008

In 2008 a total number of 554 new cases of tuberculosis (TB) were diagnosed in Sweden compared with 491 in 2007, an increase of 13%. The number and proportion of culture confirmed cases increased from 365 (73%) in 2007 to 436 (79%) in 2008. *Mycobacterium tuberculosis* was identified in 432 cases, *Mycobacterium africanum* in two patients and Mycobacterium bovis in two patients. During 2008 the proportions of patients diagnosed with isoniazid resistant TB and MDR-TB were about the same as in 2007 and remaining on a higher level than the previous seven-year period.

Isolates of *M. tuberculosis* or *M. africanum* resistant against at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) were identified in 57 patients (31 males and 26 females) corresponding to 13.1% of the 434 patients with culture confirmed TB, Table 4.14. Two patients with *M. bovis* isolates are not included since these strains are naturally resistant to pyrazinamid.

Resistant TB-bacteria were found in 4.0% of the Swedish born TB patients (3/75), in 18.2% of Somalian patients (20/110) and in 13.7% of those born abroad in other countries (34/249). Resistance against isoniazid was reported in isolates from 11.8% of all patients (4% of Swedish born patients, 16.4% of patients from Somalia and 12% of those born abroad in other countries). Resistance against rifampicin was shown in 3.5%, pyrazinamid in 4.1% and ethambutol in 1.4% of all culture confirmed cases.

Isolates resistant against at least isoniazid and rifampicin (MDR-TB) were found in 3.2% of all foreign born patients with culture confirmed TB (14/359), 6.4% of those coming from Somalia (7/110) and 2.8% from other countries (7/249). No MDR-TB was found in TB patients born in Sweden.

Thirty patients of the total 434 culture confirmed cases had a previous history of TB after 1949 (7%), thus they were classified as retreatment cases. Resistant TB was reported in 30% (9/30) including MDR-TB in 16.7% (5/30) of these cases. The corresponding figures for new or never treated cases were 12% for any resistance and 2.2% for MDR, respectively.

Genetic typing with RFLP (restriction fragment length polymorphism) was performed on 49 of the 57 resistant strains of *Mycobacterium tuberculosis* or *M. africanum*. Twentynine of the 49 examined isolates were identified to belong to 16 different clusters with two or more patients in each cluster. Genetic typing with RFLP indicates ongoing spread of resistant strains. However, a number of clusters include patients with different resistance patterns, either sensitive or resistant strains, thus making the interpretation of possible transmission difficult.

The proportion of patients with *M. tuberculosis* resistant against isoniazid has gradually increased from an annual average of 5% during the period 1991–1998 to 9% during the period 2000–2006 and further to 12.7% in 2007 and 11.8% in 2008. In parallel the annual proportions of MDR-TB increased from 1.1% to 1.3% and further to 4% in 2007 and 3.2% in 2008. The observed high proportions of resistance against isoniazid and also MDR-TB in Somalian TB patients claim for increased attention and action!

Sven Hoffner, Victoria Romanus

5. Highlighted areas

5.1. Antibiotic use in intensive care units (ICU)

The ICU-Strama programme was developed ten 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. A central component has been a web-based application which includes a system for automatic feed-back.

The median antibiotic consumption increased from 1256 defined daily doses per 1,000 occupied bed days (DDD_{1000}) 1999 to 1434 DDD_{1000} 2008 ($p < 0.001$), Figure 5.1.1.

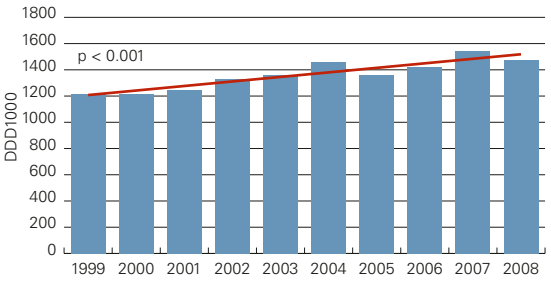

FIGURE 5.1.1. Trends in total antibiotic consumption in Swedish intensive care units, DDD_{1000}. Trend analysis performed by linear regression.

Although DDD_{1000} is a highly standardised measure that allows comparison of antibiotic consumption between different settings and countries (http://www.whocc.no/atcddd/), a couple of factors complicate such comparisons. First, a common definition for length of stay must be used. Second, antibiotic use was based on the quantities of drugs delivered by each hospital pharmacy, despite that some drugs delivered might not be administered to patients in the ICU. A third source of error is that dosing in the critically ill is influenced by many factors other than the DDD (i.e. increased dosing due to life-threatening disease, reduced dosing due to renal impairment).

Antibiotic consumption varied widely between different units during 2008, ranging between 696 and 2722 DDD_{1000} with a median of 1434 DDD_{1000}, Figure 5.1.2. This variation 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 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.

Trend analyses of usage of different classes of antibiotics were performed and showed increased carbapenem, triazole and piperacillin-tazobactam consumption ($p<0.001$), Figure 5.1.3, whereas there was no significant change in consumption of cephalosporins for the ten year period but a trend towards decreased consumption the last two years, Figure 5.1.4. Swedish guidelines for antibiotic treatment in severe infections are available from several sources including www.infektion.net, www.strama.se, www.srga.org. However, there is no agreement on a national antibiotic policy in intensive care. Strama (www.strama.se) has since 2007 recommended a reduction of cephalosporins for treatment of community acquired pneumonia and to avoid cephalosporins where there is an outbreak of ESBL producing *Enterobacteriaceae*. It is also advised to adapt the antibiotic policy to local hospital reports on antibiotic consumption and resistance. The compliance to these recommendations is measured every second year in the Strama Point Prevalence Studies (PPS), but the number of observations is too low to evaluate the precision of antibiotic use in the individual ICU.

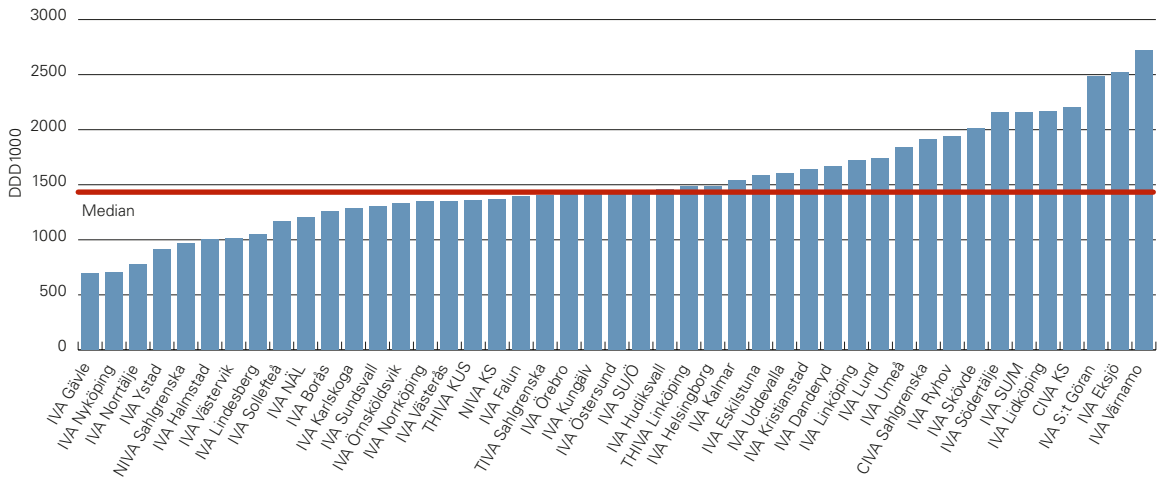

FIGURE 5.1.2. Median antibiotic consumption (DDD_{1000}) for individual ICUs during 2008.

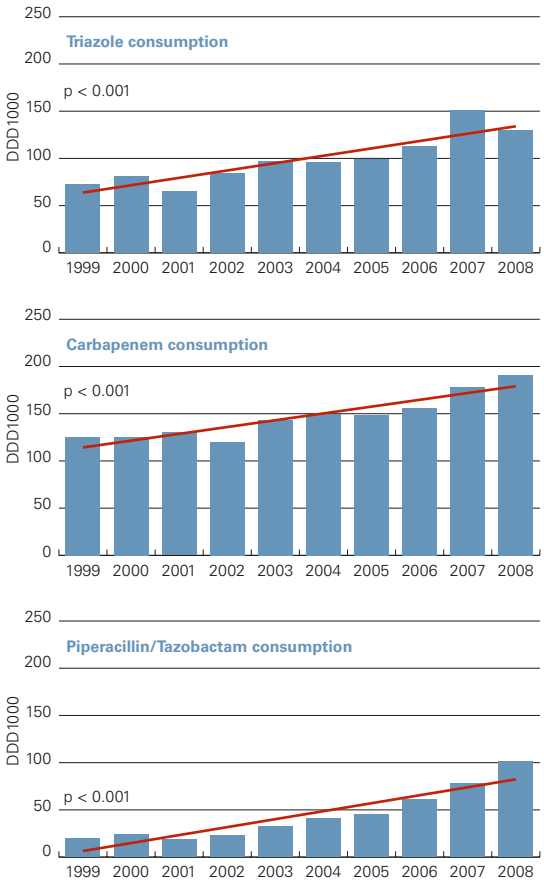

FIGURE 5.1.3. Trends in Triazole (a), Carbapenem (b) and Piperacillin-Tazobactam (c) consumption, DDD_{1000}. Trend analysis performed by linear regression.

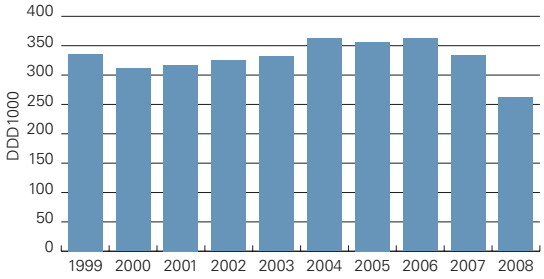

FIGURE 5.1.4. Yearly cephalosporin consumption, DDD_{1000}.

Håkan Hanberger, Faculty of Health Sciences Linköping University; **Morgan Edström,** Hospital Pharmacy Linköping University Hospital; **Hans Gill,** Department of Biomedical Engineering, Medical Informatics, Linköping University; **Sten Walther** Faculty Of Health Sciences Linköping University.

5.2. Antibiotic use and antibacterial resistance in the elderly

Prescriptions to the elderly

Individually based data from the National Board of Health and Welfare reveals that 36% of people over 80 years took delivery of at least one antibiotic prescription during 2008, compared with 33% of children 0–6 years. In addition, the elderly receive more prescriptions of antibiotics per individual, 2.1 as compared with 1.8 per year. A problem in the analysis is that antibiotics given to the elderly in nursing homes may be dispensed instead of prescribed. The lack of a uniform basis for registering antibiotic use in nursing homes makes analysis and comparisons difficult. Another problem is that antibiotic consumption in hospitals, where many patients belong to the elderly, can not be analysed according to age. Thus, the antibiotic pressure among the geriatric segment of the population is likely even higher.

The number of prescriptions per 1000 inhabitants/year (age adjusted data) is shown for the age groups 65–79 (a) and 80+ (b) in Figure 5.2.1. The figure shows that the number of prescriptions is higher in the age group 80+ (b) than among those 65–79 years old (a).

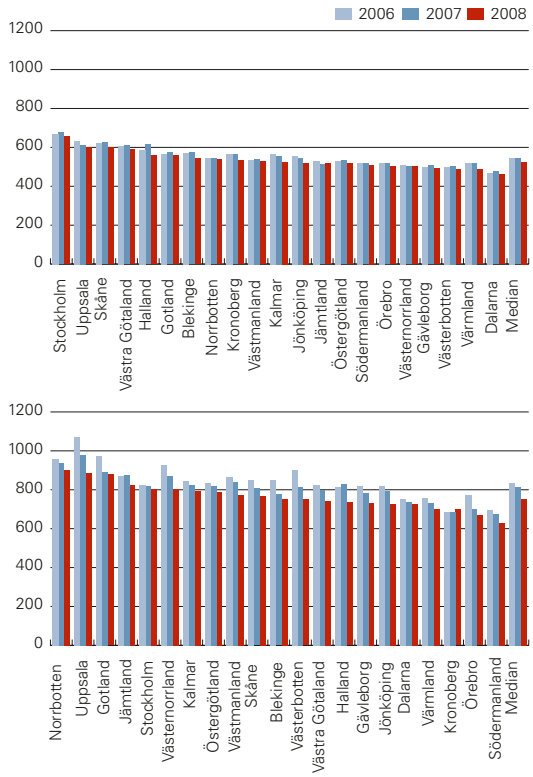

FIGURE 5.2.1. Number of prescriptions per 1000 inhabitants/ year (age adjusted data) is shown for the age groups 65–79 (a, top) and 80+ (b, bottom).

The high antibiotic pressure in the elderly has previously been documented in 2,752 residents (mean age 86 years) of 58 nursing homes, the SANT-study[1]. Among a total of 890 infection

[1] Pettersson E, Vernby Å, Mölstad S, Stålsby Lundborg C. Infections and antibiotic prescribing in Swedish nursing homes: A cross-sectional study. Scand J Infect Dis 2008;40:393-398.

episodes 84% were treated with antibiotics of which 38% without any direct physical examination. Among those receiving antibiotics 43% had received a previous course during the preceding 3-month period.

Among antibiotics predominantly used for lower urinary tract infections (UTI), the proportion of the not recommended alternative fluoroquionolones is shown for women in the age groups 65–79 and 80+, respectively, in Figure 5.2.2. It can be seen that there is quite a wide variation between Dalarna, Jämtland and Västerbotten having the best compliance to recommendations, and Kronoberg and Stockholm counties with the poorest compliance.

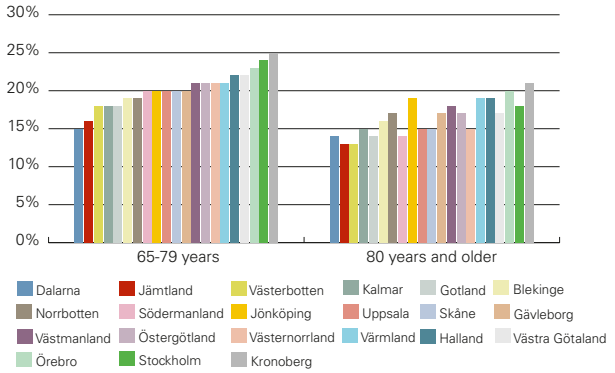

FIGURE 5.2.2. The proportion of fluoroquionolones among antibiotics predominantly used for lower urinary tract infections (UTI) is shown for women in the age groups 65–79 and 80+, respectively. Presciptions/1000 inhabitants and year, 2008.

Figure 5.2.3. illustrates that tetracyclines account for approximately 30% of all prescriptions of antibiotics predominantly used for respiratory tract infections. The reason why this proportion is so high is not known. Penicillin is the recommended alternative for community acquired pneumonia and antibiotic treatment in acute bronchitis is not recommended although it could be difficult to distinguish between pneumonia and acute bronchitis in the elderly.

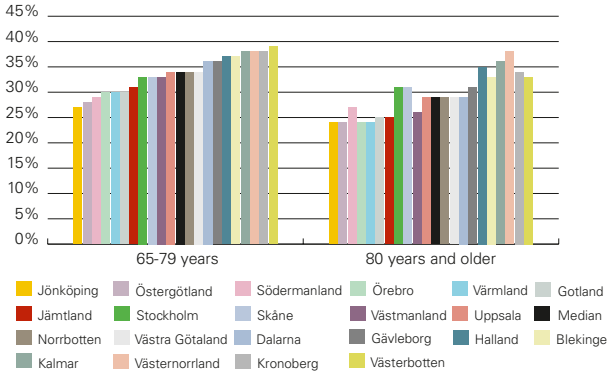

FIGURE 5.2.3. Proportion of tetracyclines among antibiotics most frequently prescribed for respiratory tract infections (penicillin V, amoxicillin and macrolides). Presciptions/1000 inhabitants and year, 2008.

Antibiotic use in geriatric clinics

An increasing number of geriatric clinics and hospitals have enrolled for Strama's Point Prevalence Studies. The total number of observed geriatric patients in the four studies have been 3571, of whom 825 (23%) received antibiotics on the day of the survey. Lower urinary tract infection was the most common diagnosis and accounted for 1/3 of the treatments. Second most common indication was skin and soft tissue infections (19%) followed by lower respiratory tract infections (13%). Figure 5.2.4. shows that fluoroquinolones, cephalosporins and penicillins with extended spectrum were the most commonly used antibiotics in the geriatric clinics.

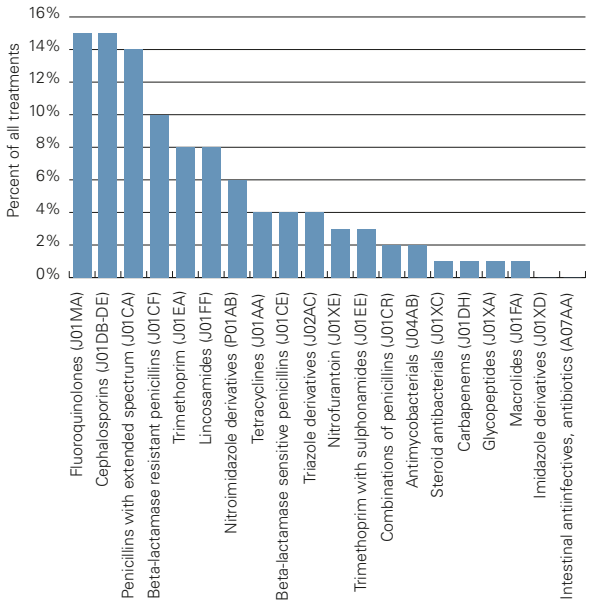

FIGURE 5.2.4. Distribution of antibiotic use in geriatric clinics during Stramas four Point Prevalence studies 2003–2008.

The treatment of community acquired lower UTI in women showed poor compliance to guidelines with quinolones and trimethoprim accounting for 55% of the courses. Likewise, the compliance to recommendations for the treatment of community acquired pneumonia was questionable; 60% received cephalosporins and only 20% penicillin V or G, which is recommended to mild and moderate cases. Data on disease severity (CRB 65 score) were not however, recorded in the studies.

The results of both the PPS and SANT suggest a lack of adherence to the guidelines for antibiotic choice for treatment of lower UTI in elderly women. This stands in contrast to the improvement seen in the latest years when analysing data on the treatment of this condition in younger women. In SANT it was also found that the prescribed courses were too long, only 6% received 5 days or shorter treatment. Even though neither PPS nor SANT was designed to evaluate the quality of the diagnostics as a basis for the prescription, the impression was that the high proportion of UTI-treatments probably partly was due to over-treatment of asymptomatic bacterieuria in women, a condition which does not need antibiotic treatment.

Antibiotic resistance

MRSA-meticillinresistant *Staphylococcus aureus*

The annual number, and the incidence, of reported MRSA-cases acquired domestically has slowly increased in the age groups above 70 years of age since reporting was introduced, Figure 5.2.5.), during the last years however, at a lower rate than in the younger population. Their relative proportion in relation to those younger than 70 years has steadily decreased due to an increase of community acquired cases in the younger population as shown in Figure 4.3.

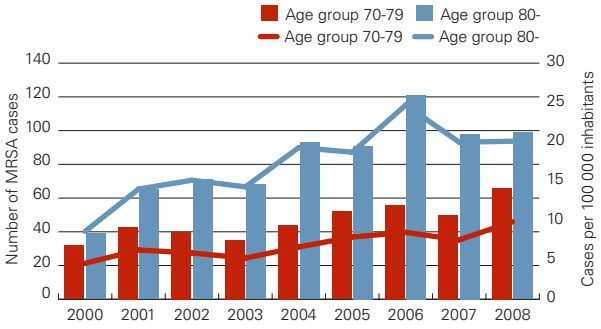

FIGURE 5.2.5. Number of reported domestic MRSA cases and incidence in age groups 70–79 and 80+.

ESBL – *Enterobacteriaceae* producing extended spectrum betalactamases

The incidence of reported findings of ESBL is also increasing with age, Figure 5.2.6.

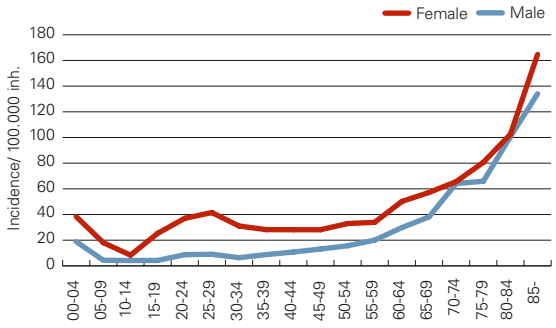

FIGURE 5.2.6. Age-adjusted incidence of notified cases 2008 of ESBL – Enterobacteriaceae producing extended spectrum betalactamases, in different age-groups.

VRE – Vancomycinresistant *Enterococcus faecium* and *E. faecalis*

The hitherto largest outbreak of VRE, first recognised in 2007 (see section 5.4) has mainly affected hospitalised elderly people in Stockholm and Västmanland counties and in a nursing home in Halland county, Figure 5.2.7.

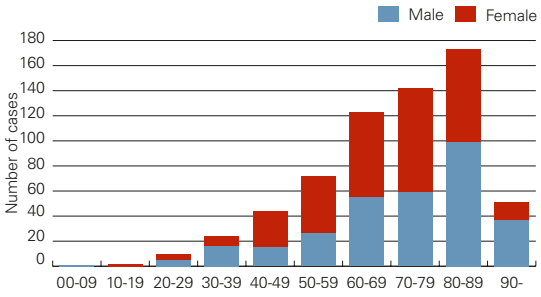

FIGURE 5.2.7. Age-distribution of all VRE-cases identified in Sweden after the detection of an outbreak of vancomycinresistant *Enterococcus faecium VanB* in the fall of 2007.

Conclusions

Available data show that the antibiotic pressure is high in the elderly. The compliance to recommendations for treatment of lower urinary tract infections in elderly women may be improved. Information that there is no indication for treatment of asymptomatic bacteriuria with antibiotics should be spread. Resistance in bacteria spread via the oral-fecal route such as ESBL and VRE seem to be of increasing importance among the elderly, whereas the situation with regard to MRSA seem to be relatively stable.

Ulrica Dohnhammar, Strama; **Mats Erntell,** Communicable Disease Control, Halland County Council; **Gunilla Skoog,** Strama; **Tomas Söderblom,** Dep of Epidemiology, Swedish Institute for Infectious Disease Control; **Lars Kärvestedt,** Stockholms sjukhem; **Christer Norman,** Strama; **Johan Struwe,** Strama/Dep of Epidemiology, Swedish Institute for Infectious Disease Control.

5.3 Antibacterials prescribed in dentistry

Dentists account for approximately 7% of all recipes of antibiotics in community care. Around 80% of this is penicillin V and the rest is mainly divided between amoxicillin, clindamycin and metronidazole. Notably, there is great variance within Sweden, with more than twice as many prescriptions in Stockholm and Skåne as in Västerbotten county, Figure 5.3.1.

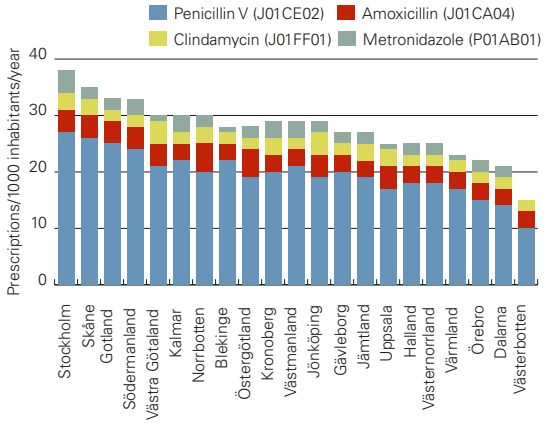

FIGURE 5.3.1. Antimicrobials prescribed by dentists, per county. Prescriptions/1000 inhabitants/year.

The number of prescriptions from dentists has increased during the last 10 years. The reason for this is unknown. Prescribing of both penicillin V and amoxicillin has increased by 25% each since 2000, Figure 5.3.2. The sizes of packages prescribed indicate that these substances are used in both prophylaxis and treatment (data not shown). During the same period the sale of clindamycin has almost tripled. This is of particular interest due to the high risk for severe side effects caused by *Clostridium difficile* attributed to clindamycin. The main recommended indication for clindamycin is as an alternative for patients with penicillin allergy. If this is the explanation to the increase or not, remains to be investigated.

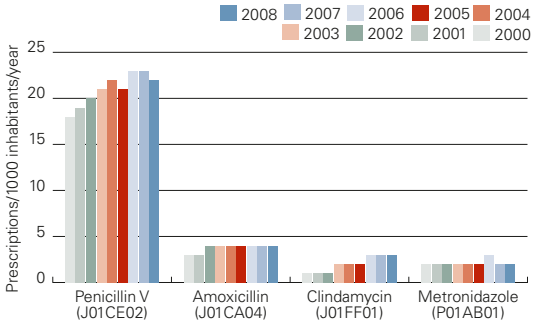

FIGURE 5.3.2. Antimicrobials prescribed by dentists. Prescriptions/1000 inhabitants/year, 2000–2008.

Ulrica Dohnhammar, Strama; **Johan Struwe,** Strama; **Johan Blomgren,** Dep of Oral Medicine Sahlgrenska University hospital, **Gunnar Dahlén,** Dep of Oral Microbiology Göteborg University; **Anders Heimdahl,** Dep of Oral Surgery Karolinska Institute; **Ylva Britt Wahlin,** Dep of Oral Diagnostics, Umeå University; **Mikael Zimmerman,** BZB CareSystems.

5.4 A nationwide outbreak of vancomycinresistant *Enterococcus faecium VanB*

Vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE), infection as well as colonisation, have been mandatory notifiable according to the Swedish Communicable Diseases Act since year 2000. Mandatory contact tracing was implemented 2004. During 2000–2006 the number of reported VRE-cases has varied from 18 to 47 annually. Previously in Sweden, only a few minor outbreaks with VRE have been recognised.

An increase of VRE was recognised in Stockholm county during the autumn 2007 and was reported in Swedres 2007. During 2008 the outbreak continued in Stockholm county and large outbreaks were subsequently reported from Västmanland and Halland counties. Due to the exchange of patients between regions, an increased number of VRE cases has also been reported from Uppsala County.

The recognition of the outbreak has led to intensive contact tracing, screening and other infection control measures.

Since the outbreak started in 2007 altogether 661 cases of VRE have been reported from 13 counties. 641 cases acquired VRE domestically and 18 cases abroad. 95% (n=612) of the domestic cases were health-care related. Among the domestic cases 66% were identified through contact tracing and 16% by screening. 9% had clinical symptoms and in another 9% the indication for sampling was unknown. According to the first laboratory confirmation 82% (n=549) were isolated from faeces, 5% (n=34) from wounds, 5% (n=31) from urine and 5 cases (0.75%) isolated in blood. The mean age for the domestic VRE cases was 70 years.

Typing of epidemic VRE and antibiotic resistance

Verification of the resistance mechanism showed that 544 of the domestic cases were *E. faecium* with *vanB*-gene and 94 *E. faecium* with *vanA*-gene, Table 5.4.1. In another 10 cases either the species or the resistance gene was not reported.

TABLE 5.4.1. Species and genotype for the domestic VRE cases 2008? E.fm = *Enterococcus faecium*, E.fs = *Enterococcus faecalis*

County	Number of cases	E.fm, *vanA*	E.fm, *vanB*	E.fs, *vanA*	E.fs, *vanB*
Stockholm	450	93	356	1	-
Västmanland	83	1	82	-	-
Halland	86	-	86	-	-
Uppsala	13	-	12	-	-
Others (n=6)	9	-	8	-	-

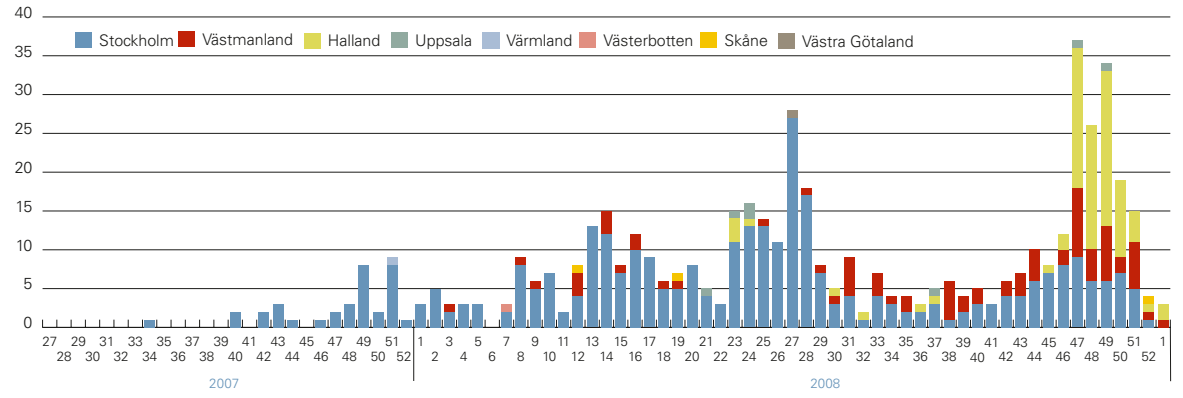

FIGURE 5.4.1. Epidemic curve for clonal spread of health-care related domestic *Enterococcus faecium* with *vanB*

Epidemiological typing of the *Enterococcus faecium* isolates with the *vanB* 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 related strains/alternatively clonal dissemination. Preliminary, and 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 identified 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 also resistant to ampicillin, imipenem, ciprofloxacin and macrolides but showed only low-level resistance to gentamicin. The epidemic curve for isolates showing the same PFGE-pattern is shown in Figure 5.4.1.

The intensive sampling surprisingly yielded a high number of *E. faecium vanA* in Stockholm county. Epidemiological analysis and PFGE showed that these were related to other types of *E. faecium* strains than the epidemic strain.

Conclusions

The reasons for the extensive dissemination in the country and in the affected counties, respectively, are still unclear but under investigation. Intensive efforts have been made in the respective region to control the outbreaks. In addition to standard infection control measures like isolation of the infected patient and broad screening whenever a new case was found, also an ambitious teaching programme in infection control for all staff, increased awareness of hand hygiene for patients and visitors, banning of food buffets from wards and probiotic treatment has been implemented in the affected hospitals.

At present there appears to be a decrease in the number of detected new cases, but it is too early to judge if this is permanent. A national working-group has been formed and a strategy for laboratory coordination of typing developed.

Tomas Söderblom, Dep of Epidemiology, Swedish Institute for Infectious Disease Control; **Olov Aspevall,** Infection Control, Karolinska University Hospital Huddinge; **Mats Erntell,** Communicable Disease Control, Halmstad Hospital; **Ingegerd Gustafsson,** Dep of Clinical Microbiology, Halmstad Hospital; **Göran Hedin,** Dep of Clinical Microbiology, Falun Hospital; **Daniel Heimer,** Dep of Clinical Microbiology and Infection Control, Västerås Hospital; **Ingegerd Hökeberg,** Communicable Disease Control, Karolinska University Hospital; **Karin Kidd-Ljunggren,** Infection Control, Halmstad Hospital; **Åsa Melhus,** Dep of Clinical Microbiology, Akademiska University Hospital; **Barbro Olsson-Liljequist,** Dep of Bacteriology, Swedish Institute for Infectious Disease Control; **Jan Smedjegård,** Communicable Disease Control, Västmanland County Council; **Staffan Sylvan,** Communicable Disease Control, Akademiska University Hospital; **Karin Tegmark-Wisell,** Dep of Bacteriology, Swedish Institute for Infectious Disease Control; **Magnus Thore,** Dep of Bacteriology, Swedish Institute for Infectious Disease Control; **Johan Struwe,** Strama/Dep of Epidemiology, Swedish Institute for Infectious Disease Control.

5.5 Increase of the proportion of *Haemophilus influenzae* with betalactamases

During the winter 2007–2008 the laboratory in Malmö noted an increase in the proportion of *Haemophilus influenzae* with betalactamases (6 mm penicillin V zone). This was later confirmed by other laboratories and in the results from ResNet, RSQC 2008, Figure 5.5.1.

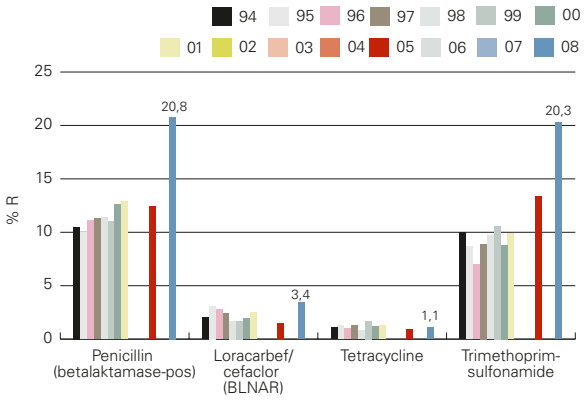

FIGURE 5.5.1. Resistance in *H. influenzae* collected in the annual RSQC programme (approximately 3000 isolates per year). No data available for 2002–2004 and 2006–2007.

Figure 5.5.1 also shows that there was a concommitant increase in the trimethoprim-sulfamethoxazole resistance, suggesting that the increase might be clonally related. This has prompted further investigations to see whether this increase is due to the spread of one or several clones in Sweden.

In order to better understand the epidemiology of the resistant *Haemophilus influenzae* isolates we retrospectively collected data on the age distribution of patients being infected with betalactamase-producing isolates during the ResNet (RSQC) data collection period 2008. The age distribution among 487/517 (94%) of the patients with betalactamase-producing isolates for which information could be retrieved is shown in Figure 5.5.2.

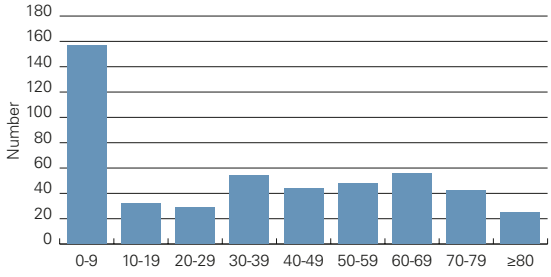

Figure 5.5.2. Age distribution of patients with betalactamase-producing *Haemophilus influenzae* in the RSQC survey 2008.

One third of the patients were children 0–9 years, and the remaining isolates were evenly distributed among all other age groups. This age distribution was comparable among patients with betalactamase-producing *Haemophilus influenzae* when looking into regional databases in Skåne and Västra Götaland regions and Kronoberg county.

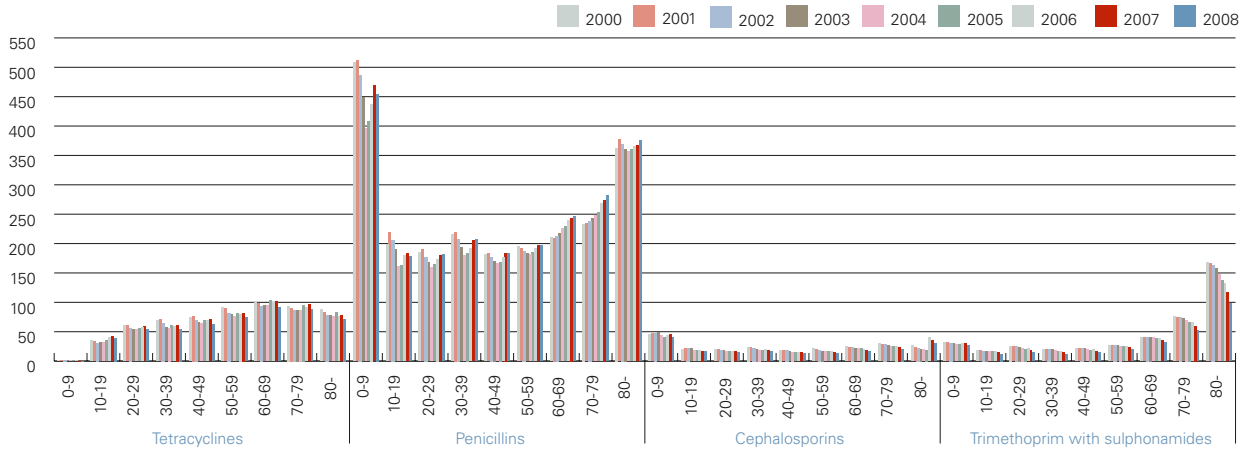

FIGURE 5.5.3. The use of antibiotics mainly used for respiratory tract infections in different age groups. Prescpitions/1000 inhabitants/year.

Figure 5.5.3 illustrates that there has not been any major shift in antibiotic use from narrow spectrum penicillin to antibiotics with broader spectrum during the last decade. This may speak in favour of a clonal spread rather than a shift in antibiotic use as the main driver for the change in resistance rates.

Conclusion

The increased resistance in *Haemophilus influenzae* is worrisome, but should not lead to any change in the present recommendations in the treatment of benign upper respiratory infections in primary health care such as acute mediaotitis and rhinosinuitis, as most of them are self-limiting even without antibiotics. Epidemiological typing will be performed on representative isolates to investigate a possible clonal relationship.

Eva Melander, Laboratory medicine/Hospital hygiene, Malmö University Hospital; **Tinna Åhrén,** Infection Control unit and Clin Bacteriology, Sahlgrenska University Hospital; **Gunnar Kahlmeter,** Dep of Clin Microbiology, Växjö Central Hospital; **Jonatan Dahlkvist,** Drug Management and Informatics, Stockholm County Council; **Christer Norman,** Strama; **Barbro Olsson-Liljequist,** Dep of Bacteriology, Swedish Institute for Infectious Disease Control; **Johan Struwe,** Strama/Dep of Epidemiology, Swedish Institute for Infectious Disease Control.

5.6 Prevalence of wildtype clones among some common pathogens in Kronoberg County.

To further understand the impact of antibiotic resistance on empiric treatment and to understand development of antibiotic resistance it is important to analyse routine resistance data in several ways. Figure 5.6.1 shows the rate of isolates susceptible to all commonly used antibitotics rather than the commonly used techniques to show individual resistance rates over time.

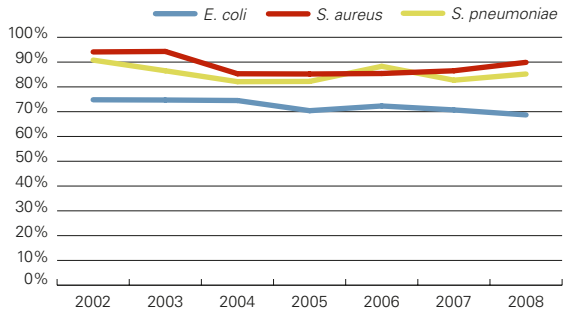

FIGURE 5.6.1. Prevalence of "wildtype" clones (% of isolates devoid of any resistance to a large number of antimicrobial agents) in Kronoberg County for some common pathogens.

The graph illustrates that antimicrobial resistance development primarily occurs in clones already resistant to one or several antimicrobials. Although the proportion of strains totally devoid of antimicrobial resistance is still high in Sweden (corresponding figures for *E. coli* in Spain and Portugal are 50%), the risk of failing with empirical therapy is increasing.

Gunnar Kahlmeter, Dep of Clin Microbiology, Växjö Central Hospital; **Martin Sundqvist,** Dep of Infectious Diseases, Växjö Central Hospital.

Appendix 1. Abbreviations

ABU	Asymptomatic bacteriuria
AST	Antibiotic susceptibility testing
ATC	The Anatomical Therapeutic Chemical classification system
BLNAR	Betalactamase negative ampicillin resistant
CDCDC	County Department for Communicable Disease Control
DDD	Defined daily dose
DST	Drug susceptibility testing
EARSS	European Antimicrobial Resistance Surveillance System
ESBL	Extended spectrum betalactamase
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
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
TB	Tuberculosis
TEM	Serin-betalactamase
UTI	Urinary tract infection
VIM	Integron-encoded metallo-betalactamace
VRE	Vancomycin resistant enterococci

Appendix 2. Demographics and denominator data

TABLE APP 2.1. Population by county and age group December 31st, 2007.

	0-6 years	7-19 years	20-59 years	60-79 years	80 years	All ages
Stockholm	176 065	299 593	1 075 518	313 612	84 728	1 949 516
Uppsala	26 053	52 720	173 328	56 394	14 775	323 270
Södermanland	20 121	43 450	130 581	55 907	15 131	265 190
Östergötland	31 464	68 240	216 893	80 542	23 670	420 809
Jönköping	26 269	56 915	166 701	63 956	19 769	333 610
Kronoberg	13 680	29 054	91 461	35 760	10 832	180 787
Kalmar	15 549	37 383	114 133	51 687	15 082	233 834
Gotland	3 681	9 488	28 524	12 162	3 267	57 122
Blekinge	11 040	23 229	75 213	33 206	9 212	151 900
Skåne	94 308	186 594	627 514	225 742	65 199	1 199 357
Halland	23 610	49 289	144 912	57 512	16 070	291 393
Västra Götaland	120 481	247 368	813 506	283 391	82 548	1 547 294
Värmland	18 513	43 356	135 967	58 943	17 047	273 826
Örebro	20 310	44 670	139 546	55 276	16 265	276 067
Västmanland	18 271	40 442	125 581	51 069	13 830	249 193
Dalarna	18 971	44 851	134 833	59 609	17 354	275 618
Gävleborg	19 136	43 499	135 876	60 215	16 830	275 556
Västernorrland	17 608	37 748	119 273	54 047	14 773	243 449
Jämtland	9 111	19 903	63 196	26 536	8 191	126 937
Västerbotten	18 652	41 278	134 155	50 005	13 503	257 593
Norrbotten	17 074	39 722	126 341	54 582	12 883	250 602
Sweden	719 967	1 458 792	4 773 052	1 740 153	490 959	9 182 923

TABLE APP 2.2. Population of Sweden 2000-2008 (the numbers represents the population on December 31st the previous year).

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

TABLE APP 2.3. Number of admissions and patient-days in somatic medical care 2006-2007.

	Patient-days	
	2006	2007
Stockholm	1617616	1291013
Uppsala	290597	294355
Södermanland	258018	251242
Östergötland	300953	314572
Jönköping	330655	311519
Kronoberg	180039	148346
Kalmar	223035	212446
Gotland	53533	52340
Blekinge	156472	143853
Skåne	1179747	1133429
Halland	253933	235671
Västra Götaland	1571130	1498342
Värmland	242936	246473
Örebro	258861	252833
Västmanland	253676	240762
Dalarna	252806	223019
Gävleborg	229064	239620
Västernorrland	243998	234511
Jämtland	126414	122325
Västerbotten	297329	296568
Norrbotten	262023	236848

TABLE APP 2.5. Denominator data from the microbiological laboratories. NP = test not performed, NA = data not available

	Number of analyses 2008							Number of positive cultures 2008					
Laboratory	**Blood (pair of bottles)**	**Cerebro-spinal fluid (CSF)**	**Nasopharynx**	**Throat**	**General culture**	**Screen MRB**	**Faeces SSYC**	**Faeces *Clostridium difficile* (toxin)**	***Staphylococcus aureus***	***Streptococcus pneumoniae***	***Streptococcus pyogenes***	***Escherichia coli***	***Clostridium difficile* (toxinpositive)**
Borås	14224	169	3277	5167	10930	1322	7439	1905	4557	910	1093	7404	201
Eskilstuna (Unilabs)	8246	164	6175	5002	8398	1055	4412	2181	3947	914	1007	7093	300
Falun	13726	353	2796	1967	10041	2411	4416	1742	4072	481	807	7304	361
Gävle	10027	182	1733	1344	8311	2934	3708	2100	3729	326	405	6602	394
Göteborg	20742	875	3194	3877	14829	36927	10901	3922	11952	888	1194	16926	NA
Halmstad	9925	146	2268	2577	8649	14671	6332	2086	3288	300	704	6837	325
KS/HS Stockholm	64611	2658	35181	13162	76801	170112	24351	12093	24315	4959	3727	39758	1593
Jönköping	14100	200	3770	4280	12880	7200	7770	2640	6040	650	1110	9610	530
Kalmar	9501	149	3698	2711	6691	4153	4754	1474	4177	619	606	6900	181
Karlskrona	5191	35	1285	2625	5478	1199	3983	1444	1947	253	382	4304	354
Karlstad	14269	211	1237	2606	12187	5555	4638	1941	5580	328	761	7505	273
Kristianstad	8196	94	5074	5074	11343	5713	5695	2104	4021	874	928	8643	282
Linköping	15751	750	5408	3570	19832	12894	8467	3652	4449	687	657	7428	555
Lund	24305	1326	11338	7659	25247	14207	14510	4056	11465	2815	3048	17527	511
Malmö	22081	324	5968	6663	18083	50120	11991	4291	8403	2056	1614	15700	589
Aleris Medilab	NP	NP	10458	5015	8637	11886	9496	1130	3871	1299	1176	8407	54
St:Göran (Unilabs)	6509	184	5449	5148	15458	27637	9202	1903	5247	952	1070	9870	494
Skövde (Unilabs)	11306	151	2419	3076	6556	6778	5532	1997	3990	452	605	8981	235
Sunderby, Luleå	8216	146	2548	3175	8145	2256	3856	1376	3182	352	638	7435	265
Sundsvall	9233	118	2635	2071	7574	12970	4105	1701	3437	510	537	7300	230
Uddevalla	16970	180	1900	3240	8650	5090	5640	1580	4460	490	685	9490	230
Umeå	12074	748	2670	2708	11833	5557	5014	1573	3994	499	762	9248	96
Uppsala	18418	788	5022	2629	14058	25350	5718	3006	5135	842	674	7998	582
Visby	3106	23	2363	738	2954	NP	1245	780	1354	339	193	2043	129
Västerås	9362	133	2609	2202	8843	8897	3165	1718	3508	489	448	7336	698
Växjö	5938	89	2186	2434	6162	1400	4086	1331	2659	366	521	5112	111
Örebro	14062	315	8479	1970	13715	5819	5221	2684	5543	1196	711	7708	344
Östersund	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total	370089	10511	141140	102690	362285	444113	185647	68410	148322	24846	26063	260469	9917

MRB = multiresistant bacteria

SSYC = *Salmonella, Shigella, Yersinia* and *Campylobacter* spp.

Appendix 3 Surveillance of antibiotic consumption

Statistical sources and units of measurement

The ATC classification system and defined daily doses (DDD)

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

Swedish national statistics on drug utilisation

Since 1975, the National Corporation of Swedish Pharmacies regularly produces sales statistics on drugs, for the country as a whole and for individual counties. The sales are registered as number of DDDs, cash value and number of packages. 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/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.

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 primary health care. Among others this data gives information on the number of individuals treated with at least one course of antibiotics during a specific period of time, i.e. number of users per 1000 inhabitants and year (Users/1000/year). It is also possible to follow the number of purchases per person.

Number of admissions and patient-days

Each of the 21 county councils in Sweden deliver once a year data to the National Patient Register kept by The National Board on Health ad Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Since data for 2007 is not available until August denominator data from 2006 and sales data from 2007 are used in some figures in this report. The number of admissions and patient-days in Swedish medical care 1997–2006 is shown in Appendix 2, Table App 2.3. The Swedish Association of Local Authorities and Regions keeps a searchable database at the web, http://www.skl.se/artikel.asp?A=3768&C=1801.

The present system for surveillance of antibiotic consumption has been investigated and analysed by order of the government. Together with suggestions for future improvements it was reported back to the government on the first European Antibiotic Awareness Day Nov 18th, 2008.

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

Notification shall be done within 24 hours, in duplicate to the County Medical Officer for Communicable Disease Control (smittskyddsläkare) and to the Swedish Institute for 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 (http://www.smittskyddsinstitutet.se) and yearly in "Communicable Diseases in Sweden – the Yearly Report of the Department of Epidemiology" and in this report. Data on drug-resistant TB is also annually published in "the Swedish Tuberculosis Index".

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

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

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

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100–200 consecutive clinical isolates of a number of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. On one or several occasions *Escherichia coli*, *Enterococcus faecalis/E.faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella* 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/E. faecium*, and monitors variations in antimicrobial resistance over time and place. From 2005 invasive isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are also part of the scheme.

Participation in EARSS was initially intended for member states of the European Union, also including Norway and Iceland, but in year 2000 six countries in eastern Europe were included, and by 2003 28 countries provide susceptibility data regularly. Information about EARSS, as well as a database yielding information about the susceptibility results for each country, year and pathogen, is available through a web-site (www.earss.rivm.nl).

Data collected by EARSS should be routinely generated quantitative data (MICs or inhibition zones), but the data presented are only in the format of susceptibility 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 SWEDRES 2007 and 2088 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.

The present systems for surveillance of antibiotic resistance has been investigated and analysed by order of the government. Together with suggestions for future improvements it was reported back to the government on the first European Antibiotic Awareness Day Nov 18th, 2008.

Appendix 6. Recent publications (2006-2008)

Use of antibiotics

André M, Hedin K, Håkansson A, Mölstad S, Rodhe N, Petersson C. More physician consultations and antibiotic prescriptions in families with high concern about infectious illness – adequate response to infection-prone child or self-fulfilling prophecy? Family Practice 2007;24:302-7.

Dumpis U, Gulbinovic J, Struwe J, Lagergren L, Grishkevichus L, Bergman U. Differences in antibiotic prescribing in three university hospitals in the Baltic region revealed by a simple protocol for quality assessment of therapeutic indications. Int J Clin Pharm Ther 2007;45:568-576 .

Erlandsson M, Burman LG, Cars O, Gill H, Nilsson LE, Walther SM, Hanberger H, the STRAMA ICU Study Group. Prescription of antibiotic agents in Swedish intensive care units is empiric and precise. Scand J Infect Dis 2007;39:63–69.

Grigoryan L, Burgerhof J, Jaaijer-Ruskamp F, Degener J, Deschepper R, Monnet DL, Di Matteo A, Scicluna E, Bara AC, Stålsby Lundborg C, Birkin J. Is self-medication with antibiotics in Europe driven by prescribed use? JAC 2007;59:152-6.

Grigoryan L, Haaijer-Ruskamp FM, Johannes Burgerhof GM, Mechtler R, Deschepper R, Tambic-Andrasevic A, Andrajati R, Monnet DL, Cunney R, Di Matteo A, Edelstein Hm, Valinteliene R, Alkerwi A, Scicluna EA, Grzesiowski P, Bara AC, Tesar T, Cizman M, Campos J, Stålsby Lundborg C, Birkin J. Self-medication with antibiotics in the general population: a survey in nineteen European countries. Emerg Inf Dis 2006;12:452-9.

Hedin K, André M, Håkansson A, Mölstad S, Rodhe N, Petersson C. A population-based study of different antibiotic prescribing in different areas. Br J Gen Pract. 2006 Sep;56(530):680-5

Hedin K, André M, Mölstad S, Rodhe N, Peterson C. Infections in families with small children – use of social insurance and health care. Scand J Prim Health Care 2006 Jun;24(2):98-103

Hedin K, Petersson C, Cars H, Beckman A, Håkansson A. Infection prevention at day-care centres: Feasibility and possible effects of intervention. Scand J of Prim Health Care 2006;24:44-49.

Mölstad S, Erntell M, Hanberger H, Melander E, Norman C, Skoog G, Stålsby Lundborg C, Söderström A, Torell E, Cars O. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. Lancet Infect Dis 2008;8:125-32.

Pettersson E, Vernby Å, Mölstad S, Stålsby Lundborg C. Infections and antibiotic prescribing in Swedish nursing homes: A cross-sectional study. Scand J Inf Dis 2008;40:5,393-398.

André M, Vernby Å, Odenholt I, Stålsby Lundborg C, Axelsson I, Eriksson M, Runehagen A, Schwan Å and Mölstad S. Diagnosis-prescribing surveys in 2000, 2002 and 2005 in Swedish general practice: Consultations, diagnosis, diagnostics and treatment choices. Scand J Inf Dis 2008;40:8,648-654.

Vlahovic-Palevski V, Dumpis U, Mitt P, Struwe J, Palevska G, Stimac D, Lagergren Å, Bergman U. Benchmaking antimicrobial drug use at university hospitals in five European countries. Clin Microbiol Infect 2007;13:277-283.

Antimicrobial resistance

Agvald Öhman C, Lund B, Hedin G, Hjelmqvist H, Struwe J, Edlund C. ICU stay promotes enrichment and dissemination of multi-resistant coagulase-negative staphylococcal strains. Scand J Infect Dis 2006;38:441-447.

Blahna MT, Zalewski CA, Reuer J, Kahlmeter G, Foxman B, Marrs CF. The role of horizontal gene transfer in the spread of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* in Europe and Canada. J Antimicrob Chemother 2006;57:666-672.

Cars O, Olsson-Liljequist B, Short summary of Swedres 2005, a report on Swedish antibiotic utilisation and resistance. Eurosurveillance 2007;12:225.

Cookson B, Robinson A, Monk AB, Murchan S, Deplano A, deRyck R, Struelens MJ, Scheel C, Fussing V, Salmenlinna S, Vuopio-Varkila J, Cuny C, Witte W, Tassios PT, Legakis NJ, van Leeuwen W, van Belkum A, Vindel A, Garaizar J, Haeggman S, Olsson-Liljequist B, Ransjö U, Muller-Premru M, Hryniewicz W, Ronney A, O´Connell B, Short BD, Thomas J, O´Hanlon S, Enright MC. Evaluation of molecular typing methods in characterizing a European collection of epidemic methicillin-resistant *Staphylococcus aureus* strains: the HARMONY collection. J Clin Microbiol 2007;45:1830-7.

Erlandsson M., Burman L. G., Cars O, Gill H, Nilsson L. E, Walther S, Hanberger H, and the ICU-STRAMA Study Group. Prescription of antibiotic agents in Swedish intensive care units is empiric and precise Scand J Infect Dis 2007;39:63-69.

Grape M, Motakefi A, Pavuluri S, Kahlmeter G. Standard and real-time multiplex PCR-methods for detection of trimethoprim resistance of genes in large collections of bacteria. Clin Microbiol Infect 2007;13:1112-8.

Hanberger H., Burman L. G., Cars O, Erlandsson M., Gill H, Nilsson L. E, Nordlinder D, Walther S. and the ICU-STRAMA Study Group. Low antibiotic resistance rates in *S aureus*, *E coli* and *Klebsiella* but not in *Enterobacter* and *P. aeruginosa*: a prospective observational study in 14 Swedish ICUs over a five year period. Submitted Acta Anaesth Scand 2007.

Hanberger H, Arman D, Gill H, Jindrák V, Kalenic S, Kurcz A, Licker M, Naaber P, Scicluna EA, Vanis V, Walther SM. Surveillance of microbial resistance in European Intensive Care Units: a first report from the Care-ICU programme for improved infection control. Intensive Care Med. 2009;35:91-100. Epub 2008 Aug 1.

Hedberg ST, Fredlund H, Nicolas P, Caugant DA, Olcén P, Unemo M. Antibiotic susceptibility and characteristics of *Neisseria meningitidis* isolates from the African meningitis belt 2000-2006 – phenotypic and genotypic perspectives. Antimicrob Agents Chemother. 2009 Feb 2. [Epub ahead of print].

Hellmark B, Söderquist B, Unemo M. Simultaneous species identification and detection of rifampicin resistance in staphylococci by sequencing of the rpoB gene. Eur J Clin Microbiol Infect Dis 2009;28:183-90.

Hellmark B, Unemo M, Nilsdotter-Augustinsson Å, and Bo Söderquist. Antibiotic susceptibility among *Staphylococcus epidermidis* isolated from prosthetic joint infections with special focus on rifampicin and variability of the rpoB gene. Clin Microbiol Infect 2009 Jan 22. [Epub ahead of print].

Högberg L, Ekdahl K, Sjöström K, Olsson-Liljequist B, Walder M, Melander E, Rringberg H, Normark BH. Penicillin-resistant pneumococci in Sweden 1997-2003; increased multiresistance despite stable prevalence and decreased antibiotic use. Microb Drug Resist 2006;12:16-22.

Kahlmeter G, Brown DF, Goldstein FW, MacGowan AP, Mouton JW, Odenholt I, Rodloff A, Soussy CJ, Steinbakk M, Soriano F, Stetsiouk O. European Committee on Antimicrobial Susceptibility Testing (EUCAST) Technical notes on antimicrobial susceptibility testing. Clin Microbiol Infect 2006;12:501-3.

Kubanova A, Frigo N, Kubanov A, Sidorenko S, Priputnevich T, Vachnina T, Al-Khafaji N, Polevshikova S, Solomka V, Domeika M, Unemo M. National surveillance of antimicrobial susceptibility in *Neisseria gonorrhoeae* in 2005-2006 and recommendations of first-line antimicrobials for gonorrhoea treatment in Russia. Sex Transm Infect. 2008;84:285-9.

Lindberg R, Fredlund H, Nicholas R, Unemo M. *Neisseria gonorrhoeae* isolates with reduced susceptibility to cefixime and ceftriaxone: association with genetic polymorphisms in penA, mtrR, porB1b, and ponA. Antimicrob Agents Chemother 2007;51:2117-22.

Lindbäck E, Islam S, Unemo M, Lang C, Wretlind B. Transformation of ciprofloxacin-resistant *Neisseria gonorrhoeae* gyrA, parE and porB1b genes. Int J Antimicrob Agents 2006;28:206-11.

Lindbäck E, Unemo M, Akhras M, Gharizadeh B, Fredlund H, Pourmand N, Wretlind B, Lindberg R, Fredlund H, Nicholas R, Unemo M. *Neisseria gonorrhoeae* isolates with reduced susceptibility to cefixime and ceftriaxone: association with genetic polymorphisms in penA, mtrR, porB1b, and ponA. Antimicrob Agents Chemother 2007;51:2117-22.

Lindbäck E, Unemo M, Akhras M, Gharizadeh B, Fredlund H, Pourmand N, Wretlind B. Pyrosequencing of the DNA gyrase gene in *Neisseria* species: effective indicator of ciprofloxacin resistance in *Neisseria gonorrhoeae*. APMIS 2006;114:837-41.

Lundbäck D, Fredlund H, Berglund T, Wretlind B, Unemo M. Molecular epidemiology of *Neisseria gonorrhoeae* – identification of the first presumed Swedish transmission chain of an azithromycin-resistant strain. APMIS 2006;114:67-71.

Norén T, Åkerlund T, Wullt M, Burman LG, Unemo M. Mutations in fusA associated with post-therapy fusidic acid resistance in *Clostridium difficile*. Antimicrob Agents Chemother 2007;51:1840-3.

Olsen B, Hadad R, Fredlund H, Unemo M. The *Neisseria gonorrhoeae* population in Sweden during 2005-phenotypes, genotypes and antibiotic resistance. APMIS 2008;116:181-9.

O'Neill AJ, McLaws F, Kahlmeter G, Henriksen AS, Chopra I. Genetic basis of resistance to fusidic acid in staphylococci. Antimicrob Agents Chemother 2007;51:1737-40.

Skov R, Smyth R, Larsen AR, Bolmström A, Karlsson Å, Mills K, Frimodt-Moller N, Kahlmeter G. Phenotypic detection of methicillin resistance in *Staphylococcus aureus* by disk diffusion testing and Etest on Mueller-Hinton agar. J Clin Microbiol 2006;44:4395-9.

Stenhem M, Ortqvist A, Ringberg H, Larsson L, Olsson-Liljequist B, Haeggman S, Ekdahl K, Andersson A, A von Rosen I, Ardung B, Eliasson I, Fridh G, Hedin G, Helisoja R, Isaksson B, Karlman K, Kransberg L, Lennell A, Lindblom A, Lindh G, Lundholm R, Nilsson I, Nilsson L, Nilsson P, Nilsson P, Thollstrom UB, Abom PE. Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Sweden 2000-2003, increasing incidence and regional differences. BMC Infect Dis 2006; 6: 30.

Sundqvist M, Kahlmeter G. Effect of excluding duplicate isolates of *Escherichia coli* and *Staphylococcus aureus* in a 14 year consecutive database. J Antimicrob Chemother 2007;59:913-8.

Söderblom T, Struwe J. Extended spectrum betalactamase-producing *Enterobacteriaceae*: the first six months of notifications according to the Swedish communicable disease act. Eurosurveillance weekly 2007;12(10).

Taha MK, Vázquez JA, Hong E, Bennett DE, Bertrand S, Bukovski S, Cafferkey MT, Carion F, Christensen JJ, Diggle M, Edwards G, Enríquez R, Fazio C, Frosch M, Heuberger S, Hoffmann S, Jolley KA, Kadlubowski M, Kechrid A, Kesanopoulos K, Kriz P, Lambertsen L, Levenet I, Musilek M, Paragi M, Saguer A, Skoczynska A, Stefanelli P, Thulin S, Tzanakaki G, Unemo M, Vogel U, Zarantonelli ML. Target gene sequencing to characterize the penicillin G susceptibility of *Neisseria meningitidis*. Antimicrob Agents Chemother 2007;51:2784-92.

Tegmark Wisell K, Hæggman S, Gezelius L, Thompson O, Gustafsson I, Ripa T, Olsson-Liljequist B. Identification of *Klebsiella pneumoniae* carbapenemase (KPC) in Sweden. Eurosurveillance 2007; 12: E071220.3.

Thulin S, Olcén P, Fredlund H, Unemo M. Total variation in the penA gene of *Neisseria meningitidis*: correlation between susceptibility to beta-lactam antibiotics and penA gene heterogeneity. Antimicrob Agents Chemother 2006;50:3317-24.

Thulin S, Olcén P, Fredlund H, Unemo M. Combined real-time PCR and pyrosequencing strategy for objective, sensitive, specific, and high throughput identification of reduced susceptibility to penicillins in *Neisseria meningitidis*. Antimicrob Agents Chemother 2008;52:753-6.

Unemo M, Sjöstrand A, Akhras M, Gharizadeh B, Lindbäck E, Pourmand N, Wretlind B, Fredlund H. Molecular characterization of *Neisseria gonorrhoeae* identifies transmission and resistance of one ciprofloxacin-resistant strain. APMIS 2007;115:231-41.

Unemo M, Olcén P, Fredlund H, Thulin S. Real-time PCR and subsequent pyrosequencing for screening of penA mosaic alleles and prediction of reduced susceptibility to expanded-spectrum cephalosporins in *Neisseria gonorrhoeae*. APMIS 2008;116:1004-8.

Vorobieva V, Firsova N, Ababkova T, Leniv I, Haldorsen BC, Unemo M, Skogen V. Antibiotic susceptibility of *Neisseria gonorrhoeae* in Arkhangelsk, Russia. Sex Transm Infect 2007;83:133-5.

Vorobieva V, Firsova N, Ababkova T, Leniv I, Haldorsen BC, Unemo M, Skogen V. Antibiotic susceptibility of *Neisseria gonorrhoeae* in Arkhangelsk, Russia. Sex Transm Infect 2006 Sep 13; [Epub ahead of print].

Österlund A, Kahlmeter G, Hæggman S, Olsson-Liljequist B,; Swedish Study Group on Fusidic Acid Resistant *S Aureus*. *Staphylococcus aureus* resistant to fusidic acid among Swedish children: a follow-up study. Scand J Infect Dis 2006; 38: 332-334.

Workshop

Management of lower urinaty tract infections (in swedish), Medical Products Agency, April 2007, www.lakemadelsverket.se

Management of Respiratory Tract Infections (in swedish), Medical Products Agency 2008, www.lakemadelsverket.se

Websites

www.strama.se

www.srga.org

www.srga.org/resnet_sok.htm

www.smittskyddsinstitutet.se

http://www4.smittskyddsinstitutet.se/careicu/index.jsp.

Strama

Swedish Strategic Programme
against Antibiotic Resistance

SMITTSKYDDSINSTITUTET

Swedish Institute for Infectious Disease Control