2013

SWEDRES | SVARM

Use of antimicrobials and occurrence of antimicrobial resistance in Sweden

Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

SVA NATIONAL VETERINARY INSTITUTE

A report on Swedish Antibiotic Utilisation and Resistance in Human Medicine (SWEDRES) and Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM)

Published by:
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ISSN 1650-6332

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Suggested citation:
SWEDRES-SVARM 2013. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala ISSN 1650-6332

Print & Layout: Edita Västra Aros AB

Omslag: Ingvar Westerdahl/Thomas Isaksson

Preface

The 2013 Swedish report from the monitoring of antimicrobial resistance and antimicrobial usage in human and veterinary medicine, SWEDRES-SVARM, is an integrated report from the Swedish Public Health Agency and the National Veterinary Institute (SVA), with data from humans, animals and food. It is one of the products that is a result of the successful collaboration between the human and veterinary sector in Sweden. The recent launch of a new national public health institute in Sweden shows an important political commitment to public health and will further strengthen the possibilities to coordinate the work with antibiotic resistance among the many different actors that need to be involved to make the work successful. The agency now has a wide mandate to work in the whole field of public health which opens possibilities to both strengthen our efforts in the technical aspects, such as measuring and following attitudes in the population and in the strategic work both nationally and internationally.

Antibiotic resistance is one area where the human veterinary collaboration is both essential and very useful. It is necessary to address and reduce the use and bring down the misuse of antimicrobials in both humans and animals, which otherwise will further undermine the usefulness of antibiotics by selecting for antimicrobial resistance. The information provided in this report will make it possible to focus the efforts where they are most effective and to follow-up the effects of such interventions.

This year's report shows that we have a stable trend in diminishing use of antibiotics in both the human and veterinary field and furthermore there is a clear trend towards using antibiotics that we believe affects resistance the least. Unfortunately, in spite of this relative success, the prevalence of resistant bacteria keeps increasing although Sweden still has a very favorable situation compared to most other countries and the levels continue to be very low.

Even if Sweden is far from spared from problems with antibiotic resistance, we can conclude that in a global perspective we have a much better situation compared to most countries. Consequently, further efforts are needed to counter the selection and spread of resistance, and one key component in that work is high quality information about the current situation.

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Acknowledgements

The external group of antibiotic sales data of the Public Health Agency of Sweden: Ingrid Brännström, Jonatan Dahlqvist, Mats Erntell, Annika Hahlin, Mikael Hoffmann and Pinelopi Lundquist

Data on antibiotic use in relation to number of admissions and number of patient days in somatic hospital care during 2009-2013 were kindly provided by pharmacists in local Strama-groups.

Stramarådet (Strama advisory board against antibiotic resistance of the Public Health Agency of Sweden) for supporting the work with SWEDRES.

The national surveillance of antibiotic resistance would not have been possible without the contribution of data and active support of all the Swedish clinical microbiology laboratories.

Complementary epidemiological information on clinical notifications has been performed by the local County Departments for Communicable Disease Control.

Data on antimicrobials for animals sold with special license were kindly provided by pharmaceutical companies.

Kerstin Ortman and Anders Linder at Eurofins Food & Agro, Skara for providing SVA with clinical isolates and susceptibility results from clinical submissions from animals.

Anna Edberg at the journal Råd & Rön for placing isolates of *Escherichia coli* and *Campylobacter jejuni* from broiler meat at the disposal of SVA.

Content

Sammanfattning/Summary

Sammanfattning

Rapporten visar att situationen avseende antibiotikaresistens hos bakterier från såväl människor som djur är gynnsam i ett internationellt perspektiv. Detta bekräftar att den svenska strategin att verka för ansvarsfull användning av antibiotika och att begränsa spridning av resistens är effektiv. Årets rapport visar trots det också på några oönskade trender, exempelvis flera utbrott där VRE spridits på sjukhus.

Förbrukning av antibiotika

Antibiotikaförbrukning inom humanmedicin

Den totala antibiotikaförsäljningen minskade med 6 procent (från 14.2 till 13.4 DDD per 1000 invånare och dag) under 2013 jämfört med 2012. I öppenvård minskade försäljningen med 8 procent, från 374 till 343 recept per 1000 invånare och år. Minskningen sågs i alla åldersgrupper och den största minskningen sågs bland barn 0-6 år (19 procent). Antibiotikaförsäljningen minskade i samtliga 21 län. Skillnaden mellan länen är dock fortfarande stor och varierar från 374 recept per 1000 invånare i Skåne till 267 i Västerbotten. Minskningen omfattade samtliga antibiotikagrupper, förutom pivmecillinam (J01CA08) och nitrofurantoin (J01XE01) som ökade vilket är positivt eftersom dessa är rekommenderade för urinvägsinfektioner. Betalaktamaskänsliga penicilliner tillsammans med tetracykliner var de antibiotika som förskrevs mest på recept under 2013.

Antibiotika som ofta används mot luftvägsinfektioner (LVI) är den grupp av antibiotika som användes mest och under 2013 är det i denna grupp av antibiotika som den största minskningen sker (14 procent). Minskningen är främst relaterad till en stor nedgång i försäljning av doxycyklin (18 procent), makrolider (26 procent) och penicillin V (13 procent). Den kraftiga nedgången av doxycyklin och makrolider kan delvis förklaras av en lägre förekomst av *Mycoplasma pneumoniae* under vintersäsongen 2012/2013 jämfört med vintersäsongen 2011/2012 samt leveransproblem av erytromycin under våren 2013. Minskningen av antibiotika mot LVI ses dock över hela året, vilket talar för en verklig minskning av användningen.

Behandlingen av nedre urinvägsinfektion (UVI) hos kvinnor ser ut att följa nationella rekommendationer. Användningen av de två förstahandspreparaten, pivmecillinam och nitrofurantoin, har successivt ökat och utgjorde under året 77 procent av den totala försäljningen av antibiotika som ofta används mot UVI hos kvinnor (18-79 år). Försäljningen av kinoloner och trimetoprim fortsatte att minska (5 procent och 15 procent respektive) i denna patientgrupp, vilket är enligt nationella rekommendationer.

I slutenvård minskade antibiotikaförsäljningen något (1,8 procent) under 2013 jämfört med 2012. Detta är första året under 2000-talet som antibiotikaförsäljningen minskar inom slutenvård. Minskningen i användning av cefalosporiner som setts de senaste åren fortsätter och från 2006 till 2013 har försäljningen av cefalosporiner minskat med 51 procent. Inom slutenvård finns det också en förskjutning från andra generationens till tredje generationens cefalosporiner eftersom dessa utgör en säkrare empirisk antibiotikabehandling. Bredspektrumantibiotika, som karbapenemer och piperacillin med tazobaktam, används allt oftare och det finns en möjlig koppling till ett ökande antal infektioner orsakade av bakterier med ESBL.

Försäljning av antimykotika

Jämfört med 2012 ökade den totala användningen av antimykotika på svenska sjukhus med 2 procent till 61 DDD per miljon invånare och dag. Liksom tidigare är flukonazol det mest förskrivna preparatet och utgör två tredjedelar av all sjukhusförskrivning. Av preparat med bredare antifungal täckning ökade amphotericin B med 40 procent och är återigen det näst vanligaste preparatet. Användningen av amphotericin B har varierat kraftig mellan åren och även mellan olika sjukhus vilket kan tyda på att enstaka patienter med långa behandlingstider kan påverka statistiken. Echinokandinerna som grupp utgör tillsammans en lika stor andel av den totala förbrukningen, det vill säga 12 procent. Från att ha varit det absolut dominerande preparatet har caspofungin förlorat en stor del av sin dominans och utgör nu cirka 60 procent av den totala användningen. Anidulafungin och det nyare preparatet mikafungin har nu 30 respektive 10 procent av marknaden. Den totala förbrukningen av bredspektrumazoler är relativt oförändrad, men vorikonazol som fortfarande är det mest förskrivna preparatet fortsätter att minska till förmån för posakonazol. En förklaring till det sistnämnda är troligtvis användningen av posaconazol som profylax mot invasiva svampinfektioner hos patienter med blodcancersjukdomar.

Veterinärmedicin

Farhågor om bortfall i statistiken efter omregleringen av apoteksmarknaden har framförts. Bortfallet berör troligen främst injektionsläkemedel. SVA har skattat omfattningen av problemet till 5-10 procent av den totala försäljningssiffran.

Uttryckt som mg aktiv substans per skattad kilo levandevikt av livsmedelsproducerande djur var försäljningen 2013 14 mg/kg vilket är 25 procent lägre än 2009. Även om bortfallet ovan beaktas så har användningen minskat över tid.

Human- och veterinärmedicin

En jämförelse av försäljningen av antibiotika för systemiskt bruk och som medel vid tarminfektioner visade att 62,5 och 10,8 ton sålts för användning inom humanmedicin respektive veterinärmedicin. Användning inom humanvården dominerade alla antibiotikaklasser utom trimetoprim-sulfa och aminoglykosider.

Anmälningspliktig resistens

ESBL-producerande Enterobacteriaceae

Totalt rapporterades 8131 fall av Enterobacteriaceae med betalaktamaser med utvidgat spektrum (ESBL) under 2013 vilket var en ökning med 13 procent. Ökningen skedde i 16 län, och liksom tidigare år var *Escherichia coli* den helt dominerande bakteriearten som förekom hos 89 procent av fallen. På andra plats kom *Klebsiella pneumoniae* som fanns hos 7 procent av fallen. Bakteriefynden gjordes framför allt i urinprov, och den pågående ökningen i förekomst av resistenta bakterier kan på sikt komplicera behandlingen av dessa förhållandevis enkla infektioner.

En viss typ av ESBL, så kallad $ESBL_{CARBA}$, utgör en mer elakartad resistensmekanism, och bakterier med sådan resistens blev under 2012 anmälningspliktiga både av den behandlande läkaren och av laboratoriet som gjort fyndet. Totalt 39 fall upptäcktes 2013, och de två vanligaste enzymtyperna var NDM och OXA-48. Trots den ringa förekomsten hittills så är en ökad vaksamhet mot dessa extremt resistenta bakterier nödvändig för att vi tidigt ska upptäcka dem och också kunna förhindra spridningen av dem inom vården, eftersom behandlingsalternativen vid en eventuell infektion är få eller inga.

Tillgänglig information visar att ESBL-bildande bakterier är ovanliga hos svenska djur. Undantaget är fjäderfä där *Escherichia coli* med $ESBL_M$-resistens finns i tarminnehåll hos en stor andel av djuren. Överföring av bakterierna till människor tycks dock vara ovanligt eftersom endast en mindre andel av ESBL-producerande bakterier från människor är av typen $ESBL_M$.

MRSA

Totalt anmäldes 2454 nya fall av meticillinresistenta *Staphylococcus aureus* (MRSA) 2013, vilket är en ökning med 17 procent. Det var nästan lika vanligt med smitta utomlands (37 procent) som med smitta i Sverige (43 procent). Samhällsförvärvad smitta var vanligare bland de inhemskt smittade fallen (65 procent) än bland de utomlands smittade (45 procent). Sjukhusförvärvad smitta var vanligare bland importerade fall (30 procent) än bland inhemska (13 procent). Invasiva infektioner med MRSA rapporterades hos 42 personer under 2013. Epidemiologisk typning med *spa*-typning visade att de fem vanligaste *spa*-typerna var t008, t002, t223, t044 och t127. Andelen PVL-positiva MRSA hade ökat något till 37 procent.

Förekomsten av MRSA hos djur är fortfarande låg vilket begränsar risken för spridning från djur till människa. Under 2013 isolerades MRSA från fem hundar, en katt, en häst och en mjölkko. Hos sällskapsdjur dominerar samma typer av MRSA som hos människor, vilket tyder på att människor är smittkällan. Hos hästar dominerar lantbruksdjurstypen MRSA CC398.

MRSP

Under 2013 anmäldes 33 fall av meticillinresistent *Staphylococcus pseudintermedius* (MRSP) hos hund och katt. Antalet fall har successivt minskat sedan 2009 då 130 fall anmäldes. Under året har inga fall hos människor rapporterats till nationella myndigheter men MRSP är inte generellt anmälningspliktig i humansjukvården.

PNSP

Under 2012 förändrades definitionen för anmälningsplikt av *Streptococcus pneumoniae* med nedsatt känslighet för penicillin (PNSP) till att gälla enbart isolat med MIC av penicillin större än 1 mg/L, vilket har medfört en kraftig minskning av antalet anmälda fall. För att kunna följa effekten av vaccination mot pneumokocker samlar Folkhälsomyndigheten regelbundet in PNSP-isolat med MIC ≥ 0,5 mg/L för serotypning. De vanligast förekommande serotyperna var 19F, 35B, 19A, NT, 6B, 3, 14, 9V och 23F.

VRE

Totalt anmäldes 227 nya fall av vankomycinresistenta enterokocker (VRE) under 2013, vilket var en ökning med 49 procent. Merparten av isolaten var *Enterococcus faecium*, Till skillnad mot 2012 är nu *vanB* (126 fall) vanligare än *vanA* (94 fall). Tio sjukvårdsrelaterade utbrott har rapporterats under året i sex län, alla med *E. faecium* varav sex med *vanA* och fyra med *vanB*. Det största utbrottet, Gävleborgs län, pågår fortfarande (4 april 2014) och omfattar hittills cirka 200 fall.

Tidigare data från SVARM visar att *Enterococcus faecium* som bär *vanA*-genen förekommer hos svensk kyckling. VRE-fall med *vanA* hos människor har varit associerade till sjukhusvård utomlands eller smittspridning på sjukhus i Sverige. Epidemiologisk typning tidigare har visat att smittan inte är associerad till svenska kycklingar.

Resistens hos zoonotiska smittämnen

Salmonella är ovanligt hos djur i Sverige och oftast är isolerade stammar känsliga för antibiotika som används vid behandling av människor. Resistens mot tredje generationens cefalosporiner har inte påvisats och resistens mot antibiotikagruppen fluorokinoloner är mycket ovanligt. Det gynnsamma läget gör att djur i Sverige är en osannolik källa till antibiotikaresistent Salmonella hos människor.

Campylobakterstammar från djur i Sverige är oftast känsliga för relevanta antibiotika och exempelvis är resistens mot erytromycin mycket ovanligt. Campylobakter som isoleras från människor är däremot ofta resistenta och det är därför osannolikt att de stammarna kommer från svenska djur även om en anmärkningsvärt stor andel *Campylobacter jejuni* från nötkreatur och kycklingkött är resistent mot fluorokinoloner.

Resistens hos kliniska isolat från människor

Isolat från blododlingar av sju definierade bakteriearter ingår i det europeiska nätverket för resistensövervakning, EARS-Net. Från Sverige medverkar 20 laboratorier, vilket ger en täckning av ca 80 procent av befolkningen, och följande fynd gjordes 2013. *Escherichia coli* förekom i 22 procent av de positiva blododlingarna och *S. aureus* i 11 procent. De övriga fem bakteriearterna som ingår i övervakningen är viktiga men utgjorde ändå en avsevärt mindre andel av de positiva

odlingarna. Hos *E. coli* och *K. pneumoniae* har andelen cefalosporinresistenta och ESBL-producerande isolat ökat varje år och uppgick till 4,9 respektive 3,1 procent 2013. Andelen MRSA av drygt 3400 rapporterade *S. aureus* var 1,2 procent, vilket ur ett europeiskt perspektiv är en låg siffra. VRE påvisades inte alls, och andelen PNSP av de knappt 1000 *S. pneumoniae* var 6,6 procent.

I den andra delen av den nationella resistensövervakningen, tillgänglig i applikationen ResNet, undersöks samma bakteriearter som de som ingår i EARS-Net. Alla kliniska laboratorier ombeds testa isolat från urinvägs-, sår- eller luftvägsinfektioner, och avsikten är att bättre kunna spegla situationen i öppenvården. Andelen resistenta bakterieisolat i de båda övervakningssystemen är dock förvånansvärt lika.

För vissa bakteriearter krävs speciella övervakningsprogram och/eller speciallaboratorier som kan utföra analyserna. Det gäller dels tarmbakterien *Clostridium difficile* som kan orsaka svåra diarré-tillstånd, och dels bakteriearterna *Neisseria gonorrhoeae* (gonokocker), *N. meningitidis* (meningokocker) och *Mycobacterium tuberculosis* (tuberkulos-bakterien). Övervakningsprogrammet för *C. difficile* visade att resistens mot moxifloxacin var kopplat till vissa typer av bakterien och också till olika regioner i landet. Hos *N. gonorrhoeae* ses en alltmer ökad frekvens av stammar som är resistenta mot de antibiotika som är sistahandsalternativ för empirisk terapi, medan problemen med resistens inte finns på samma sätt hos *N. meningitidis*. Resistens hos *M. tuberculosis* är en ständigt aktuell frågeställning, och den noggranna övervakningen i Sverige visar att situationen än så länge är under kontroll.

Resistens hos kliniska isolat från djur

Bakterier som orsakar sjukdom hos djur är oftast känsliga för antibiotika som används vid behandling. Bakterier som orsakar luftvägsinfektioner hos lantbrukets djur och hos hästar är exempelvis generellt känsliga för bensylpenicillin. Penicillinresistens är däremot vanligt hos *Staphylococcus pseudintermedius* från hundar och förekommer hos *Staphylococcus aureus* från hästar. Resistens hos *Escherichia coli* från flera djurslag förekommer också men är vanligast hos isolat från träckprover från unga kalvar. Resistensundersökning är motiverad för val av rätt antibiotikum vid behandling, särskilt för stafylokocker och *Escherichia coli*.

Indikatorbakterier från friska djur

Resistens hos *Escherichia coli*, *Enterococcus faecalis* och *Enterococcus faecium* från tarmfloran hos friska djur indikerar utbredningen av förvärvad resistens hos bakterier i en djurpopulation och indirekt antibiotikaanvändningens omfattning. Även om bakterierna sällan orsakar sjukdom kan de vara reservoarer för resistensgener som kan spridas till sjukdomsframkallande bakterier hos djur och människor. I Sverige är förekomsten av resistens hos dessa indikatorbakterier låg hos de flesta undersökta djurslag och i ett internationellt perspektiv är situationen gynnsam.

Summary

The Swedish situation regarding antimicrobial resistance in bacteria from humans and animals is still favorable when seen in an international perspective. This confirms that the Swedish strategies to promote rational use and to contain antimicrobial resistance in bacteria from animals and humans are effective. Still, this year's report also describes unfavorable trends, e.g. several hospital outbreaks with VRE.

Use of antimicrobials

Antibiotic use in humans

The total sale of antibiotics decreased by 6 percent in 2013 as compared with 2012 (from 14.2 to 13.4 DDD per 1000 inhabitants and day). In outpatient care, the antibiotic sale decreased by 8 percent, from 374 to 343 prescriptions per 1000 inhabitants and year. The decrease was seen in all age groups and is most evident among children 0-6 years (19 percent). In total, a decreased number of antibiotic prescriptions was seen in all 21 counties during 2013. There are still great regional differences and number of prescriptions per 1000 inhabitants range from 374 in Skåne County to 267 in Västerbotten County. The decrease encompassed all antibiotic groups, except pivmecillinam (J01CA08) and nitrofurantoin (J01XE) which increased. The increase of pivmecillinam and nitrorurantoin is according to guidelines since they are recommended as first line antibiotics for urinary tract infections. Beta-lactamase sensitive penicillins together with tetracyclines were the most commonly used antibiotics in outpatient care.

Antibiotics commonly used to treat respiratory tract infections (RTI) are the most frequently prescribed group of antibiotics and in 2013 the sale decreased by 14 percent. The decrease is mainly related to a great drop in use of doxycycline (18 percent), macrolides (26 percent) and penicillin V (13 percent). The increased frequency of *Mycoplasma pneumoniae* seen during the winter season 2011/2012, as well as a shortage of erythromycin during spring 2013, may affect the statistic and can partly explain the decrease of macrolides and doxycycline during 2013. However, the decrease in sale of antibiotics commonly used to treat RTI is noticeable throughout the year. This indicates other explanations for the great drop.

Treatment of lower urinary tract infections (UTI) in women appears to follow national recommendations. Usage of the two first line recommended substances, pivmecillinam and nitrofurantoin, has gradually increased and in 2013 these substances represented 77 percent of the total sale of antibiotics commonly used to treat UTI in this population. In 2013, the sale of fluoroquinolones and trimethoprim continued to decrease (5 percent and 15 percent respectively) according to recommendations.

The total sale of antibiotics in hospital care decreased by 1.8 percent during 2013, from 1.63 DDD per 1000 inhabitants and day in 2012 to 1.60 in 2013. This is the first year since 2000 with a decreased antibiotic sale in hospital care. The decrease in the sale of cephalosporins that have been evident the latest years continued, from 2006 to 2013 the sales decreased by 51 percent. There is also a shift from second generation to third generation cephalosporins as these substances provide a more secure empirical antibiotic treatment. Broad spectrum antibiotics such as carbapenems and piperacillin with tazobactam are used more often and there is a possible connection to an increased number of infections caused by bacteria with ESBL.

Sale of antifungals

Compared to 2012, the total sale of antifungal drugs for systemic use increased by 2 percent, yielding a national average of 61 DDD per million inhabitants and day. Every year since 2000 except for 2011 there has been a small but steady increase in the total sale of antifungals. Since the year 2000 when the total sale was 40 DDD per million inhabitants and day, the increase has been 50 percent.

Fluconazole still constitutes the absolute majority of the antifungals sale, 67 percent or 41 DDD per million inhabitants and day. Amphotericin B is the second most used compound. The sale of amphotericin B increased by 40 percent compared to 2012, and now stands for 12 percent of the total sale of antifungals.

Since 2005 there has been a small but steady increase in the sale of the echinocandins. In 2013 the sale increased by 8.5 percent, making the total amount 7.0 DDD per million inhabitants and day, and the group now constitutes 12 percent of all systemic antifungals used in hospitals. The sale of caspofungin which has been available in Sweden since 2002 has reduced for every year. It now constitutes 60 percent of the echinocandins down from 78 percent in 2012. Anidulafungin increased its share from 18 percent to 30 percent last year. The third member of the group micafungin that for the first time appeared in the statistics last year now constitutes 10 percent of the total echinocandin sale. Many of the counties with tertiary care hospitals have largely increased their use of both anidulafungin and micafungin at the expense of caspofungin.

Antibiotic sales in veterinary medicine

Following a reregulation of the Swedish pharmacy market, concerns have been raised about lack of completeness of sales data from pharmacies. Most likely, this problem primarily affects sales of injectable drugs. SVA has estimated the lack of completeness to 5-10 percent of the total sales.

Expressed as mg per 'population correction unit' (PCU), the sales in 2012 were 14 mg/PCU. This is 25 percent lower than in 2009. Thus, even if the lack of completeness is taken into account there is a decrease in sales over time

Comparing sales for humans and animals

When antimicrobials sold for systemic use and as intestinal anti-infectives were compared, a total of 62.5 and 10.8 tonnes were used in human and veterinary medicine, respectively. Human use by far outweighs animal use for most classes, except for trimethoprim-sulphonamides and aminoglycosides.

Notifiable resistance

ESBL

A total of 8131 cases of extended spectrum betalactamase (ESBL)-producing Enterobacteriaceae were notified in 2013, corresponding to an incidence of 84 cases per 100 000 inhabitants. The increase was 13 percent compared to 2012, and it was seen in 16 counties. The most commonly reported species was *Escherichia coli* with 88 percent of all cases, followed by *Klebsiella pneumoniae* with 7 percent. Most ESBL-producing bacteria were found in urine samples (59 percent), and the increasing prevalence will soon complicate the empiric treatment of these relatively harmless infections.

A special type of ESBLs, so called $ESBL_{CARBA}$, constitutes a more vicious resistance mechanism. Bacteria with this extended resistance mechanism became notifiable from both clinicians and laboratories in 2012. Thirty-nine cases were detected in 2013, and the two most common types of enzymes were NDM and OXA-48. It is necessary to have an active surveillance of these new extremely resistant bacteria in order to detect them at an early stage and thereby hinder their spread within the health care system, because the treatment alternatives are few if any.

The available data indicate that ESBL-producing bacteria are rare in animals in Sweden. An exception is poultry where *Escherichia coli* producing CMY-2 ($ESBL_{M}$) is found in intestinal content in a large proportion of birds. However, transmission of such bacteria to humans seems to be rare since this type of ESBL-resistance is uncommon in isolates from humans.

MRSA

The total number of cases of methicillin resistant *Staphylococcus aureus* (MRSA) was 2454 in 2013, an increase by 17 percent compared to 2012. According to the systematically reviewed notification reports, the infection was acquired in Sweden (43 percent) only slightly more often than abroad (37 percent), but in many cases the country of acquisition could not be defined. Community-acquired infections dominated among domestic cases (65 percent) but were less frequent among imported cases (45 percent). Hospital-acquired infections were comparatively more common in imported cases (30 percent) than among domestic cases (13 percent), indicating continued good compliance to basic hygiene principles among healthcare staff. Forty-two invasive isolates of MRSA were reported in 2013. Epidemiological typing of isolates by *spa*-typing showed that the five most commonly encountered *spa*-types in 2011 were t008, t002, t223, t044, and t127. The prevalence of MRSA with PVL toxin had increased to 37 percent.

The prevalence of MRSA in animals is still low which limits spread from animals to humans. During 2013, MRSA was isolated from five dogs, one cat, one horse and one dairy cow. In companion animals, the same types of MRSA as in humans dominate, indicating a human source of MRSA in these animals. In horses, livestock-associated MRSA CC398 dominates.

MRSP

In 2013, 33 cases of methicillin resistant *Staphylococcus pseudintermedius* (MRSP) in dogs and cats were reported. The number of cases each year has declined since 2009 when 130 cases were notified. No human cases were reported in 2013 but MRSP is not generally notifiable to the national authorities.

PNSP

In 2012 the definition for *Streptococcus pneumoniae* with reduced susceptibility to penicillin (PNSP) was changed to include only isolates with MIC of penicillin > 1 mg/L, and this resulted in a dramatic decrease in reported cases. In order to follow and evaluate the effect of vaccination against pneumococcal disease, SMI has continued to collect and perform serotyping on PNSP-isolates according to the previous definition (MIC ≥ 0.5 mg/L). The most commonly encountered serotypes were 19F, 35B, 19A, NT, 6B, 3, 14, 9V and 23F.

VRE

In 2013 a total of 227 new cases of vancomycin resistant enterococci (VRE) were reported, an increase with 49 percent compared to 2012. The majority of isolates were *Enterococcus faecium*, and in contrast to 2013 isolates with resistance gene *vanB* outnumbered those with *vanA* gene. Ten healthcare related outbreaks were reported from six counties, all with *E. faecium*, six with *vanA* and four with *vanB*. The largest outbreak, in Gävleborg county, is still ongoing (April 4 2014), and comprises approximately 200 cases so far.

Previous data from SVARM show that *Enterococcus faecium* with the *vanA* gene are present among Swedish broilers. The majority of human cases of VRE with the *vanA* gene was associated with health care abroad or outbreaks in Swedish hospitals and therefore an association to Swedish broilers seems unlikely.

Zoonotic pathogens

Salmonella is rare in animals in Sweden and few incidents involve multiresistant strains. ESBL-resistance has not been found and resistance to fluoroquinolones is rare. The favorable situation makes animals in Sweden an unlikely source of resistant *Salmonella* infecting humans.

Campylobacter from animals in Sweden are mostly susceptible and for example resistance to erythromycin is most uncommon. A substantial proportion of *Campylobacter jejuni* from cattle and broiler meat are however resistant to quinolones. Nevertheless, animals in Sweden are an unlikely source for *Campylobacter* with the high resistance levels seen in isolates from humans.

Human clinical isolates

EARS-Net surveillance

Invasive isolates of seven defined bacterial species have been reported to EARSS/EARS-Net since 2000. *Escherichia coli* was the most frequently found pathogen in blood cultures and

constituted 22 percent, followed by *Staphylococcus aureus* at 11 percent. The five other pathogens in the EARS-Net system were all much less frequently found. In *E. coli* and *K. pneumoniae* the levels of resistance to third generation cephalosporins had increased to 4.9 and 3.1 percent, respectively. MRSA isolates accounted for 1.2 percent of all invasive *Staphylococcus aureus*, which is low in the European perspective. The rates of non-susceptibility to penicillins in *Streptococcus pneumoniae* (referred to as PNSP) was higher than in previous years, now 6.6 percent. There were no VRE reported among invasive isolates of *Enterococcus faecalis* and *Enterococcus faecium*, but high-level resistance to aminoglycosides (HLAR) was common with 13 and 20 percent, respectively.

National surveillance and quality assurance programme, displayed in ResNet

The same bacterial species as in EARS-Net are part of the ResNet programme, but samples from urinary tract infections (*E. coli* and *K. pneumoniae*), skin and soft tissue infections (*S. aureus*), respiratory tract infections (*S. pneumoniae* and *H. influenzae*) or all sources (*P. aeruginosa*) are included. In general, the same rates of resistance were found in these two programmes.

Other bacterial species are included in special surveillance programmes and are often referred to special laboratories, like *Clostridium difficile* and *Mycobacterium tuberculosis* (SMI), and *Neisseria gonorrhoeae* and *N. meningitidis* (National reference laboratory in Örebro).

Surveillance of *C. difficile* showed that moxifloxacin resistance was related to certain types of the pathogen and also to certain regions of Sweden. Among *N. gonorrhoeae* there is an increasing frequency of strains resistant to the antibiotics of last resort for empiric therapy, whereas there are no such problems in *N. meningitidis*. Rates of resistance to antituberculosis drugs in *M. tuberculosis* are carefully monitored and the situation seems to be under control.

Animal clinical isolates

Bacteria causing clinical disease in animals are mostly susceptible to relevant antimicrobials. Respiratory pathogens from farm animals and horses are generally susceptible to bensylpenicillin. Penicillin resistance is common in *Staphylococcus pseudintermedius* from dogs and occurs in *Staphylococcus aureus* from horses. Resistance in *Escherichia coli* occurs in all animals but is most prominent in enteric isolates from young calves. Susceptibility testing to guide antimicrobial therapy is especially warranted for staphylococci and *Escherichia coli*.

Indicator bacteria from healthy animals

Resistance in *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus faecium* from the enteric flora of healthy animals indicates the prevalence of acquired resistance in an animal population and indirectly the magnitude of antimicrobial use. These bacteria are unlikely to cause disease but they can be reservoirs for resistance genes that can spread to bacteria that cause infections in animals or humans. Prevalence of resistance in indicator bacteria from Swedish animals is low and the situation is favorable in an international perspective.

Guidance for readers

The SWEDRES-SVARM report is the result of cooperation between the Public Health Agency of Sweden and the National Veterinary Institute to present data relating to both humans and animals on the use of antimicrobials and on antimicrobial resistance. Data on occurrence of notifiable diseases caused by resistant bacteria as well as data on resistance in zoonotic bacteria and in bacteria from clinical submissions is presented. In addition, data on resistance in so called indicator bacteria from healthy animals and from food of animal origin is presented.

Data on resistance in bacteria from humans is obtained from several sources and national programmes and compiled by the Public Health Agency of Sweden in SWEDRES. In contrast, data on animals and food, compiled by the National Veterinary Institute, is from the national monitoring programme in the veterinary field SVARM. This programme is specifically designed to monitor resistance in bacteria from animals and food and is organized and run at the National Veterinary Institute. However, data presented in this report also emanate from other sources such as the SVARMpat project and specific research projects. For details on data sources see section Background material and references.

Antimicrobial resistance

SWEDRES

Most of the data on resistance in SWEDRES is from routine susceptibility testing at clinical laboratories. The results are mostly presented as percent resistance in tables or graphs. The methods used for antimicrobial susceptibility testing, whether MIC determination or disk diffusion inhibition zones, are standardized by European Committee on Antimicrobial Susceptibility Testing (EUCAST) and available online at www.eucast.org. EUCAST also presents yearly updated interpretative criteria for clinical use in human medicine, i.e. clinical breakpoints, also available at www.eucast.org. In SWEDRES, only MIC results for *Clostridium difficile* were interpreted using ECOFFs.

SVARM

All data on resistance in SVARM is from MIC determinations performed at the National Veterinary Institute using broth microdilution following the standards of the Clinical and Laboratory Standards Institute (CLSI 2014). MICs for isolates of zoonotic and indicator bacteria are interpreted by ECOFFs and also clinical isolates from animals are classified by ECOFFs when such values are available. Interpretive criteria used are given in the section Materials and methods, resistance in bacteria from animals.

ECOFFs classify isolates with acquired reduced susceptibility as non-wild type (see above), In SVARM, non-wild type isolates are called “resistant”. This classification is relevant for monitoring purposes, but it should be understood that resistance defined in this manner not always implies clinical resistance.

Since the first report from SVARM, some interpretive criteria (ECOFFs) have been changed by EUCAST. To facilitate comparisons when retrospect data is presented, levels of resistance have been recalculated using current interpretive criteria if not otherwise stated.

Indicator bacteria in SVARM

In SVARM, *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus faecium* serve as indicators for presence of antimicrobial resistance in the enteric flora of healthy animals and in the flora contaminating food. The prevalence of acquired resistance in such commensal bacteria in animals indicates the magnitude of the selective pressure from use of antimicrobials in an animal population. Most bacteria of the enteric flora are unlikely to cause disease, but they can be reservoirs for resistance genes that can spread to bacteria that cause infections in animals or humans. Prevalence of resistance in indicator bacteria contaminating meat indicates the magnitude of the potential human exposure to such reservoirs in food producing animals.

Presentation of MIC distributions in SVARM

Results from MIC determinations are presented as distributions of MICs in tables of a uniform design as below. Distributions are given as percentages of isolates tested. In the tables, white fields denote range of dilutions tested for each antimicrobial and vertical bold lines indicate cut-off values used to define resistance.

The percentage of isolates with a certain MIC of an antimicrobial is given in the corresponding white field. For MICs above the range tested of an antimicrobial (>X mg/L)

Example of a table with distributions of MICs

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)											
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ciprofloxacin	21	21.0	52.0	6.0			1.0			20.0			
Erythromycin	0				93.0	4.0	3.0						
Tetracycline	2		75.0	22.0	1.0			1.0	1.0				

Abbreviations of generic antimicrobial names

When abbreviations for antibacterials were needed in tables or graphs the following were used.

Amp	Ampicillin	Ery	Erythromycin	Oxa	Oxacillin
Bac	Bacitracin	Flf	Florfenicol	Pen	Penicillin G
Caz	Ceftazidime	Fox	Cefoxitin	Rif	Rifampicin
Cdr	Cefadroxil	Fus	Fusidic acid	Str	Streptomycin
Cer	Ceftiofur	Gen	Gentamicin	Sul	Sulphonamide
Cet	Cephalothin	Imp	Imipenem	Tet	Tetracycline
Chl	Chloramphenicol	Kan	Kanamycin	Tmp	Trimethoprim
Cip	Ciprofloxacin	Lin	Linezolid	Tsu	Trimethoprim-sulphonamide
Cli	Clindamycin	Mec	Mecillinam	Tob	Tobramycin
Col	Colistin	Mer	Meropenem	Van	Vancomycin
Ctx	Cefotaxime	Nal	Nalidixic acid	Vir	Virginiamycin
Enr	Enrofloxacin	Nar	Narasin		

the percentage is given in the field closest to the range, i.e. in the first shaded field to the right of the tested range. For MICs equal to or lower than the lowest concentration tested for an antimicrobial (≤Y mg/L) the percentage is given as the lowest tested concentration, i.e. in the first white field of the tested range.

Multidrug resistance

The terms multidrug resistance (MDR), multiresistance and multiresistant are in SVARM used for isolates with phenotypically identified acquired resistance to three or more antimicrobial classes. This implies, for example, that resistance to ciprofloxacin, enrofloxacin and nalidixic acid represents resistance to one class of antimicrobials.

Antimicrobial use

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

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

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

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

Treatment recommendations are adopted locally by the county drug and therapeutics committee, and therefore the prescribed daily doses for certain indications can vary between counties. This should be kept in mind, as it may affect the comparisons based on the statistics.

Abbreviations

ABU	Asymptomatic bacteriuria
AST	Antibiotic susceptibility testing
ATC	Anatomical therapeutic chemical classification system
BLNAR	Beta-lactamase negative ampicillin resistant (in *Haemophilus influenzae*)
CC	Clonal cluster, used in the context of epidemiological typing
CDA	Communicable disease act
CDI	*Clostridium difficile* infection
CMO	County medical officer
DDD	Defined daily dose
ECDC	European Centre for Disease Prevention and Control
ECOFF	Epidemiological cut-off value for non-susceptibility
EARSS/EARS-Net	European antimicrobial resistance surveillance system/network
ESC	Extended spectrum cephalosporin
ESBL	Extended spectrum beta-lactamase
$ESBL_A$	Extended spectrum beta-lactamase, plasmid-mediated, inhibited by clavulanic acid (A = classical)
$ESBL_M$	Extended spectrum beta-lactamase inhibited by cloxacillin, also called plasmid-mediated AmpC (M = miscellaneous)
$ESBL_{CARBA}$	Extended spectrum beta-lactamase with activity against carbapenems
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GAS	Group A streptococci or *Streptococcus pyogenes*
GBS	Group B streptococci or *Streptococcus agalactiae*
HLAR	High-level aminoglycoside resistance (e.g. in Enterococcus)
ICU	Intensive care unit
MDR	Multidrug resistance
MIC	Minimal inhibitory concentration
MLST	Multilocus sequence typing
MRB	Multi-resistant bacteria
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSP	Methicillin resistant *Staphylococcus pseudintermedius*
NordicAST	Nordic Committee on Antimicrobial Susceptibility Testing
PFGE	Pulsed-field gel electrophoresis
PNSP	Penicillin non-susceptible pneumococci
PRIS	Primary care record of infection in Sweden
PVL	Panton-Valentine leukocidin
ResNet	Webb application for Resistance surveillance and quality control programme
RTI	Respiratory tract infection
spa	The gene coding for staphylococcal protein A
SSTI	Skin and soft tissue infection
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
TB	Tuberculosis
UTI	Urinary tract infection
VRE	Vancomycin resistant enterococci
XDR	Extreme drug resistance (used for *Mycobacterium tuberculosis*)

Use of antimicrobials

Total sales of antibiotics in humans

In 2013, the total sale of antibiotics (J01 excl. methenamine) in Sweden (outpatient care and hospital care) decreased by 6% compared with 2012 (from 14.2 to 13.4 DDD per 1000 inhabitants and day), Table 1.1.

Eighty-eight percent of all antibiotics sale in Sweden 2013 were sold on prescriptions, Figure 1.1. This proportion vary within the country, from 91% in Halland County to 84% in Västerbotten County, Figure 1.2. Even though the majority of all antibiotics is prescribed in outpatient care, studies have shown that one of three inpatients in Swedish hospitals are treated with antibiotics.

The overall consumption has followed a wavy pattern over the years. In total, the sale of antibiotics has decreased with 7% since 2000, from 14.5 to 13.4 DDD per 1000 inhabitants and day, Figure 1.1.

Beta-lactamase sensitive penicillins and tetracyclines are the two antibiotics that were used in greatest amount in Sweden in 2013, Figure 1.3.

TABLE 1.1. Sales of antibiotics in outpatient care (sale on prescriptions) and in hospital care (sale on requisition including hospitals and parts of nursing homes) in Sweden, 2000-2013, DDD/1000 inhabitants and day. Hospital data for 2013 excludes Jönköping county November-December 2013.

		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
J01 exclusive J01XX05	Total care	14.5	14.7	14.4	14.4	14.1	14.6	15.0	15.4	15.2	14.4	14.3	14.5	14.2	13.4
J01 exclusive J01XX05	Outpatient care	13.1	13.3	13.0	12.8	12.6	13.0	13.3	13.7	13.5	12.8	12.7	12.8	12.5	11.7
J01 exclusive J01XX05	Hospital care	1.18	1.22	1.25	1.33	1.36	1.43	1.49	1.55	1.52	1.48	1.52	1.59	1.63	1.60
J01	Total care	16.1	16.3	16.1	16.1	16.0	16.5	16.9	17.3	16.8	15.8	15.7	15.7	15.5	14.7
J01	Outpatient care	14.6	14.8	14.6	14.5	14.3	14.8	15.1	15.4	15.1	14.2	14.0	14.0	13.8	13.0
J01	Hospital care	1.21	1.25	1.27	1.37	1.43	1.50	1.56	1.62	1.57	1.52	1.55	1.61	1.65	1.62
J01XX05	Total care	1.56	1.55	1.64	1.72	1.86	1.88	1.88	1.81	1.60	1.43	1.33	1.28	1.27	1.24
J01XX05	Outpatient care	1.48	1.49	1.60	1.67	1.78	1.80	1.81	1.74	1.55	1.40	1.30	1.26	1.25	1.22
J01XX05	Hospital care	0.03	0.03	0.03	0.05	0.07	0.07	0.07	0.07	0.05	0.03	0.03	0.02	0.02	0.02

FIGURE 1.1. Sale of antibiotics (J01 excl. methenamine) in outpatient care (sale on prescriptions) and in hospital care (sale on requisition including hospitals and parts of nursing homes) in Sweden, 2000-2013, DDD/1000 inhabitants and day. Hospital data for 2013 excludes Jönköping county November-December 2013.

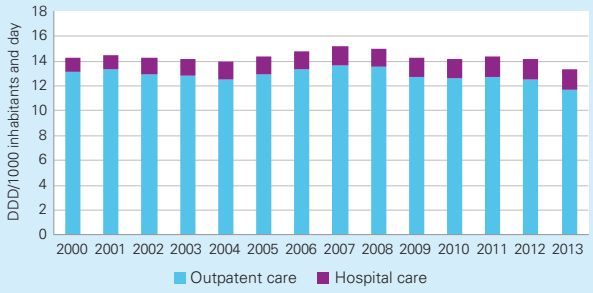


FIGURE 1.2. Sale of antibiotics (J01 excl. methenamine) in outpatient care (sale on prescriptions) and in hospital care (sale on requisition including hospitals and parts of nursing homes) per county, 2013, DDD/1000 inhabitants and day. Hospital data for 2013 excludes Jönköping county November-December 2013.

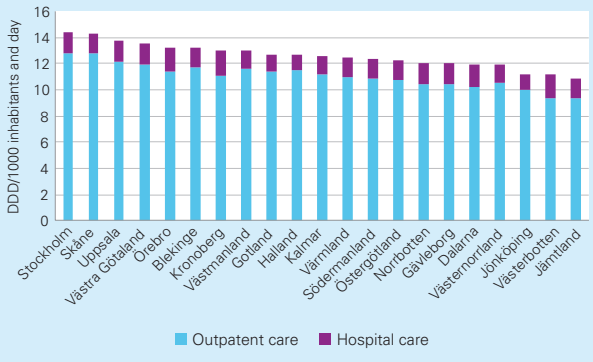
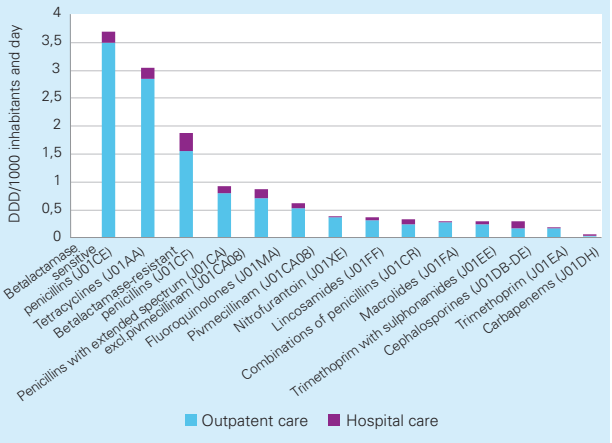


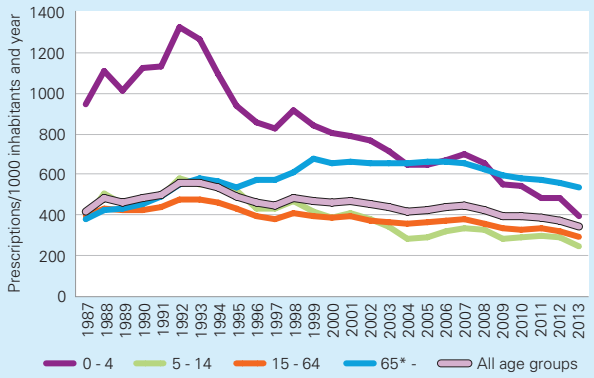
FIGURE 1.3. Antibiotics (ATC-5) in outpatient care (sale on prescriptions) and hospital care (sale on requisition including hospitals and parts of nursing homes) in 2013, DDD/1000 inhabitants and day.



Antibiotics in outpatient care

Sales of antibiotics in outpatient care (includes all sales on prescriptions) continued to decrease (8%) in 2013, from 374 to 343 prescriptions per 1000 inhabitants and year, Figure 1.4.

FIGURE 1.4. The sales of antibacterial drugs for systemic use in outpatient care (sales on prescriptions) 1987- 2013, prescriptions/1000 inhabitants and year, both sexes, different age groups. The sale in 2013 decreased in all age group.



*1987-2000 includes antibiotic sale to people aged 65 -99 years. From 1999, the statistic includes antibiotic sale on Apo-Dose.

The decrease in antibiotic sale during 2013 was seen in all age groups and is most evident among the youngest age groups, 0-4 years and 5-14 years (19% and 16% respectively). In children, 0-4 years, the sale has decreased by 70% since 1992, from 1328 to 392 prescriptions per 1000 inhabitants and year.

Since 2009, the age group 65 year and older has the highest use of antibiotics in Sweden, measured as prescriptions per 1000 inhabitants and year, Figure 1.4. As mentioned earlier in the chapter Guidance for readers, some of the antibiotic use among elderly people is not included in the statistics and possible under-reporting in the age group 65 years and older must be taken into account. A closer look into these age groups shows a steady decrease (65-69 years, 70-79 years and 80 years and older) and that the greatest reduction since year 2000 is seen among the oldest (80 years and above), from 928 to 654 prescriptions per 1000 inhabitants and year, Table 1.2.

The decrease in antibiotics sale in outpatient care during 2013 encompasses a majority of all antibiotic groups, except nitrofurantoin (J01XE) and pivmecillinam (J01CA08), two antibiotics commonly used to treat lower urinary tract infections in women, Figure 1.5.

Beta-lactamase sensitive penicillins (J01CE) and tetracyclines (J01AA) were the most commonly prescribed antibiotics in 2013, Figure 1.5 and Table 1.2. The sale of beta-lactamase sensitive penicillins (J01CE) decreased by 13%, from 116 to 101 prescriptions per 1000 inhabitants in 2013 compared with 2012. Doxycycline (J01AA02) is the most frequently used tetracycline and represents 74% of the sales in this group of substances measured as prescriptions per 1000 inhabitants and year.

Macrolides (J01FA) and tetracyclines (J01AA) are the two antibiotic groups with the greatest decrease during 2013 compared with 2012 (26% and 15% respectively), Figure 1.5. Both macrolides and tetracyclines are antibiotics commonly used to treat infections caused by *Mycoplasma pneumoniae* and during the winter season 2011/2012 an increased frequency of *Mycoplasma pneumoniae* was seen in Sweden (Linde A et al., 2012). The frequency of *Mycoplasma pneumoniae* has decreased since winter season 2011/2012 which can partly explain the decreased sale of macrolides and tetracyclines. In addition, there was a shortage of erythromycin (J01FA01) during spring 2013, which may also explain some of the observed reduction in macrolide use. However, a great

FIGURE 1.5. Sales of antibiotics in outpatient care (includes sale on prescriptions) 2000-2013, prescriptions/1000 inhabitants and year, both sexes, all ages. The data are sorted according to ATC codes. All agents except pivmecillinam and nitrofurantoin decreased during 2013.

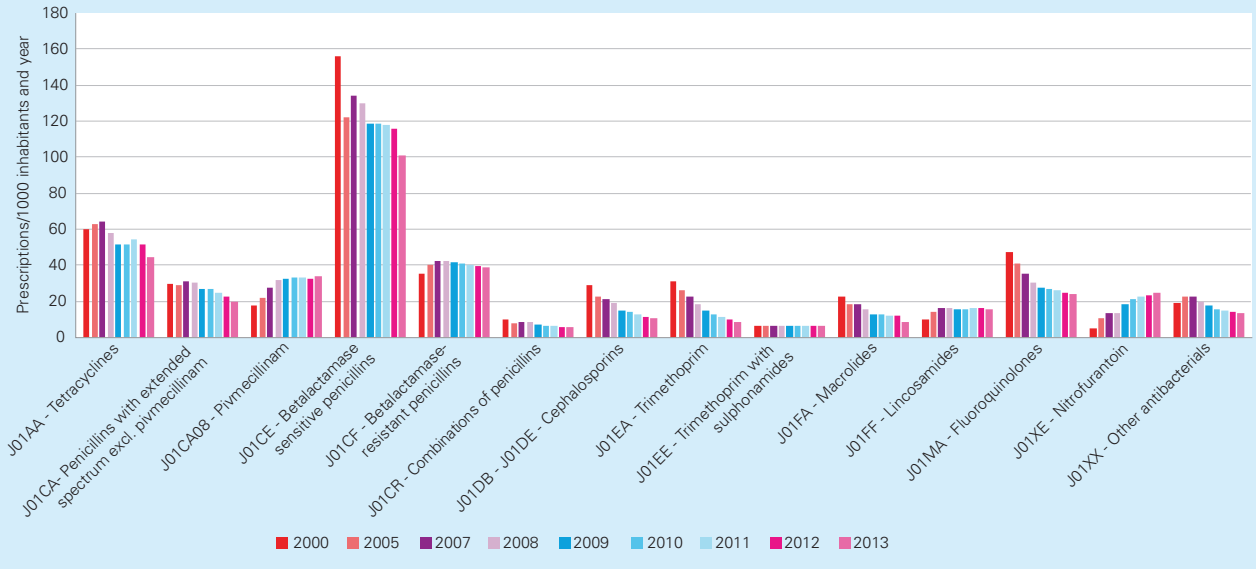
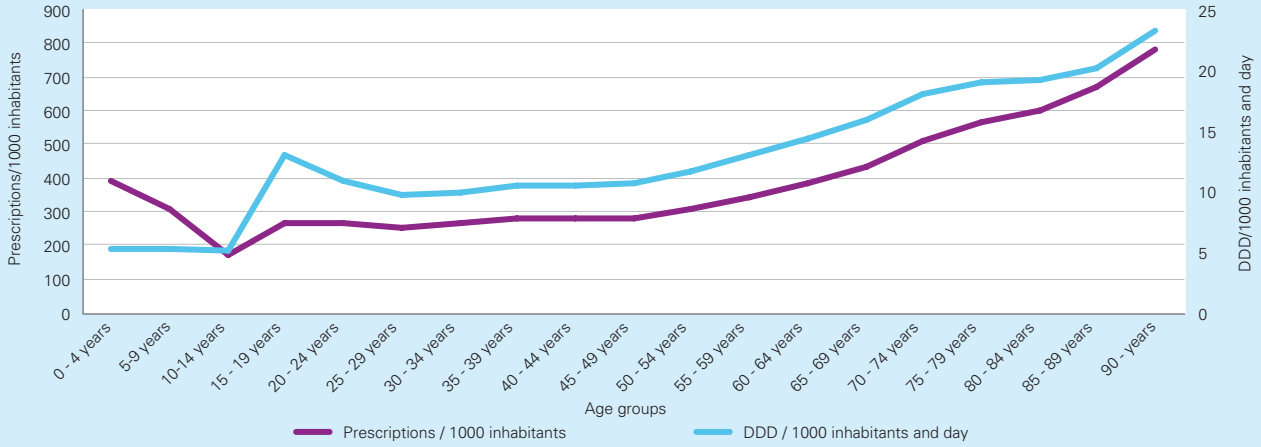


FIGURE 1.6. Sales of antibiotics (J01 excl. methenamin) in outpatient care (sales on prescriptions) in different age groups, measured by both prescriptions/1000 inhabitants and year and as DDD/1000 inhabitants and day, in 2013.



decrease in the sales are seen in most of the antibiotic groups during 2013, Figure 1.5 and Table 1.2. There are probably additional reasons and explanations for the large reduction which will be discussed in coming chapters.

Gender differences

Out of all antibiotic prescribed in Sweden during 2013, 60% were prescribed to females and 40% to males. This proportion has almost been constant over time and the decrease in antibiotic use that has been seen during the last years has affected both genders equally. During 2013, the antibiotic sale decreased by 9% (men) and 8% (females). Read more about gender differences in antibiotic use in SWEDRES 2011 (SWEDRES/SVARM 2011).

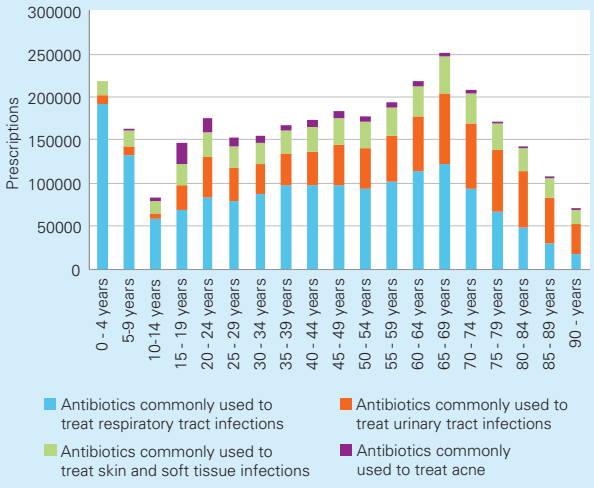
Antibiotics commonly used to treat RTI, UTI and SSTI

In different age groups

The antibiotic use is greatest in the age groups 65 years and older, both measured as prescriptions/1000 inhabitants and years or as DDD/1000 inhabitants and day, Figure 1.6. However, even though the antibiotic use is high among children and the elderly, other age groups represent a great share of the total antibiotic consumption, Figure 1.7.

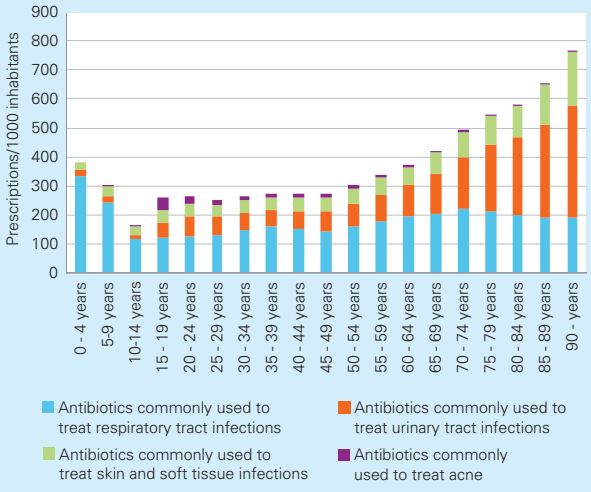
Figure 1.7 and 1.8 illustrate the consumption of different antibiotics in different age groups. In children, antibiotic commonly used to treat respiratory tract infections are the most frequently prescribed antibiotics and represents 90% of the total antibiotic sale. In the elderly age groups antibiotic commonly used to treat urinary tract infections are as

FIGURE 1.7. Antibiotics commonly used to treat: respiratory tract infections (J01AA02*, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infections (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), skin and soft tissue infections (J01FF01 and J01CF05), acne (J01AA02**, J01AA04, J01AA06 and J01AA07), both sexes, different age groups, prescriptions in 2013.



*Excludes packages containing more than 50 tablets,
** Includes packages containing more than 50 tablets.

FIGURE 1.8. Antibiotics commonly used to treat: respiratory tract infections (J01AA02*, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infections (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), skin and soft tissue infections (J01FF01 and J01CF05), acne (J01AA02**, J01AA04, J01AA06 and J01AA07), both sexes, different age groups, prescriptions/1000 inhabitants in 2013.



*Excludes packages containing more than 50 tablets,
** Includes packages containing more than 50 tablets.

TABLE 1.2. Antibiotics in outpatient care, classes of antibiotics and age groups. DDD/1000 inhabitants and day, prescriptions/1000 inhabitants and year and user/1000 inhabitants and year.

Age groups (years)	DDD/1000 and day							Prescriptions/1000 and year							User/1000 and year						
	2007	2008	2009	2010	2011	2012	2013	2007	2008	2009	2010	2011	2012	2013	2007	2008	2009	2010	2011	2012	2013
Tetracyclines (J01AA)																					
0-6	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0
7-19	3.23	3.25	3.31	3.40	3.48	3.29	3.06	33.9	32.0	31.6	32.5	35.1	31.2	27.6	21.3	19.5	19.2	20.1	22.9	19.6	16.8
20-64	3.77	3.56	3.30	3.35	3.54	3.43	3.10	71.9	64.5	56.2	56.3	60.2	56.5	47.7	56.3	50.3	43.6	43.8	47.2	43.8	36.4
65-79	4.21	3.99	3.64	3.60	3.78	3.75	3.36	98.8	90.6	79.9	78.0	81.1	80.0	68.9	75.4	68.8	61.2	60.1	62.1	61.3	52.5
80-	2.93	2.77	2.43	2.32	2.35	2.41	2.15	77.8	71.7	62.2	58.6	58.8	59.8	52.5	62.1	57.1	49.7	46.8	47.2	47.7	41.9
All age groups	3.44	3.28	3.08	3.11	3.25	3.15	2.85	64.3	58.3	51.7	51.6	54.7	52.0	44.4	49.0	44.1	38.8	38.9	41.7	39.2	33.1
Penicillins with extended spectrum (J01CA) excl. Pivmecillinam (J01CA08)																					
0-6	1.74	1.70	1.52	1.62	1.35	1.32	1.07	95.2	90.8	72.7	73.3	59.1	54.9	43.8	72.5	69.0	56.5	57.4	45.3	42.1	33.6
7-19	0.46	0.43	0.39	0.43	0.43	0.37	0.32	14.5	13.6	11.8	12.4	12.0	10.1	8.5	12.7	11.7	10.1	10.6	10.1	8.3	6.9
20-64	0.84	0.82	0.72	0.73	0.69	0.64	0.59	21.2	20.6	18.2	18.0	16.9	15.4	13.9	18.1	17.4	15.4	15.3	14.1	12.6	11.2
65-79	1.74	1.75	1.67	1.62	1.59	1.55	1.50	45.6	45.0	41.7	40.2	38.7	37.0	34.3	36.5	35.8	32.8	31.9	30.6	29.2	26.8
80-	1.79	1.82	1.76	1.74	1.75	1.77	1.73	46.8	46.5	44.0	42.1	41.0	39.7	37.7	38.0	37.9	35.4	34.1	33.2	32.3	30.4
All age groups	1.02	1.01	0.93	0.94	0.89	0.85	0.79	31.0	30.5	26.9	26.9	24.4	22.7	20.1	24.7	23.9	21.1	21.1	19.3	17.7	15.6
Pivmecillinam (J01CA08)																					
0-6	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.5	0.7	0.8	1.1	1.0	1.0	1.0	0.5	0.6	0.8	1.0	1.0	0.9	0.9
7-19	0.19	0.24	0.24	0.24	0.22	0.21	0.20	12.4	15.5	16.1	15.9	15.7	14.4	13.8	10.9	13.5	13.9	13.9	13.5	12.5	12.0
20-64	0.38	0.45	0.45	0.46	0.45	0.44	0.46	23.0	27.8	28.2	28.6	29.2	28.7	29.5	19.6	23.2	23.6	24.0	24.3	23.8	24.3
65-79	0.87	0.98	0.98	0.97	0.95	0.93	0.98	50.6	57.7	57.9	57.5	58.7	57.3	59.3	39.4	44.1	43.7	43.3	44.0	42.8	44.0
80-	1.84	1.94	1.92	1.90	1.79	1.75	1.83	109.3	116.6	115.8	115.0	112.6	109.3	112.3	81.9	85.5	83.9	83.1	81.4	78.4	80.5
All age groups	0.46	0.53	0.54	0.53	0.52	0.51	0.53	27.6	32.2	32.8	33.0	33.5	32.8	33.7	22.5	25.8	26.0	26.2	26.4	25.7	26.3
Beta-lactamase sensitive penicillins (J01CE)																					
0-6	4.03	4.13	3.56	3.71	3.52	3.78	3.07	350.7	343.7	287.4	290.6	271.1	285.9	226.3	251.3	244.4	211.8	218.7	198.8	205.6	169.8
7-19	3.68	3.63	3.46	3.52	3.61	3.47	2.92	142.5	135.0	123.3	124.6	127.5	124.1	103.6	116.3	109.6	100.9	102.1	103.5	99.1	83.9
20-64	4.53	4.43	4.05	3.99	4.09	3.95	3.55	113.0	108.5	98.2	96.8	98.6	95.1	84.8	95.5	91.6	84.3	83.4	85.0	81.4	72.7
65-79	4.42	4.40	4.16	4.01	4.18	3.96	3.86	106.0	104.1	97.8	94.5	98.4	93.9	89.9	89.0	87.4	83.2	81.0	84.4	80.3	76.4
80-	3.36	3.50	3.38	3.29	3.33	3.34	3.24	84.2	85.7	81.7	79.5	80.4	81.0	78.3	72.3	72.7	69.9	68.3	69.5	69.6	67.4
All age groups	4.30	4.25	3.96	3.93	3.99	3.88	3.49	134.3	130.0	118.6	118.4	117.7	115.7	101.1	108.8	104.9	96.2	96.1	96.2	93.5	82.7
Beta-lactamase resistant penicillins (J01CF)																					
0-6	0.33	0.33	0.31	0.30	0.28	0.29	0.26	32.9	32.8	30.8	29.4	28.0	29.0	26.1	25.9	25.6	24.3	23.4	22.0	22.9	20.4
7-19	0.69	0.80	0.79	0.77	0.76	0.77	0.78	31.9	31.9	31.2	31.0	30.0	28.5	27.8	26.2	26.0	25.4	25.5	24.6	23.1	22.6
20-64	1.04	1.22	1.20	1.18	1.19	1.27	1.31	34.9	34.8	34.0	34.2	33.9	33.0	32.2	27.6	27.4	26.9	27.4	27.0	26.3	25.6
65-79	2.24	2.63	2.55	2.52	2.51	2.67	2.77	61.4	62.5	60.8	60.0	58.5	58.1	57.1	40.4	40.9	39.9	40.3	39.5	38.6	38.1
80-	4.40	4.99	4.92	4.92	4.69	4.85	5.11	122.6	122.1	119.4	113.2	106.2	103.2	103.2	68.0	67.1	65.5	66.8	64.8	63.2	63.4
All age groups	1.25	1.46	1.45	1.43	1.42	1.51	1.56	42.2	42.3	41.7	41.3	40.3	39.5	38.7	30.9	30.8	30.2	30.6	29.9	29.2	28.5
Combinations of penicillins (J01CR)																					
0-6	0.75	0.67	0.52	0.39	0.28	0.26	0.21	52.7	46.4	33.7	25.3	17.8	16.7	13.9	36.2	31.9	24.0	17.9	12.3	11.1	8.8
7-19	0.21	0.20	0.18	0.17	0.16	0.14	0.14	6.4	6.0	5.4	4.9	4.7	4.0	3.9	4.9	4.5	4.1	3.8	3.6	3.0	2.8
20-64	0.21	0.22	0.21	0.22	0.22	0.22	0.22	4.5	4.7	4.4	4.7	4.7	4.7	4.7	4.0	4.1	3.8	4.0	4.0	3.9	3.9
65-79	0.23	0.27	0.29	0.31	0.32	0.34	0.34	4.8	5.5	5.7	6.1	6.3	6.7	6.8	3.9	4.3	4.6	4.8	5.0	5.1	5.2
80-	0.17	0.20	0.22	0.24	0.27	0.29	0.32	3.4	4.1	4.3	4.8	5.2	5.8	6.2	2.7	3.2	3.4	3.9	4.1	4.3	4.6
All age groups	0.26	0.26	0.24	0.24	0.24	0.23	0.23	8.5	8.3	7.2	6.7	6.1	6.0	5.8	6.5	6.3	5.5	5.2	4.7	4.6	4.4
Cephalosporins (J01DB-DE)																					
0-6	0.52	0.46	0.36	0.34	0.32	0.32	0.27	49.7	43.6	34.1	33.2	31.6	29.2	25.7	39.0	34.9	28.2	27.7	25.6	24.1	21.2
7-19	0.29	0.26	0.21	0.20	0.18	0.16	0.15	20.2	18.4	14.9	13.8	12.8	11.6	10.4	17.1	15.6	12.7	11.6	10.7	9.6	8.5
20-64	0.29	0.26	0.20	0.18	0.15	0.14	0.12	16.4	14.6	11.5	10.3	9.2	8.2	7.3	13.8	12.3	9.7	8.7	7.7	6.8	6.0
65-79	0.43	0.39	0.31	0.29	0.23	0.20	0.19	21.7	19.1	14.9	13.9	12.6	11.0	10.4	17.0	14.8	11.5	10.6	9.5	8.2	7.8
80-	0.65	0.54	0.41	0.38	0.34	0.32	0.31	35.4	29.4	22.7	21.6	19.9	18.5	17.6	27.5	23.0	17.9	16.6	15.5	14.2	13.4
All age groups	0.35	0.31	0.25	0.23	0.20	0.18	0.16	21.5	19.0	15.2	14.1	12.8	11.5	10.4	17.4	15.4	12.3	11.4	10.3	9.2	8.3

Age groups (years)	DDD/1000 and day							Prescriptions/1000 and year							User/1000 and year						
	2007	2008	2009	2010	2011	2012	2013	2007	2008	2009	2010	2011	2012	2013	2007	2008	2009	2010	2011	2012	2013
Trimethoprim (J01EA)																					
0-6	0.12	0.10	0.09	0.09	0.08	0.08	0.07	15.4	14.0	12.6	12.2	11.3	11.0	10.0	10.8	10.1	9.7	9.5	8.8	8.4	7.6
7-19	0.18	0.15	0.11	0.10	0.08	0.06	0.05	10.9	8.9	7.0	5.9	4.8	3.9	3.3	9.4	7.7	6.0	5.1	4.1	3.3	2.7
20-64	0.31	0.26	0.20	0.17	0.15	0.13	0.11	15.6	12.7	9.4	7.8	6.5	5.4	4.5	13.0	10.5	7.7	6.4	5.2	4.3	3.5
65-79	0.90	0.76	0.61	0.57	0.50	0.43	0.39	42.0	34.7	27.5	24.3	20.9	17.7	15.5	30.9	25.1	19.6	17.3	14.6	12.3	10.7
80-	1.91	1.58	1.30	1.23	1.08	0.94	0.83	104.5	84.7	69.6	63.6	56.4	49.1	41.5	61.7	49.3	38.6	34.5	29.4	24.6	21.4
All age groups	0.43	0.36	0.29	0.26	0.23	0.20	0.17	22.8	18.8	14.9	13.1	11.2	9.7	8.3	17.0	13.9	10.7	9.3	7.9	6.7	5.7
Trimethoprim with sulphonamides (J01EE)																					
0-6	0.16	0.14	0.13	0.12	0.10	0.10	0.09	18.8	16.7	14.8	13.7	11.8	11.8	10.2	13.9	12.4	10.7	10.0	8.2	7.6	6.2
7-19	0.10	0.10	0.11	0.10	0.10	0.10	0.10	4.1	4.2	4.3	4.0	4.1	3.9	3.8	2.6	2.6	2.6	2.4	2.5	2.2	2.1
20-64	0.16	0.17	0.18	0.19	0.19	0.19	0.20	3.5	3.6	3.8	4.0	4.2	4.3	4.6	2.3	2.4	2.5	2.6	2.7	2.6	2.6
65-79	0.42	0.48	0.52	0.52	0.54	0.54	0.56	10.2	11.3	11.7	12.1	12.2	12.2	12.4	7.1	7.9	8.2	8.5	8.5	8.3	8.4
80-	0.39	0.43	0.43	0.46	0.46	0.47	0.51	12.2	13.1	12.5	13.1	12.5	12.6	13.0	9.1	10.0	9.7	10.1	9.8	9.5	9.7
All age groups	0.20	0.21	0.22	0.23	0.24	0.24	0.25	6.4	6.5	6.6	6.8	6.7	6.6	6.7	4.2	4.3	4.3	4.3	4.2	4.1	4.0
Macrolides (J01FA)																					
0-6	0.85	0.68	0.51	0.53	0.51	0.39	0.26	38.1	29.9	22.4	23.1	22.2	18.1	12.1	31.2	24.0	18.1	18.7	18.3	14.8	9.5
7-19	0.51	0.38	0.31	0.33	0.40	0.32	0.24	21.7	15.4	12.7	13.8	15.4	13.2	8.3	17.0	11.7	9.7	10.7	12.1	10.0	5.8
20-64	0.36	0.33	0.28	0.28	0.28	0.30	0.27	16.5	14.3	12.0	11.9	10.4	11.4	8.7	13.1	11.3	9.5	9.5	8.3	8.8	6.4
65-79	0.35	0.34	0.32	0.30	0.32	0.32	0.33	13.9	12.4	11.1	10.3	9.3	10.4	8.7	10.6	9.3	8.2	7.6	6.7	7.4	5.6
80-	0.24	0.23	0.23	0.21	0.20	0.19	0.20	8.7	8.4	7.4	6.9	6.0	6.4	5.7	6.8	6.4	5.5	5.3	4.4	4.8	4.0
All age groups	0.42	0.36	0.31	0.31	0.32	0.31	0.27	18.4	15.3	12.8	12.8	11.9	11.9	8.9	14.5	11.9	9.9	10.0	9.3	9.1	6.3
Lincosamides (J01FF)																					
0-6	0.03	0.02	0.02	0.02	0.02	0.03	0.02	5.3	5.0	5.2	5.0	5.3	6.5	5.0	4.0	3.8	3.8	3.9	4.0	4.9	3.7
7-19	0.12	0.12	0.12	0.12	0.12	0.12	0.11	8.3	8.4	8.2	8.1	8.0	7.9	7.4	6.7	6.8	6.6	6.5	6.5	6.5	5.9
20-64	0.32	0.32	0.31	0.31	0.32	0.32	0.31	16.3	16.3	15.7	15.6	16.0	15.8	15.4	12.5	12.7	12.4	12.4	12.7	12.5	12.2
65-79	0.59	0.61	0.61	0.59	0.59	0.58	0.58	25.8	26.2	25.4	25.0	24.6	24.2	24.3	16.9	17.3	17.1	16.9	16.8	16.8	16.8
80-	0.74	0.76	0.72	0.73	0.71	0.70	0.71	32.8	33.2	31.0	31.7	30.8	30.2	29.9	18.7	19.3	18.8	19.2	19.0	18.7	18.9
All age groups	0.32	0.33	0.32	0.32	0.33	0.32	0.32	16.3	16.4	15.9	15.9	16.0	16.0	15.6	11.8	12.0	11.7	11.7	11.9	11.9	11.6
Fluoroquinolones (J01MA)																					
0-6	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.8	0.7	0.7	0.8	0.7	0.7	0.9	0.4	0.4	0.4	0.5	0.4	0.5	0.5
7-19	0.13	0.12	0.12	0.12	0.12	0.11	0.11	5.5	4.8	4.3	4.3	4.3	4.0	3.6	4.4	3.8	3.5	3.5	3.4	3.2	2.9
20-64	0.86	0.78	0.72	0.68	0.68	0.65	0.62	31.4	27.0	23.8	22.9	21.9	20.8	19.7	22.6	19.5	17.3	16.7	15.9	15.1	14.4
65-79	2.10	1.90	1.84	1.79	1.77	1.73	1.64	81.4	70.8	65.6	63.8	61.1	58.8	55.7	55.1	48.3	44.9	43.9	41.8	40.4	38.6
80-	2.74	2.41	2.25	2.26	2.18	2.08	2.00	119.7	98.5	88.2	87.3	82.0	77.6	73.7	81.6	68.4	61.4	60.9	57.8	54.9	52.6
All age groups	0.93	0.84	0.80	0.78	0.77	0.75	0.71	35.7	30.6	27.8	27.1	26.1	25.0	23.8	25.0	21.7	19.6	19.2	18.4	17.7	16.9
Nitrofurantoin (J01XE)																					
0-6	0.07	0.06	0.06	0.06	0.06	0.05	0.05	6.3	6.2	6.9	7.2	7.3	7.0	7.1	4.3	4.3	5.0	5.1	5.1	5.0	5.1
7-19	0.14	0.13	0.15	0.14	0.14	0.13	0.13	6.7	6.6	9.2	10.6	10.8	10.4	10.1	5.7	5.7	7.9	9.0	9.2	8.9	8.6
20-64	0.25	0.24	0.27	0.27	0.28	0.29	0.30	11.3	11.1	15.3	17.8	19.1	19.8	20.5	9.3	9.1	12.5	14.6	15.6	16.1	16.6
65-79	0.53	0.55	0.62	0.61	0.64	0.67	0.72	22.6	24.2	32.6	37.3	39.9	41.5	44.0	16.9	18.1	24.0	27.5	29.3	30.3	31.9
80-	0.97	0.95	1.05	1.06	1.12	1.15	1.23	46.7	47.7	61.7	70.6	76.0	77.4	80.6	30.4	31.3	40.3	45.6	47.8	49.0	51.6
All age groups	0.30	0.29	0.32	0.32	0.34	0.35	0.37	13.5	13.6	18.5	21.3	22.8	23.5	24.5	10.4	10.5	14.1	16.3	17.3	17.8	18.4
All agents (J01 excl. Methenamine)																					
0-6	8.61	8.32	7.11	7.21	6.55	6.66	5.43	666.8	630.8	522.4	515.0	467.6	471.9	382.4	358.6	342.4	299.5	300.7	273.3	274.4	232.0
7-19	9.95	9.83	9.52	9.65	9.83	9.27	8.33	319.8	301.4	280.8	282.5	286.1	268.0	232.7	206.5	194.6	182.5	183.8	185.5	173.2	152.1
20-64	13.34	13.09	12.14	12.03	12.25	11.98	11.19	380.4	361.7	331.8	329.9	331.7	320.0	294.4	234.9	224.7	209.1	207.8	208.9	200.7	184.9
65-79	19.13	19.16	18.23	17.78	18.00	17.76	17.28	587.3	566.6	535.0	525.3	524.7	510.7	489.2	306.9	297.5	282.9	278.6	278.9	270.6	258.1
80-	22.25	22.24	21.13	20.85	20.38	20.34	20.22	807.9	765.1	723.5	710.9	690.7	673.0	654.2	373.0	357.7	340.2	336.1	330.9	323.2	314.7
All age groups	13.70	13.53	12.76	12.68	12.76	12.51	11.74	443.8	423.1	391.9	390.3	385.3	373.9	342.7	255.9	245.1	228.3	227.5	226.3	218.7	201.0

common as antibiotics commonly used to treat respiratory tract infections. In contrast, in the age group 15-19 years, antibiotics commonly used to treat acne represent a larger proportion. This kind of antibiotics are prescribed with long treatment duration, hence the peak seen in figure 1.5 for this age group measured as DDD per 1000 inhabitants and day.

Antibiotics commonly used to treat RTI

Antibiotics commonly used to treat respiratory tract infections (RTI) are the most frequently prescribed antibiotics in Sweden. Among these substances we also find the greatest decrease in sale during 2013 (14%), as well as over time in terms of number of prescriptions per 1000 inhabitants and year, from 294 in 2000 to 178 in 2013 (61%).

Narrow spectrum penicillin, penicillin V, is the recommended first line antibiotic for treatment of community acquired RTI in Sweden (Medical Products Agency & Strama, 2008) and is the most frequently prescribed antibiotic in outpatient care, Figure 1.9. The sale of penicillin V decreased in all age groups during 2013 compared with 2012, but to a variable extent, Table 1.2.

Doxycycline is the second most frequently prescribed antibiotic agent in outpatient care. 98% of all doxycycline packages sold on prescriptions are containing less than 50 tablets, which indicates that the substance is mainly used to treat RTI.

In total, the decrease in sale 2013 was seen among all antibiotics commonly used to treat RTI. Greatest decrease was seen for doxycycline (packages smaller than 50 tablets) (18%), macrolides (26%), penicillin V (13%) and amoxicillin (11%). Doxycycline and macrolides are two antibiotics commonly used to treat *Mycoplasma pneumoniae*. The increased frequency of *Mycoplasma pneumoniae* during the winter season 2011/2012 and reported in SWEDRES 2012 may affect the statistic and can partly explain the decrease of these substances during 2013.

However, when analysing the sale of these substances during 2013 compared with 2012 a reduction is noticeable throughout the year. This indicates other explanations for the drop rather than a reduced incidence of *Mycoplasma pneumoniae*. One being increased compliance to national guidelines (Medical Products Agency and Strama, 2008) where stated that acute bronchitis (including *Mycoplasma pneuomoniae*) should generally not be be treated with antibiotics.

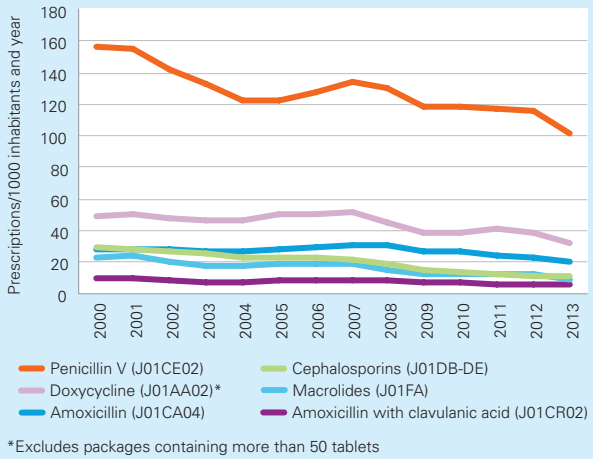
Furthermore, less seasonal variation in the sale of antibiotics commonly used to treat RTI is seen over the years, suggesting a more rational antibiotic use. In additional, even though an increased number of influenza cases were noticed in Sweden during 2013 compared with 2012 (the Public Health Agency of Sweden, cases reported from laboratories http://www.folkhalsomyndigheten.se/amnesomraden/beredskap/overvakning-och-rapportering/frivillig-laboratorierapportering/) the sale of antibiotics commonly used to treat RTI decreased during the period. This also indicates less misuse of antibiotics for influenza.

As stated in SWEDRES/SVARM 2012, new national recommendation for treatment of pharyngotonsillitis (acute sore throat) was published in 2012 (Medical Products Agency & Swedish Institute for Communicable Disease Control, 2012). Communications about treatment recommendations may be one explanation for the decreased sale of this type of antibiotics.

Antibiotics commonly used to treat UTI in women

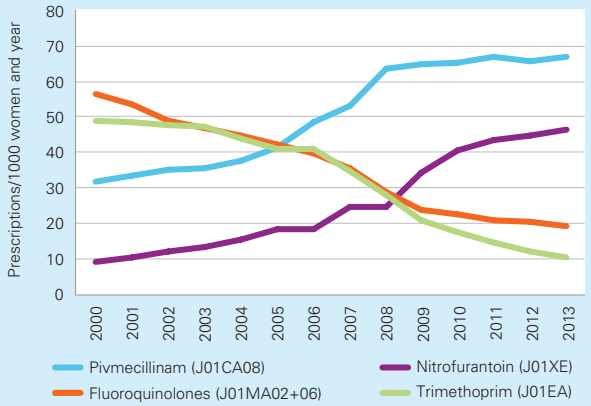
National Guidance for the treatment of lower urinary tract infections in women over 18 years (Medical Products Agency & Strama, 2007), recommends pivmecillinam and nitrofurantoin before trimethoprim, and prescribers are also encouraged to minimize the use of fluoroquinolones because of the resistance situation. The use of the two first-line drugs has increased every year and pivmecillinam and nitrofurantoin now account for 77% of antibiotics commonly used to treat this condition in women. This is a greater proportion than in 2012. Hence, a clear shift from fluoroquinolones to pivmecillinam and nitrofurantoin is seen, which is according to recommendations.

FIGURE 1.9. Sales of antibiotics commonly used to treat respiratory tract infections in outpatient care (sales on prescriptions), 2000-2013, prescriptions/1000 inhabitants and years, both sexes, all ages.



*Excludes packages containing more than 50 tablets

FIGURE 1.10. Sales of antibiotics commonly used to treat lower urinary tract infections in women (sales on prescriptions), 18-79 years, 2000-2013, prescriptions/1000 women and year



Diagnose linked prescribing data from primary care

Data regarding visits at health centers for infectious diseases have been collected since 2007 into a record called PRIS (Primary care Record of Infections in Sweden). PRIS includes items on patient age, gender, diagnosis, ATC-code for the antibiotic that has been prescribed, results of rapid antigen detection test Strep-A, C-reactive protein (CRP) test and information about whether a microbiologic sample has been taken. Each included patient has an encrypted identification number in PRIS. The purpose of the record is to study how common infections are handled and treated in primary care.

Each year, health centres are invited to participate and the numbers of participating health centres and listed populations may therefore vary over time, but data may still indicate trends in prescriptionof antibiotics in Primary care. PRIS is administrated by primary care R&D center in Jönköping County and is financed by the Public Health Agency of Sweden and the R&D unit in Jönköping County.

In 2013, 74 health centres participated in PRIS and their listed population was 684584 persons. In 2013, 276493 visits for infectious diseases were registered which represented 29% of all visits in this population. Visits during out of hours or during weekends are not included and would probably add approximately 20% more visits. A total of 401 visits for infections per 1000 listed patients were registered, 126 (39%) of whom received an antibiotic prescription. In addition, 34 prescriptions per 1000 listed were identified that could not be linked to a specific visit or diagnose. In total, 160 antibiotic prescriptions per 1000 listed were issued in 2013, in comparison with 185 in 2012. Prescriptions without a diagnosis might be due to prescriptions by phone after worsening of illness, after receiving a test result or simply administrative mistakes.

TABLE 1.14. Use and result of strep A test in patients treated with antibiotics for tonsillitis/pharyngitis.

	2011		2012		2013	
	number	%	number	%	number	%
positive strep a-test	9847	54	9711	57	6566	59
Negative Strep A-test	2199	12	1569	9	1083	10
No Strep-A test	6232	34	5759	34	3499	31

The most common antibiotics prescribed without a registered diagnosis were phenoxymethylpenicillin (PcV), betalactamasresistant penicillins, pivmecillinam and tetracyclines. It can be estimated that approximately one third of these prescriptions represent an UTI, one third a skin and soft tissue infection and one third a RTI.

The ten most common infection diagnoses represented 83% of all antibiotics prescribed in 2013. Urinary tract infection followed by throat infection and ear infection led to the majority of antibiotic prescriptions, Table 1.13.

Respiratory tract infections including acute otitis media (AOM) represented 56% of all visits and 25% of these patients received an antibiotic. In comparison with 2012, there were a reduction in prescribing for respiratory tract infections, most evident for tonsillitis (24 to 15 prescriptions/1000 listed patients), AOM (15 to 12 prescriptions/1000 listed patients) and acute bronchitis (8 to 5 prescriptions /1000 listed patients). According to treatment recommendations a Strep A test or a positive culture should have been taken from most patients diagnosed with throat infections (tonsillitis and pharyngitis) before antibiotic treatment. In 2013, 59% of those who received

TABLE 1 13. The 10 diagnoses that represented 83% of all antibiotic prescriptions in 2013 in participating health centers.

	Number	% of total antibiotic precribing	Prescriptions /1000 listed patients	% prescribed antibiotics per diagnosis
Cystitis	21946	26.7	32	78
Tonsillitis	10743	13.1	15	80
Acute otitis media	8259	10	12	75
Unspecified skin infection	6263	7.6	9	53
Sinusitis	5004	6.1	7	61
Pneumonia	4624	5.6	6	62
acute bronchitis	3348	4.1	5	27
Lyme disease	3254	4	5	88
Common cold	2542	3.1	4	6
Boil	1851	2.3	3	35

antibiotics for throat infections had a positive Strep A test and 10% had a negative Strep A test, while in 31% no test had been taken at all (Table 1.14). In comparison with data from 2011 and 2012, the major change was that fewer patients had been treated with an antibiotic. However, there were wide variations comparing different health centres regarding relation between a negative Strep A test and antibiotic prescribing (Figure 1.33).

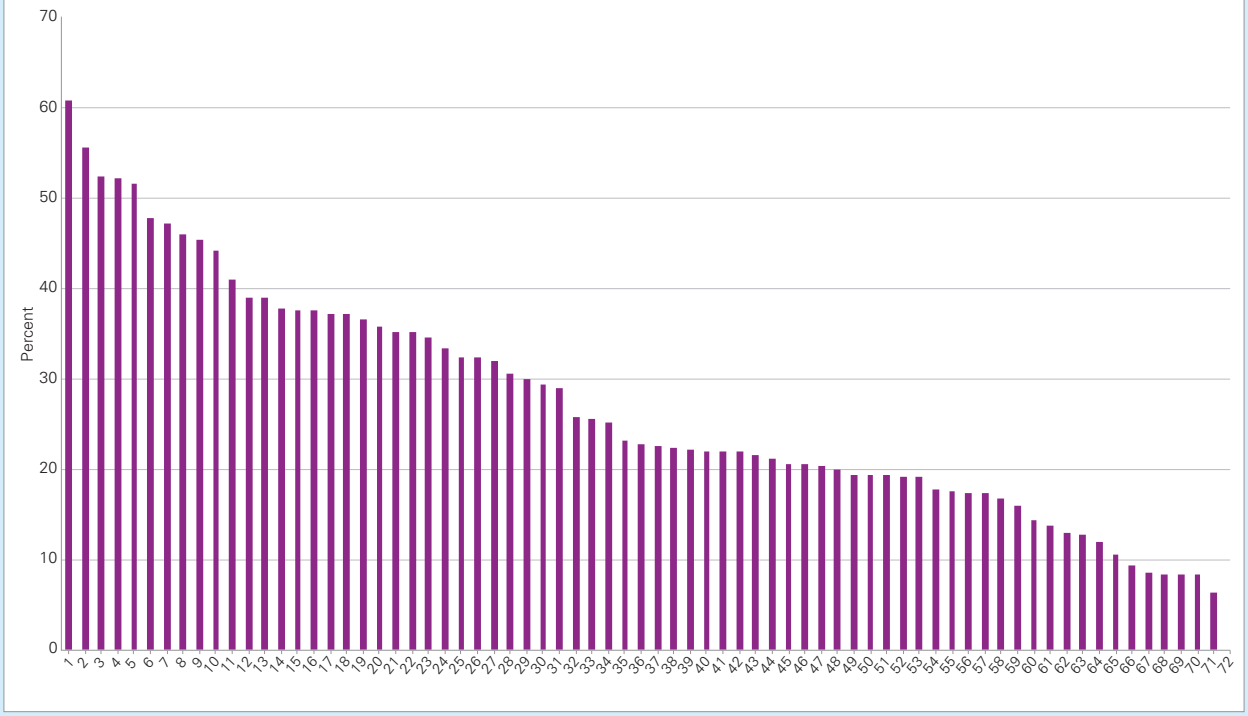
The proportion of positive Strep A tests of all taken was 34%. In 2013, 89% of those diagnosed with tonsillitis or pharyngitis and with a positive Strep test were treated with PcV (J01CE02), 4.5% with cephalosporins (J01DB-DE) and 2.2% with macrolides (J01FA) and 3.4% with lincosamides (J01FF).

In 2007, 60% of all patients diagnosed with acute bronchitis were treated with antibiotics and the corresponding figure for 2011 was 42% and for 2013 was 27%. When antibiotics were prescribed for acute bronchitis, 55% of the patients were treated with tetracyclines, 27% with PcV and 11% with amoxicillin which was similar to year 2012. The proportion of all patients diagnosed with acute bronchitis and receiving antibiotic treatment varied between the participating health centers, from 9 to 76%, such variations were noted for the majority of all diagnoses registered in PRIS. When antibiotics were prescribed for pneumonia, 52% received PcV, 32% a tetracycline and 8% amoxicillin.

In 2012, 876 visits per 1000 children 0-6 years were made and in 296 visits (34%) an antibiotic was prescribed. The corresponding figures for 2013 was 723 and 209 (29%), respectively. Of these 723 visits per 1000 children 0-6 years of age in 2013, 501 visits were for a respiratory tract infection and in 29 % of these visits an antibiotic was prescribed. The most common antibiotic was PcV, 82,5%, followed by amoxicillin 9,8 %, macrolides 3,1% and a cephalosporin in 2,1%. Of all antibiotics prescribed to children 0-6 years, 43% were for AOM, 23% for tonsillitis, 6% for impetigo and 5% for a common cold. In 2011, 77% of all children aged 1-12 years that were diagnosed with acute otitis media were treated with antibiotics. The corresponding figure for 2013 was 73%.

The indication for antibiotic treatment in patients with urinary tract infections cannot be analyzed by these kind of records. But the choice of antibiotic substance prescribed at the time of diagnosiscan be analyzed and has changed over time. In 2012, it was recommended that males with cystitis without fever, could be treated by pivmecillinam or nitrofurantoin instead of fluoroquinolones or trimetoprim. In 2010, pivmecillinam was prescribed to 12% and nitrofurantoin to 11% of men with cystitis, the corresponding figures in 2013 were 24% and 20%, respectively. In women with cystitis, 78% were prescribed an antibiotic. In 2007, the proportion of women diagnosed with a urinary tract infection and treated with

FIGURE 1.33. Proportion tonsillopharyngitis with a negative StrepA and received antibiotics. Each column represents one Health centre



the two first line substances, pivmecillinam or nitrofurantoin, was 55% and the proportion treated with trimethoprim or a fluoroquionolone was 40%. In 2013, 87% were treated with first line drugs: pivmecillinam 51% and nitrofurantoin 36%. Trimethoprim was prescribed to 7% and fluoroquinolones to 3%. The proportion of women with urinary tract infections and treated with fluoroquinolones in PRIS can be compared with the goal launched by Strama in 2009: the proportion of fluoroquinolones should not exceed 10% of antibiotics commonly prescribed to treat urinary tract infections in women. When using sales data from pharmacies for the assessment of adherence to treatment recommendations less specific targets need to be applied, as prescribing for other diagnoses cannot be effectively excluded. This illustrates the value of registries like PRIS that approves for an accurate investigation of prescribing for a certain diagnosis.

The most common skin- and soft tissue diagnoses were unspecified skin infection, followed by lyme disease, boil, erysipelas and impetigo. The most prescribed antibiotics were betalactamresistant penicillins (49%) followed by PcV (27%) and tetracyclines (11%).

Conclusion

PRIS is a valuable database for the monitoring of the treatment of infections in primary care. All participating health centres receive extensive feedback on their data in comparison with other centres and with guidelines. There are several possible sources of error in this type of registry, but it does clearly illustrate trends over time and highlights differences in treatment between different units. Since 2010, the number of visits for infections has been rather stable, but the use of antibiotics for respiratory tract infections has decreased, especially for AOM, throat infections and acute bronchitis. The choice of antibiotics in urinary tract infection for both women and men has changed. The proportion of fluoroquinolons has decreased and recommended drugs have increased in accordance with current recommendations. It is quite clear that the management of especially respiratory tract infections still can be improved. Data from the PRIS record can be made available for anyone who has a scientific question eg for a student's or resident's essay.

In 2013, the total sale of these antibiotics to women 18-79 years was at the same level as in 2012. However, the same trend as previously with reduced sale of trimethoprim (15%) and fluoroquinolones (5%) was also seen, Figure 1.10.

The total sales of antibiotics commonly used to treat UTI in women aged 18-79 years has decreased slightly over the years; by 2% since 2000, measured as prescriptions per 1000 women and year, Figure 1.12. Measured as DDD per 1000 women and day, the sale of antibiotics commonly used to treat UTI in women 18-79 years has decreased by 13% since 2007. This indicates shorter treatment duration for this condition with time, which is according to recommendations.

Antibiotics commonly used to treat UTI in men

According to tradition, ciprofloxacin and trimethoprim are the most commonly used antibiotics to treat UTI in men in Sweden. Prostatic involvement is often seen in febrile UTIs in men. This is why quinolones and trimethoprim, with good concentrations in prostate, are appropriate. It is unknown how often the prostate is really infected in symptomatic UTI without fever. Because of increasing resistance in gram-negative bacteria, nitrofurantoin and pivmecillinam may be considered as first line antibiotics. In a document published by The Public Health Agency of Sweden, experts are now recommending nitrofurantoin or pivmecillinam as first line antibiotics for treatment of symptomatic UTI without fever in men, (Public Health Agency of Sweden, 2013).

The sale of fluoroquinolones to men (aged 65 years and older) has decreased by 35% from 2000 to 2013, measured as prescriptions per 1000 men and year. The decrease continued in 2013 where the sale decreased by 5% compared with 2012. During the last years, sale of narrower spectrum pivmecillinam and nitrofurantoin has increased. In 2013, the sale of these two antibiotics increased by 26% and 17% respectively, measured by prescriptions per 1000 men and year, compared with 2012, Figure 1.11. In total, the sales of antibiotics commonly used to treat UTI in men has decreased by 28% since 2000, Figure 1.12.

Antibiotic consumption in children

The sale of antibiotics to children aged 0-6 years decreased by 19% in 2013, from 472 to 382 prescriptions per 1000 children. The reduction includes a majority of existing antibiotic agents, and the greatest decrease compared with 2012 was seen in the sale of macrolides (J01FA), lincosamides (J01FF) and betalactamase sensitive penicillins (J01CE) (33%, 22% and 21% respectively), Table 1.2.

Different kinds of penicillins are the most commonly prescribed antibiotics in this age group and penicillin V (J01CE02), amoxicillin (J01CA04) and flucloxacillin (J01CF05) represents 77% of the total sale in 2013, Table 1.2.

In an effort to find explanations for the great reduction in antibiotic sale to children in 2013, different analysis of

FIGURE 1.11. Sales of antibiotics commonly used to treat UTI in men (65 years and older) 2000-2013, measured as prescriptions/1000 men and years. An increased sale of recommended narrow spectrum pivmecillinam and nitrofurantoin is seen during the last years.

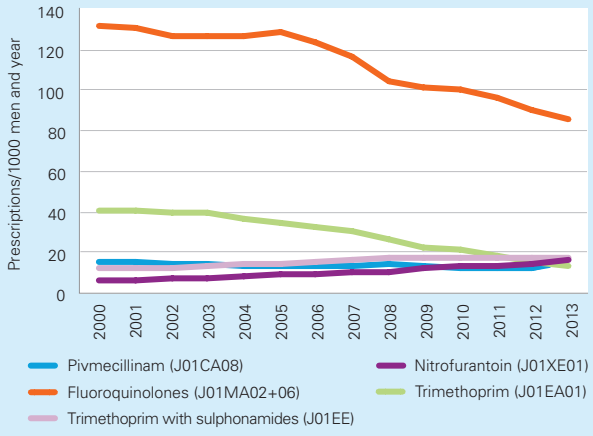


FIGURE 1.12. Sales of antibiotics commonly used to treat UTI in men (65 years and older) and women (18-79 years) 2000-2013, measured as prescriptions/1000 inhabitants and year. In total, a greater decrease in sales of these type of antibiotics is seen in men than in women.

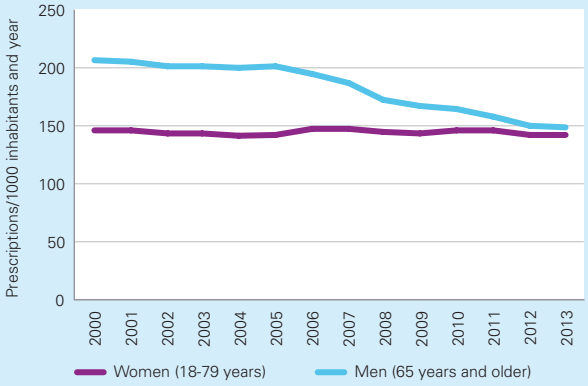
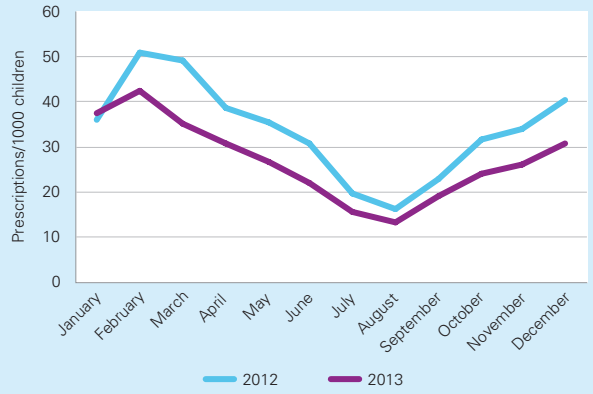
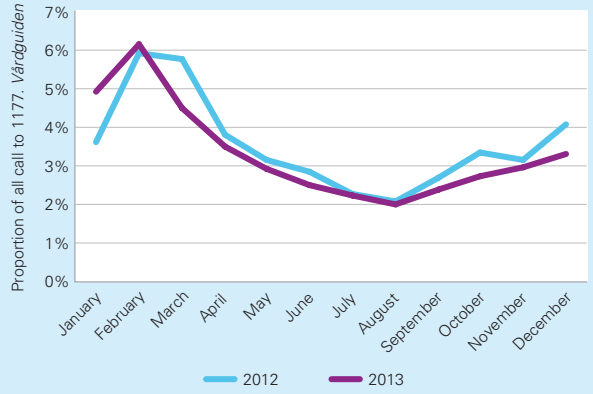


FIGURE 1.13. Sales of antibiotics commonly used to treat RTI (J01AA02*, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), in children 0-6 years, by month 2012-2013, measured as prescriptions/1000 children. The reduction is seen during the whole year.



*Excludes packages containing more than 50 tablets.

FIGURE 1.14. Proportion of telephone calls to the national telephone line 1177 Vårdguiden på telefon (the telephone line for healthcare counselling) concerning fever and children (calls made by parents to children 0-6 years) of all telephone calls, by month in 2012 and 2013.



the level of cold and flu during the 2013 seasons was compared with 2012. Statistics over number of telephone calls to the national telephone line (1177 Vårdguiden på telefon) (exclusive Stockholm, Södermanland, Värmland and Norrbotten County) for health care counselling have been compiled concerning calls made by parents regarding fever in children 0-6 years. Statistics on the national medical webpage (www.1177.se) regarding cold or flu was also analysed. There was no big difference in the search pattern compared with 2012 according this analysis. The great decrease in antibiotic sale seen in 2013 can rather be explained by more rational antibiotic use than less cold or flu in the society, Figure 1.13 and Figure 1.14.

New recommendations for treatment of acute otitis media were launched by Strama and the Swedish Medical Products Agency in 2010 (Medical Products Agency & Strama, 2010). The new recommendations have been attracting attention from professionals and the public which may have influenced the antibiotic use to young children.

Antibiotic use in children has also been in focus of both local and national information activities the last years.

There are still great national variations concerning antibiotic sale to children 0-6years, from 447 prescriptions per 1000 children and year in Skåne County to 215 in Jämtland County, Figure 1.15.

Data from the Swedish Prescribed Drug Register shows that the share of children treated with at least one course of any kind of antibiotic decreased in all 21 counties during 2013. The share ranges within the country from 263 users per 1000 children in Skåne County to 146 users per 1000 children in Jämtland County, Figure 1.16. Taken together, in Sweden the share of children treated with at least one course of antibiotics was 23%, which is less than in 2012, Table 1.2.

FIGURE 1.15. Sales of antibiotics (J01 excl. methenamine) on prescriptions to children 0-6 years, per county and in Sweden, prescriptions/1000 children and years. The data are sorted according to the use in 2013. A decrease is seen in all counties during 2013. At national level the sale decreased by 19%.

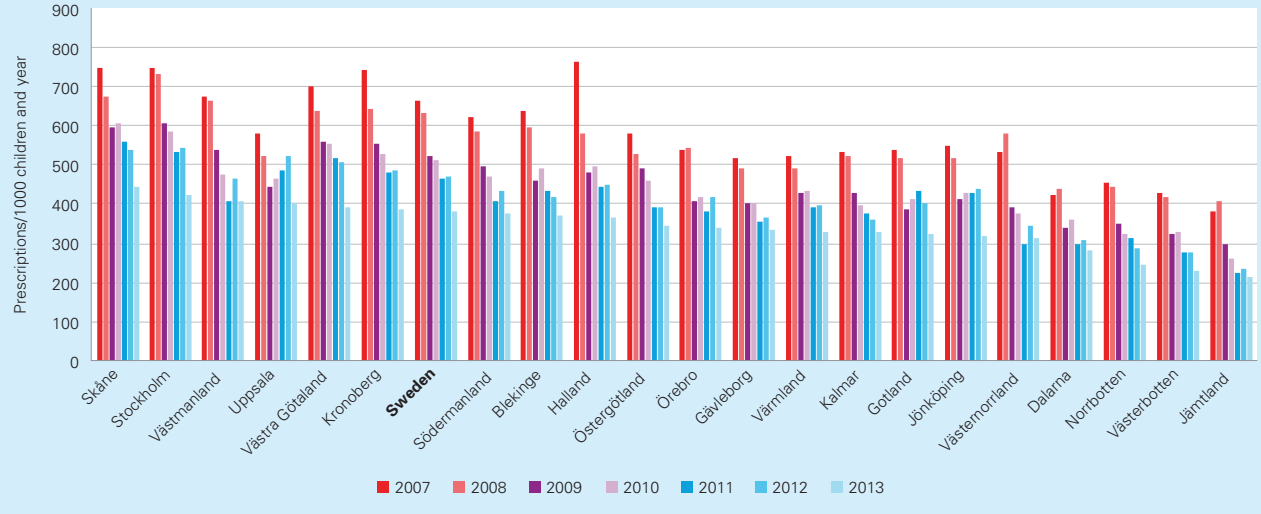


FIGURE 1.16. Share of children age 0-6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2011, 2012 and 2013 (users/1000 children and year).

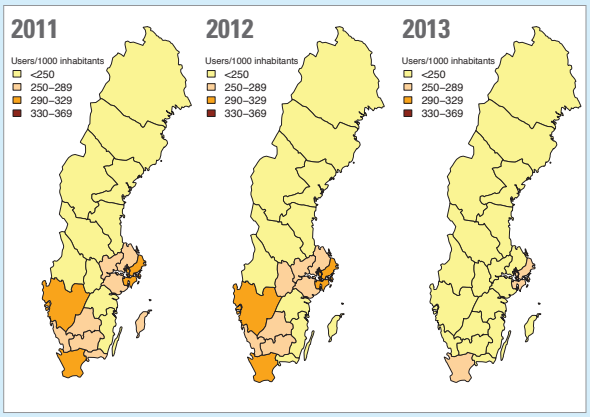
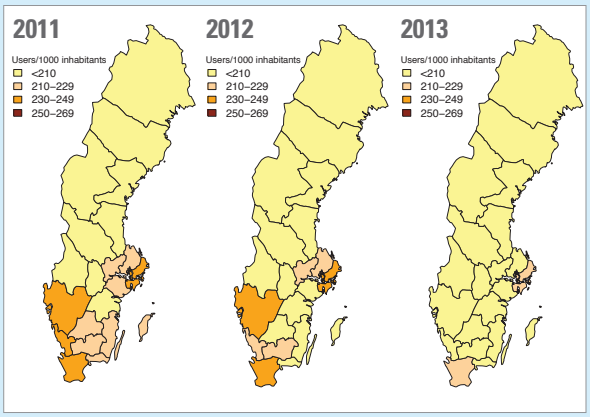


FIGURE 1.17. Share of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2011, 2012 and 2013 (users/1000 inhabitants and year).



County data

In 2013, 20% of the Swedish population was treated with at least one course of any kind of antibiotic, which is less than in 2012 where 22% was treated, Table 1.2. However, the share of people treated with antibiotics varies within Sweden, from 24% in Stockholm County and Skåne County to 16% in Västerbotten County. The antibiotic use is greatest in big cities and their surroundings. In total, the proportion of patients treated decreased in all counties in 2013, Figure 1.17.

In 2013, the average sale of antibiotics in outpatient care measured as prescriptions per 1000 inhabitants in Sweden was 343. To reach the Swedish long term target of at most 250 prescriptions per 1000 inhabitants and year the antibiotic use in Sweden must decline with 27%. Read more about the Swedish target for antibiotic use in chapter *Agreement concerning improved patient safety*. In 2013, a decreased number of prescriptions per 1000 inhabitants is seen in all 21 counties. There are great regional differences nationally and prescriptions per 1000 inhabitants range from 374 in Skåne County to 267 in Västerbotten County, Figure 1.18. The great variation between counties can probably not be explained by differences in morbidity (Hedin K, Andre M, et al. 2006), but is more likely explained by overuse of antibiotics. Studies have shown overuse of antibiotics in RTI (Mölstad S, Andre M, et al. 2009). Notably, the greatest differences in the sale of antibiotics between counties relate to treatment of RTI (Figure 1.19). This supports the hypothesis of overuse.

When promoting a reduced use of antibiotics, it is of great importance to study and analyse the incidence of morbidity and complications, to ensure that those does not increase. The Public Health Agency of Sweden is regularly analysing

FIGURE 1.18. Sale of antibiotics in outpatient care 2011-2013, prescriptions/1000 inhabitants and year. The red line indicates the Swedish long term target of at most 250 prescriptions/1000 inhabitants and year. The data are sorted according to the use in 2013.

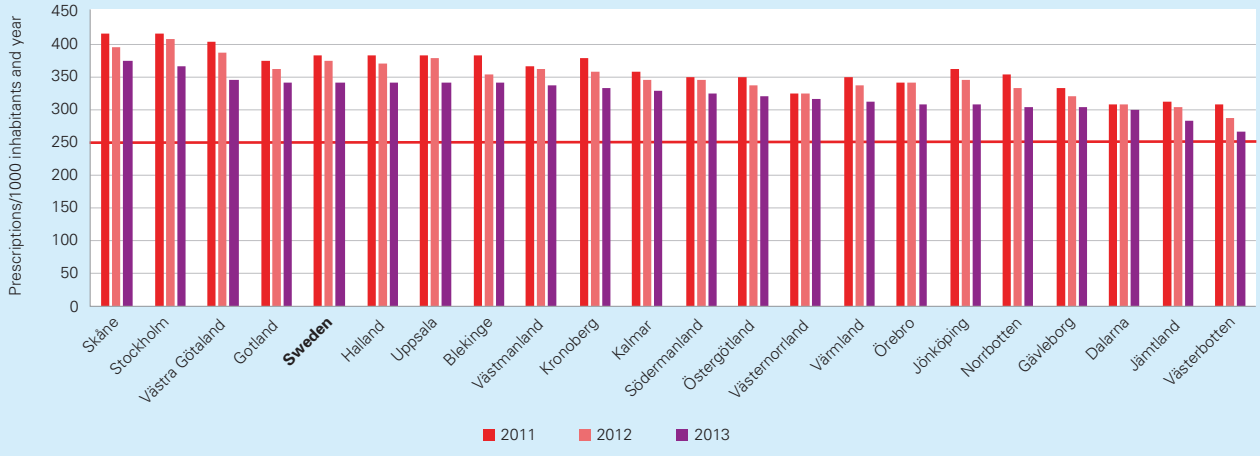
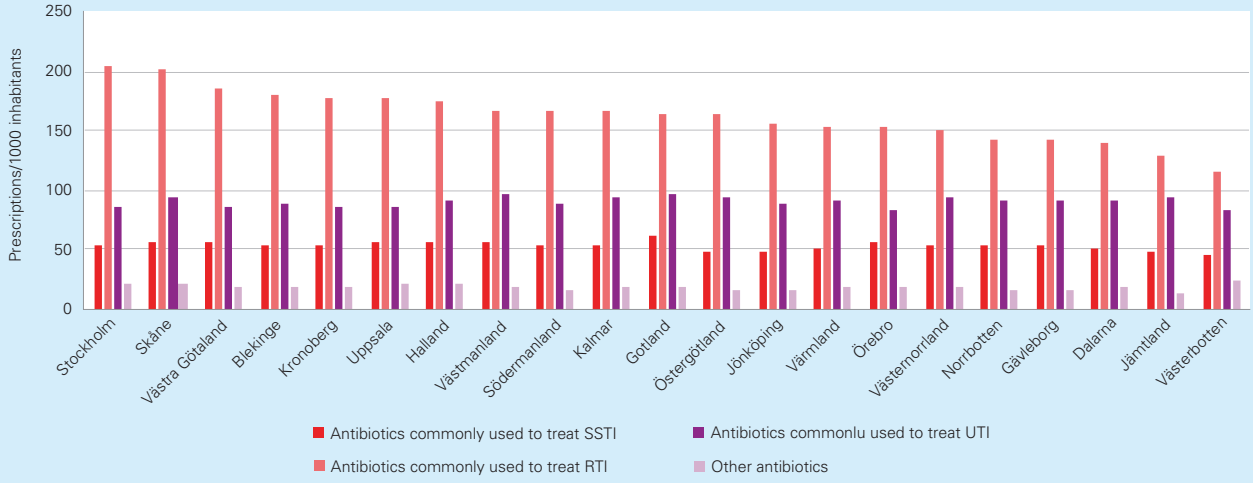
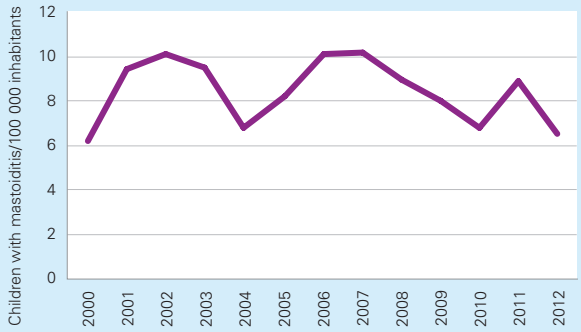


FIGURE 1.19. Sale of antibiotics commonly used to treat RTI, UTI, SSTI and other antibiotics in outpatient care 2013, per county, prescriptions/1000 inhabitants and year. The data are sorted according to the county with the highest use of antibiotics commonly used to treat RTI.



the incidence of known complications. For example, figure 1.20 shows the incidence of mastoiditis in children in Sweden 2000-2013. Despite the great decrease in antibiotic sales to children over the last years, incidence of mastoiditis have not increased. In total (all ages, both sexes), 90 cases of mastoiditis (ICD-10 H70.0) were reported to the National Board of Health and Welfare in 2013.

FIGURE 1.20. Incidence of mastoiditis (ICD-10 H70.0) in children (0-4 years) 2000-2012, statistics from the National Board of Health and Welfare (patientregistret).



As mentioned in earlier editions of SWEDRES/SVARM, Strama has proposed two qualitative goals for antibiotic prescribing in outpatient care:

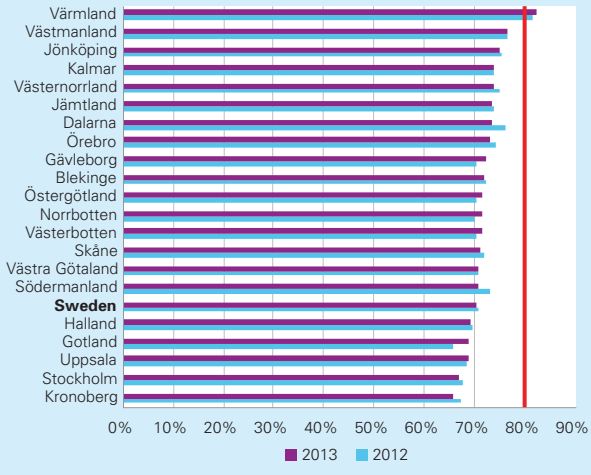
1. 80% of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years should be penicillin V (J01CE02). The numerator is penicillin V (J01CE02) and the denominator is amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulanate (J01CR02), cephalosporins (J01DB-DE)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

In 2013 the proportion of penicillin V of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years was 70% on the national level, which is the same level as in 2012. Värmland County had the greatest proportion, 82%, and Kronoberg County the lowest, 66%, Figure 1.21.

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

In Sweden the average proportion of fluoroquinolones prescribed to women aged 18-79 was 13% in 2013. Västernorrland and Kronoberg were the counties with the highest

FIGURE 1.21. Proportion penicillin V of antibiotics commonly used to treat RTI in children 0-6 years, per county. The red line indicates Strama´s goal at minimum 80% penicillin V.



Respiratory tract infections – repeated courses in outpatient antibiotic use

The purpose of this study was to investigate the treatment of respiratory tract infections[1] and to what extent repeated treatments follow within two weeks. Data from the Swedish Prescribed Drug Register were analysed with respect to what type of antibiotic that was used prior to a reiterated purchase and the choice of antibiotic in the complementary purchase.

Children have the highest fraction of repeated courses of antibiotics used to treat respiratory tract infections within 14 days, Figure 1.34. The total number of prescriptions and the number of repeated prescriptions purchased during the season Sep 2012 – Aug 2013 have decreased in all age groups compared to the season before (Sep 2011 – Aug 2012). However, the proportion of prescriptions with supplementary purchases for the same individual is more or less unaltered between seasons (slight drop in the age group 7-19 years).

Of the 26 210 reiterated prescriptions in the age group 0-6 years in 2012/13 almost 70 percent of the purchases (18 098) were made after penicillin V, Figure 1.35. 45 percent of the recipes were followed by a new course of the *same* antibiotic within 14 days (8 082 prescriptions). This figure varies somewhat among the different age groups: 55 percent (7-19 years), 40 percent (20-59 years), 44 percent (60-79 years) and 45 percent (80 years and older). This analysis, which was a follow-up of a previous highlight study for SWEDRES 2009, showed almost the same figures in the age groups 0-6 years and 20-59 years compares to the previous analysis. The results in the present analysis indicate a slight decreased fraction of a switch to the same antibiotic after penicillin V in the age groups 60-79 years and 80 years and older compared to the previous study, but a tendency toward an increase in the age group 7-19 years.

A new course of respiratory tract antibiotic within a 14-days period may have many explanations including unsuitable formulation (oral suspension, tablets) or unappreciated taste by young children, allergy, relapsed infection or lack of effect (viral or mycoplasma aetiology). One tenth of recipes for antibiotics commonly used to treat respiratory tract infections in young children are followed by a new course within 14 days. The key to improvement might lie in the prescribing situation or at the pharmacy by for example; advice on how to ease the intake, discuss formulation alternatives, motivate parents of young children, involve the child in drug therapy to ease intake, etc. The reason why nearly half of the repeated prescriptions results in an additional recipe for a course of the same antibiotic should be further investigated in the ambition to reduce ineffective overuse of antibiotics.

FIGURE 1.34. Number of prescriptions on antibiotics used to treat respiratory tract infections in outpatient care during the period Sep 2011 – Aug 2012 versus Sep 2012 – Aug 2013 in age groups. The different colors indicate the prescriptions with no supplementary purchase for the same individual within 14 days (blue) and the prescriptions followed by a another purchase (red).

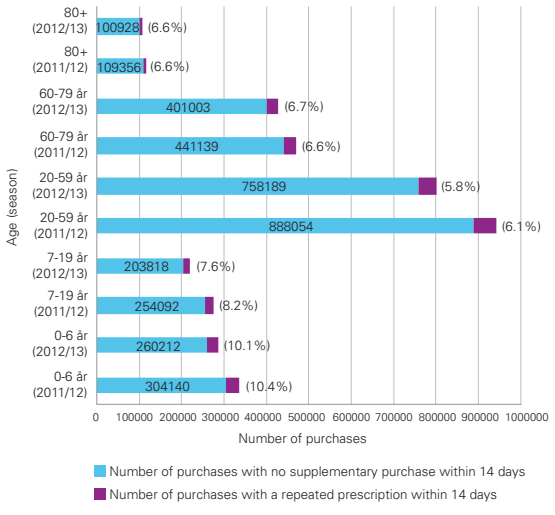
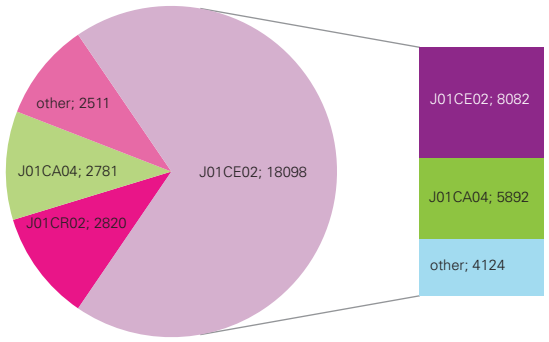


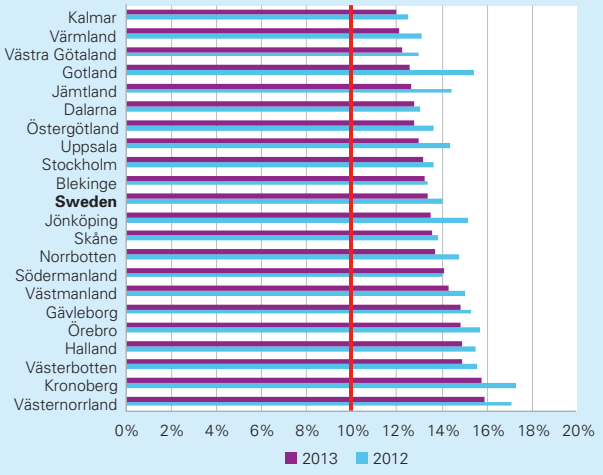
FIGURE 1.35. The type of antibiotic (atc-code) on the prescription before and after another purchase of a respiratory antibiotic within 14 days in the age group 0-6 years in 2012/13. The number of prescriptions is shown beside each atc-code. The bar on the right hand shows the choice of respiratory antibiotic that follow after penicillin V.



Antibiotic before and after a switch, age 0-6 years

[1] Antibiotics commonly used to treat respiratory tract infections (Strama): Amoxicillin-clavulanate (J01CR02), cephalosporins (J01DB-DE), doxycycline (J01AA02), macrolides (J01FA), amoxicillin (J01CA04), penicillin V (J01CE02). As the medical cause of drug therapy not is indicated in the register, some recipes for other indications than respiratory tract infections may be included.

FIGURE 1.22. Proportion of fluoroquinolones of antibiotics commonly used to treat UTI in women 18-79 years, per county. The red line indicates Strama´s goal of maximum 10% fluoroquinolones.



proportion (16%) and Kalmar was the county with lowest proportion (12%), Figure 1.22.

Agreement concerning improved patient safety

The Government and the Swedish Association of Local Authorities and Regions (SALAR) agreed in late 2010 on a performance-based reimbursement for the patient safety efforts in the county councils. The patient safety drive will continue to the end of 2014. SEK 100 million was allocated for the period October 1 2010 - September 30 2011 to improvements of rational use of antibiotics. A prerequisite for receiving compensation was that the county councils must have met a number of basic requirements. One important requirement, based on the work with antibiotic use, was the establishment of a local strategic program against antibiotic resistance (Strama) with a clear mission and adequate financing. All the county councils met this requirement. Those county councils who also worked for an increased compliance to local treatment recommendations concerning common infections in outpatient care, and also decreased the number of antibiotic prescriptions by ten percent of the difference between the number of prescriptions per 1000 inhabitants per year for the period October 1 2009 – September 30 2010, and the long term target of at most 250 prescriptions per 1000 inhabitants and year were entitled to the compensation. An assessment from The Swedish Institute for Communicable Disease Control showed that all the county councils met the requirement regarding compliance to local treatment guidelines. Five counties decreased the antibiotic prescriptions, including Stockholm, the largest county in Sweden. The county councils of Dalarna, Västernorrland and Jämtland furthermore reached the target regarding antibiotic prescriptions and shared SEK 75 million. In 2012 another SEK 100 million was allocated to improvements of rational use of antibiotics. Nine counties decreased the antibiotic prescriptions and the county councils of Blekinge, Gotland, Gävleborg and Västerbotten reached the target and shared SEK 75 million. A closer look shows some disadvantages of the chosen method. The most striking example is the small county of Gotland which reached the target 2012 mainly because of the large increase of the prescription rate in the county the preceding year, which became the baseline period in the following year.

In 2013 the quantitative antibiotic target changed with the purpose that more county councils should be able to achieve their targets. All county councils which reduce antibiotic prescriptions during the measurement period compared with the previous measurement period would be reimbursed. The qualitative target was similar to previous measurement period but in one aspect more specified. An important requirement was that county councils must show that at least 50 percent of the healthcare centers have provided the general practitioners their personal antibiotic prescribing, and furthermore compare the personal prescribing of the practitioners at the medical center and also make structured comparisons between medical centers in the county. All the county councils met the requirement of the qualitative target and for the first time all the 21 county councils decreased the antibiotic prescriptions, which meant that the allocated SEK 100 million was distributed to the county councils. The patient safety drive will continue in 2014, the last year, and no changes are made in the quantitative and qualitative targets. (http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/Patientsakerhetssatsning-2013/).

Antibiotics in dentistry

The sale of antibiotics prescribed by dentists decreases by 8% in 2013 compared with 2012, from 26 to 24 prescriptions per 1000 inhabitants and year. Penicillin V (J01CE02) is the most commonly prescribed antibiotic followed by amoxicillin (J01CA) and clindamycin (J01FFA01). These antibiotic substances represent 77%, 10% and 10% respectively of all antibioics prescribed by dentists. However, the greatest decrease in 2013 was seen for penicillin V and amoxicillin, measured as prescriptions per 1000 inhabitants and year.

Dentists accounts for approximately 7% of all antibiotic prescribing in outpatient care in Sweden. The proportion varies between 5% in some counties to 8% in some counties. The total sale of antibiotics, measured as prescriptions per 1000 inhabitants and year, decreased in 19 out of 21 counties in 2013 compared with 2012.

Antibiotics in hospital care

Sales data in this chapter originates from two different sources: 1) all antibiotics sold by requisitions, below mentioned as *hospital care*, gives a general view over usage and trends and 2) antibiotics sold by by requisitions to acute care hospitals only, *Swedish acute care hospitals*, for a more detailed analysis. Hospital care includes data from all Swedish acute care hospitals as well as data from those nursing homes and other care givers that order their antibiotics through requisitions. Some nursing homes buy antibiotics through requisitions and other by prescriptions to individual residents. In the latter case data will be included in primary health care

TABLE 1.3. Antibiotic use in hospital care 2000-2013, DDD/1000 inhabitants and day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
J01 excl methenamine	1.18	1.22	1.25	1.33	1.36	1.43	1.49	1.55	1.52	1.48	1.52	1.59	1.63	1.60
Total J01	1.21	1.25	1.27	1.37	1.43	1.50	1.56	1.62	1.57	1.52	1.55	1.61	1.65	1.62
Methenamine (J01XX05)	0.03	0.03	0.03	0.05	0.07	0.07	0.07	0.07	0.05	0.03	0.03	0.02	0.02	0.02

data, presented in the previous section. The way of retreiving antibiotics to nursing homes varies among counties but on the national level, the proportion of antibiotics in hospital care sold to acute care hospitals is about 75%. In some counties almost 100% of all antibiotics are bought by acute care hospitals and in other counties this proportion is as low as 55%.

Antibiotic use within hospital care

Antibiotic consumption has increased in Swedish hospitals over the last decade except the last year when it decreased with 1.8%. From 2000 to 2012 the consumption increased with 36% from 1.18 to 1.63 DDD/1000 inhabitants and day, Table 1.3.

Figure 1.23 shows eight groups of antibiotics often used within hospital care. The consumption of cephalosporins has decreased, whereas betalactamase-sensitive and -resistant penicillins, combinations of penicillins with beta-lactamase inhibitors and carbapenems has increased and replaced cephalosporins. Piperacillin with tazobactam stands for 79% and amoxicillin with clavulanate for 11% in the group combinations of penicillins (J01CR). Piperacillin with tazobactam still represents a small proportion (5.9%) of all antibiotic use in hospital care, but the use has increased rapidly. In 2013 it increased with 11% measured as DDD per 1000 inhabitants and day compared to 2012. The increase in piperacillin with tazobactam could be a result of stewardship favouring piperacillin with tazobactam over cephalosporins since the former is more favourable in the situation with increasing ESBL. Carbapenems are also increasing which probably is a result of an increased number of infections involving ESBL. To minimize the selection of ESBL producing bacteria, a decreased use of 2nd and 3rd generation´s cephalosporins is recommended in Sweden. According to recommendations, cephalosporins should be replaced with benzylpenicillin in non-serious community acquired pneumonia (CRB 65). In cases of febrile UTIs and abdominal infections, cephalosporins could be used. Details of local resistance is crucial and many local drug committees are emphasizing the use of piperacillin with tazobactam in these situations which contributes to the increase of J01CR over time.

Due to the rapid decrease in use of cephalosporins during the last years, the betalactamase-resistant penicillins (J01CF) are now the largest group of antibiotics in hospital care, Figure 1.23. These substances are largely used as prophylaxis before surgery. A single dose is recommended in nearly all kinds of surgical procedures for which antibiotic prophylaxis is indicated, or at most one-day prophylaxis. When analysing data from hospital care (Figure 1.23) there is still a slight increase, but data from acute care hospitals only (Table 1.4) show a slight decrease. This could possibly represent an increased use within nursing homes and other care givers outside the acute care hospitals.

The use of fluoroquinolones (J01MA) has been almost unchanged the last five years, Figure 1.23, and stands for 10% of all antibiotics within hospital care.

FIGURE 1.23. Antibiotic groups often used within hospital care 2000-2013, DDD/1000 inhabitants and day.

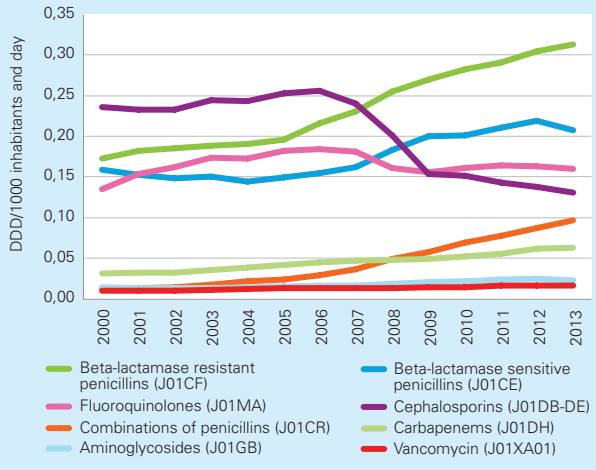
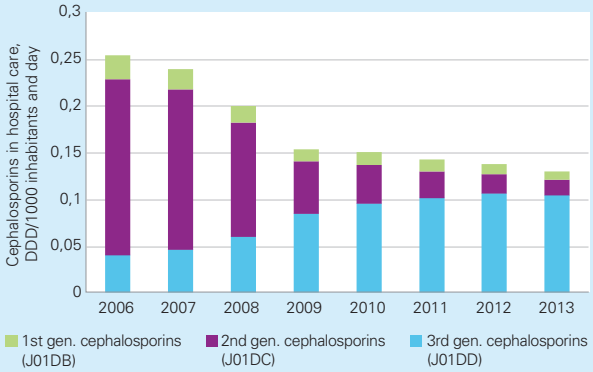


FIGURE 1.24. Cephalosporins in hospital care, DDD/1000 inhabitants and day, 2006-2013.



*Data from Jönköping county nov-dec 2013 is missing

Figure 1.24 shows that from 2006 to 2013 the sales of cephalosporins decreased by 51%, from 0.26 to 0.13 DDD per 1000 inhabitants and day. Sales of third generation cephalosporins, mainly cefotaxime and ceftazidime, has replaced the use of second generation cephalosporins (cefuroxime). The decrease in DDD is partly explained by a shift from cefuroxime to cefotaxime since the prescribed daily dose, PDD, in Sweden of these substances do not correspond to the WHO

TABLE 1.4. DDD/100 patient-days in somatic medical care in Swedish acute care hospitals 2009-2013.

	2009	2010	2011	2012	2013*
Tetracyclines (J01AA)	4.5	4.6	5.0	5.3	4.8
Penicillins with extended spectrum (J01CA)	5.8	6.0	6.5	6.9	6.5
Betalactamase sensitive penicillins (J01CE)	6.7	6.7	7.2	7.6	7.0
Betalactamase resistant penicillins (J01CF)	10.2	10.9	11.3	12.0	11.7
Combinations of penicillins (J01CR)	2.8	3.3	3.8	4.4	4.7
Cephalosporins (J01DB-DE)	7.1	7.1	6.8	6.7	6.1
Carbapenems (J01DH)	2.4	2.6	2.8	3.2	3.1
Trimethoprim (J01EA)	1.0	0.9	0.8	0.6	0.4
Trimethoprim with sulphonamides (J01EE)	2.0	2.1	2.3	2.3	2.2
Macrolides (J01FA)	0.9	0.9	1.1	1.0	0.9
Lincosamides (J01FF)	1.7	1.7	1.7	1.9	1.9
Aminoglycosides (J01GB)	1.0	1.1	1.2	1.3	1.1
Fluoroquinolones (J01MA)	5.9	6.1	6.2	6.3	5.9
Glycopeptides (J01XA)	0.8	0.8	0.9	0.9	0.9
Imidazole derivatives (J01XD)	1.3	1.3	1.2	1.1	1.0
Nitrofurantoin (J01XE)	0.4	0.4	0.5	0.5	0.5
Methenamine (J01XX05)	0.7	0.6	0.5	0.5	0.5
Linezolid (J01XX08)	0.1	0.1	0.1	0.1	0.1
All agents (J01)	55.3	57.4	59.8	62.9	59.7

*Denominator data from 2012.

definitions. According to Strama´s repeated point prevalence surveys the mean PDD for cefuroxime was 3.5 g/day and for cefotaxime 3.1 g/day and the corresponding figure defined by WHO is 3 g/day and 4 g/day respectively. The overall decrease in DDDs for cephalosporins indicates that these substances are actually replaced by other antibiotics.

As reported in earlier issues of SWEDRES/SVARM, a change toward less broad spectrum and more narrow spectrum antibiotics is desirable and has been promoted for a long time. Penicillin V and G (J01CE) is recommended by The Swedish Society of Infectious Diseases as first hand treatment in mild to moderate severe community-acquired pneumonia and the use of cephalosporins should be reduced. Stramas point prevalence surveys, performed in 2003, 2004, 2006, 2008 and 2010 confirm that the use of cephalosporins for treatment of uncomplicated community-acquired pneumonia has decreased considerably.

Antibiotic use within Swedish acute care hospitals

As mentioned above, antibiotic consumption within hospital care has increased with 36% the last decade (2000-2012) and slightly decreased the last year. When analysing data from acute care hospitals only and in relation to patient-days and admissions in somatic care there is also an increase, 14 and 7 percent respectively (2009-2012) and a slight decrease from 2012-2013, Table 1.4 and 1.5.

FIGURE 1.25. Percentage of narrow spectrum penicillins (penicillin V and G, J01CE) of all antibiotics in Swedish acute care hospitals 2013, per county.

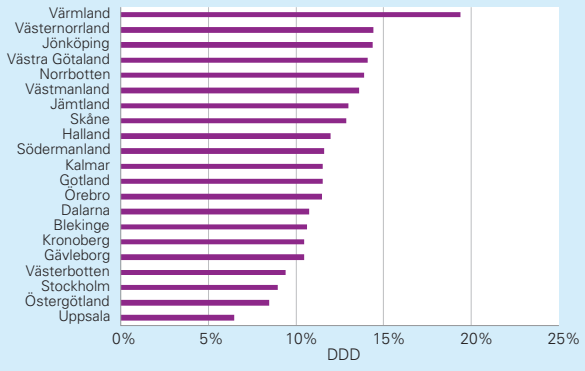
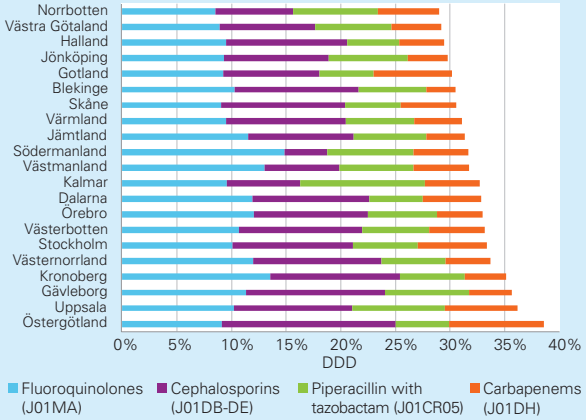


FIGURE 1.26. Percentage of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibiotics in Swedish acute care hospitals 2013, per county.



The sales data available concerning Swedish acute care hospitals show a wide variation between counties in the use of narrow-spectrum penicillins, ranging from 6% to 19% of the total hospital consumption measured as DDDs. Cephalosporin use varied between 3.9% and 15.9%, and the corresponding figures for fluoroquinolones were 8.5% to 14.8%, 4.8% to 11.4% for piperacillin-tazobactam, and 3.5% to 8.7% for carbapenems, Figures 1.25-1.26 and Table 1.6.

TABLE 1.5. DDD/100 admissions in somatic medical care in Swedish acute care hospitals 2009-2013.

	2009	2010	2011	2012	2013*
Tetracyclines (J01AA)	21.2	21.5	22.7	23.4	21.2
Penicillins with extended spectrum (J01CA)	27.5	28.0	29.5	30.6	28.8
Betalactamase sensitive penicillins (J01CE)	31.9	31.3	32.8	33.8	30.9
Betalactamase resistant penicillins (J01CF)	48.4	51.0	51.4	53.4	51.9
Combinations of penicillins (J01CR)	13.1	15.6	17.4	19.5	20.9
Cephalosporins (J01DB-DE)	33.6	33.3	31.1	29.9	27.1
Carbapenems (J01DH)	11.4	12.1	12.8	14.3	13.8
Trimethoprim (J01EA)	4.7	4.0	3.6	2.7	1.9
Trimethoprim with sulphonamides (J01EE)	9.5	9.9	10.3	10.2	9.8
Macrolides (J01FA)	4.0	4.1	4.9	4.2	4.0
Lincosamides (J01FF)	7.8	7.9	7.9	8.4	8.2
Aminoglycosides (J01GB)	4.8	5.0	5.3	5.7	5.1
Fluoroquinolones (J01MA)	27.7	28.3	28.3	28.1	26.4
Glycopeptides (J01XA)	3.6	3.7	4.1	4.1	4.0
Imidazole derivatives (J01XD)	6.4	6.0	5.4	5.1	4.3
Nitrofurantoin (J01XE)	2.0	2.0	2.1	2.1	2.1
Methenamine (J01XX05)	3.1	2.7	2.5	2.1	2.2
Linezolid (J01XX08)	0.3	0.4	0.3	0.4	0.4
All agents (J01)	261.7	267.5	273.2	278.9	264.5

*Denominator data from 2012.

TABLE 1.6. Percentage DDD of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibiotics in Swedish acute care hospitals 2012-2013, per county.

	Fluoroquinolones (J01MA)		Cephalosporins (J01DB-DE)		Piperacillin with tazobactam (J01CR05)		Carbapenems (J01DH)		All broad spectrum agents	
	2012	2013	2012	2013	2012	2013	2012	2013	2012	2013
Norrbotten	10.3	8.5	9.0	7.1	7.1	7.8	5.2	5.6	31.7	29.0
Västra Götaland	9.2	8.9	8.6	8.8	6.4	6.9	4.4	4.6	28.6	29.2
Halland	9.9	9.5	11.4	11.1	3.8	4.8	4.2	4.1	29.4	29.5
Jönköping	10.6	9.3	11.7	9.6	5.6	7.2	4.4	3.7	32.4	29.8
Gotland	9.8	9.2	8.7	8.8	4.6	5.0	6.7	7.2	29.9	30.2
Blekinge	10.6	10.3	11.1	11.3	5.5	6.2	2.8	2.6	30.0	30.5
Skåne	9.1	9.0	11.3	11.4	4.7	5.1	5.1	5.1	30.3	30.6
Värmland	9.8	9.5	11.3	10.9	5.7	6.3	2.9	4.4	29.6	31.1
Jämtland	12.5	11.5	9.4	9.6	5.5	6.7	3.4	3.5	30.7	31.4
Södermanland	14.1	14.8	3.7	3.9	7.4	7.9	4.0	5.1	29.2	31.7
Västmanland	11.9	13.0	6.8	6.9	6.5	6.8	5.6	5.1	30.8	31.8
Kalmar	9.7	9.6	9.7	6.7	8.0	11.4	3.8	5.0	31.2	32.7
Dalarna	12.0	11.9	11.9	10.7	4.4	4.9	5.2	5.3	33.4	32.8
Örebro	11.4	12.1	10.9	10.4	5.1	6.3	3.7	4.2	31.1	33.0
Västerbotten	10.4	10.6	11.6	11.3	5.1	6.2	5.0	5.1	32.0	33.2
Stockholm	9.4	10.1	12.3	11.0	5.5	5.9	6.8	6.3	34.0	33.4
Västernorrland	12.0	12.0	11.9	11.7	5.1	5.8	4.1	4.1	33.2	33.7
Kronoberg	13.4	13.6	10.6	11.9	5.2	5.9	3.4	3.7	32.7	35.1
Gävleborg	12.3	11.3	14.0	12.8	6.0	7.7	4.0	3.9	36.3	35.6
Uppsala	10.1	10.2	10.8	10.8	8.1	8.5	7.1	6.6	36.2	36.2
Östergötland	9.6	9.1	15.6	15.9	4.4	4.8	8.5	8.7	38.1	38.6

IT-tool for automatic registration of healthcare-associated and antibiotic use in hospital care (Anti infectious tool)

The anti infectious tool (AIT) was first launched as a part of the Swedish national patient safety initiative in 2012. As one of five goals in the agreement between the government and the Swedish Association of Local Authorities and Regions (SALAR) all counties should introduce and establish a computerized AIT that had been developed by the SALAR. The work was to start in 2012 and by the end of 2014 all counties shall have fully established the AIT in all inpatients settings. By the end of 2013 all counties had managed to make the system compatible with the local medication module and computerized medical record and to start at least two pilot clinics. Some counties have already introduced the AIT countywide.

The primary aim of the AIT is to reduce the amount of healthcare associated infections (HAI) and to optimize the use of antibiotics in both hospitals and in outpatient settings. Both these aims will be discussed in further details. The trigger for the system is the prescription of a medical substance with a J01 ATC code (all systemic antibiotics and methenamin). As the physician prescribes a J01 medication a pop-up window appears and two questions must be answered in order to proceed. First, whether the antibiotic is prescribed due to a community acquired infection or a HAI. Second, what the presumptive diagnosis is at the time of ordination. In the latter case the attending physician is given a list of ten common diagnoses to choose from.

The system focuses on three major risk factors for HAI, central venous catheters, ventilator-care and indwelling urinary catheter. All data on the existence of the above mentioned risk factors are automatically collected from the computerized medical record. All faecal cultures that are positive for *Clostridium difficile* are automatically registered from the the computerized laboratory system, thus minimizing the amount of extra work for the physicians.

All gathered information is easily retrievable in a database where each medical unit can see their own figures.

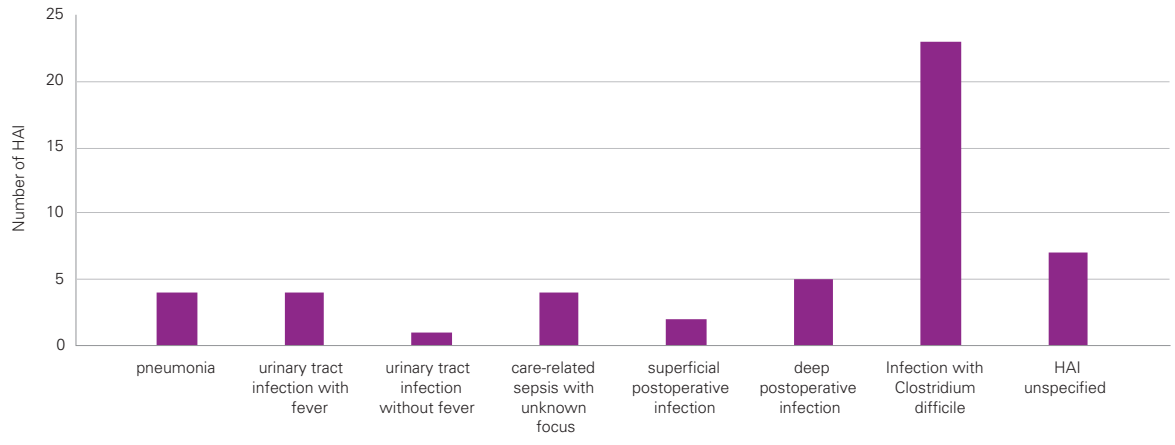
Hospital-staff with a personal internet ID (CITHS) can get access to the units/clinics data through a web based search tool. It is easy to create diagrams of the units HAIs, riskfactors or antibiotic consumption. It is also possible to see on what indication an antibiotic is given, which makes it possible to both measure compliance to local and national guidelines and to study the use of a single antibiotic substance. Data are presented as anonymous statistics and it is not possible to study a single patient. The data are owned by the local healthcare facilities.

The reliability and reproducibility of the data has been validated by the two pilot-counties; Uppsala and Västra Götaland.

Future challenges

In an era of new public management and dozens of different patient-registers and check-lists and quality enhancing programs a major obstacle for each new intervention is to gain acceptance. The amount of extra work for the attending physician is minimized. It takes approximately ten seconds to answer the two questions. In case of doubt whether an infection should be regarded as an HAI, there is a list of the definitions of HAI readily available. So far the system has been met with acceptance among the physicians. But in order to really reap the awards of the AIT the most important issue is the interpretation of data and how those are presented as feedback to each unit.

FIGURE 1.36. All HAIs at the department of infectious disease in Västmanland County hospital, September 2013- February 2014.



So far the goal from SALAR is to launch the AIT in all counties by the end of 2014, and it is then up to each county to properly administer the AIT. It is of great importance to convince the local clinic managers to allocate means and most importantly to encourage local physicians to work with the units own data.

The AIT is an important tool in the struggle against HAI and in the work to optimize the antibiotic use, but it is only a tool. In order to succeed in this important work the future management of the AIT must be secured. Data from the AIT must be analyzed and be used in feedback to prescribers and in other quality work to improve performance. The importance of active involvement of the local departments of hygiene cannot be overestimated. The local hygiene experts can for example help to interpret data and suggest interventions, but the responsibility for the implementation of those will remain with the units/clinics.

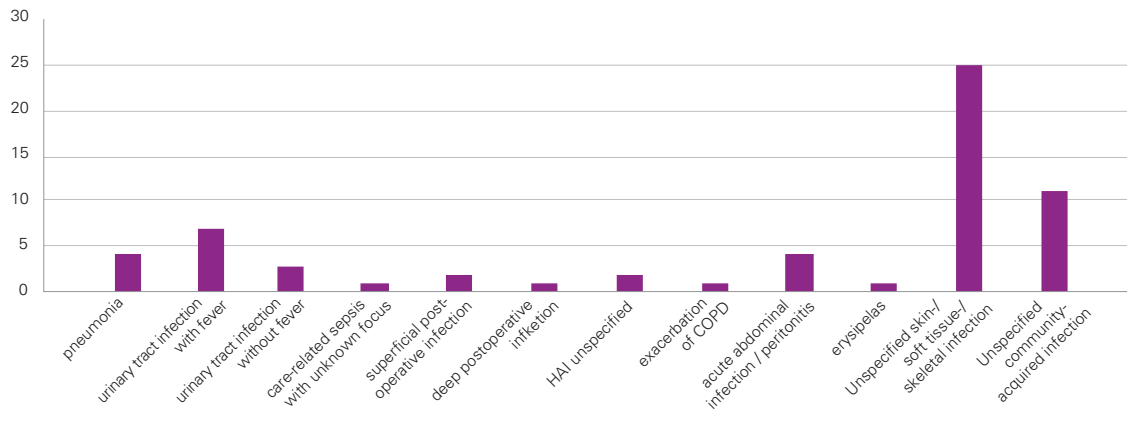
Regarding data on antibiotic use those must be interpreted together with data on the total antibiotic consumption, local figures of antibiotic resistance, and the local and national guidelines and seen in the context of the actual case-mix of patients. The local Strama groups possess all this knowledge and may therefore advantageously be actively involved in the work with optimizing antibiotic use, thus hampering the spread of antibiotic resistance.

At this point, data from AIT is only accessible in counties at local level. But, the data from AIT is also very important for the work with minimizing HAI and to optimize antibiotic use at national level. Presently it is difficult to compare data from different counties or units due to differences in local recommendations, local figures of bacterial resistance and differences in patient case mix. Therefor, a challenge for the future is to make data from the different counties comparable and valid at a national level.

Example from Västmanland County

An example can be taken from the county of Västmanland where the AIT is fully introduced since November 2013. Figure 1.36 shows all HAIs at the department of infectious disease in the County during Sep 2013- Feb 2014. It was a common apprehension that piperacillin/tazobactam was overused at the department of infectious diseases. Figures from the hospital pharmacist showed that the consumption of piperacillin/tazobactam has steadily increased at both the hospital in total and the department of infectious disease since the year 2000. With the help of the AIT it could be shown that the most common indication for prescribing piperacillin/tazobactam was skin and soft tissue infections, a condition that normally does not warrant treatment with broad spectrum antibiotics, Figure 1.37. Data from the local microbiological laboratory showed that there had been no major changes in the pattern of sensitivity for relevant bacteria in cultures taken from the department of infectious diseases. After a broad discussion among all physicians including the clinic manager and the local Strama authority it was concluded that there was an overuse of piperacillin/tazobactam on this indication and that the most probable reason was a shift among the physicians, from a majority of old physicians to younger physicians. The need for a further education on treatment of skin and soft tissue infections was noticed and is now scheduled. Without the AIT it would have been a very time consuming work to go through all patient charts to find out on what indications piperacillin/tazobactam had been given and it would also have been more difficult to convince the clinic manager to finance the education in need. With the help of the AIT those data were obtained within a few minutes.

FIGURE 1.37. Indication for prescribing piperacillin/tazobactam at department of infectious disease in Västmanland County, May 2013- February 2014.



Adverse reactions related to antibiotic use

Spontaneously reported drug-related adverse reactions are continuously entered into BiSi, a national database administered by the Swedish Medical Products Agency. The reports originate from health care professionals. The antibiotic related adverse reactions in the last five years, 2009-2013, 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=619), gastrointestinal disorders (n=198), hepato-biliary disorders (n=71), general disorders (n=109), blood disorders (n=79), neurological reactions (n=101), respiratory disorders (n=82), immune system disorders (n=85), musculoskeletal disorders (n=61), infections and infestations (n=46) and renal and urinary disorders (n=38).

The majority of the reports (58%) concern female patients, which is corresponding to the gender difference seen in the antibiotic use.

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 1.7.

We have previously reported that amended treatment recommendations resulted in changed prescription patterns for uncomplicated urinary tract infections. There was a decreased consumption of fluoroquinolones which is reflected in a decrease in reported adverse events. For nitrofurantoin which was increasingly prescribed a weak trend of a corresponding increase in the reporting of adverse reactions was noted. Due to the low number of reports and to the fact that data are based on spontaneous reporting, no clear conclusions can be made regarding these trends, Table 1.8.

TABLE 1.7. Most reported adverse drug reactions related to antibiotic agents to the Swedish Medical Products Agency 2009-2013.

Antibiotic	Total number of adverse drug reaction reports 2009 to 2013	Number of 'serious' reports	Number of fatal cases
Flucloxacillin	145	93	7
Penicillin V	141	57	0
Trimethoprim with sulphonamides	122	72	0
Nitrofurantoin	120	73	1
Clindamycin	100	54	2
Doxycyclin	85	35	0
Ciprofloxacin	82	54	0
Amoxicillin	75	28	0
Cefotaxime	69	34	1
Pivmecillinam	47	20	0

TABLE 1.8. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2009 – 2013.

	2009	2010	2011	2012	2013	2009-2013
Fluoroquinolones (J01MA)						
Total no of reports	34	28	25	19	28	134
Number of reactions						
Musculoskeletal	7	3	3	4	10	27
tendinitis	3	3	2	3	3	14
tendon rupture	3	2	3	3	3	14
Skin- and subcutaneous tissue	7	11	5	4	5	32
Psychiatric disorders	1	5	4	0	7	17
Nitrofurantoin (J01XE01)						
Total no of reports	21	24	25	30	20	120
Number of reactions						
Respiratory system	9	6	4	16	8	43
dyspnoea	2	3	1	4	5	15
interstitial pneumonia	3	2	0	2	1	8
pulmonary fibrosis	0	0	0	3	0	3
Skin- and subcutaneous tissue	4	10	10	17	6	47
General disorders	7	7	6	3	10	33
fever	4	3	3	2	4	16

Use of antifungals

Hospital care

Compared to 2012 there has been a 2% increase in the total sale of antifungal drugs for systemic use, yielding a national average of 61 DDD/ one million inhabitants and day. Every year since 2000 except for 2011 there has been a small but steady increase in the total sale of antifungals. Since the year 2000 when the total use was 40/ DDD one million inhabitants and day, the increase has been 50%. Meanwhile there has been a 38% increase in the use of antibiotics in hospital care for the same period. Compared to other European countries the Swedish consumption of antifungals is slightly below the EU median (83 DDD/ one million inhabitants and day, 2011) (European Centre for Disease Prevention and Control, 2014).

The figures vary between the different counties. Uppsala and Västernorrland, both counties with tertiary referral hospitals, have the highest consumption figures with an average of 119 DDD/ one million inhabitants and day. Historically those two counties have had the highest consumption since 2000. The lowest use was in Kronoberg with 32 DDD/ one million inhabitants and day.

Fluconazole still constitutes the absolute majority of the antifungals used, 67% or 41 DDD/ one million inhabitants and day. Amphotericin B is the second most used com-

pound up 40% compared to 2012, and now stands for 12% of the total use. The trend since 2000 shows that most of the described increase is due to an increased use of fluconazole. In the year 2000, the fluconazole use was 30 DDD/ one million inhabitants and day, representing 74% of the total use. Among antifungals with a broader spectrum, including both *Candida glabrata* and *Aspergillus sp* there has been a shift from amhotericin B that in year 2000 was the only broadspectrum antifungal available and constituted 20% of the total use, to the echinocandins that as a group today has 12% of the market.

Among the azoles with broad spectrum there has been a shift from itraconazole that in 2000 represented 3% of all antifungals to voriconazole and posaconazole that in 2013 has a marketshare of 7%. In 2013 itraconazole was hardly used at all.

Fluconazole which is a narrow spectrum antifungal with effect towards candida species (excluding among others *C. krusei* and most strains of *C. glabrata*) stands for 67 % of all consumption. It is a fungiostatic drug that is indicated for treatment of invasive non *krusei*, non *glabrata* candidosis in non neutropenic patients and for cryptococcosis. It is also used as prophylaxis against candida infection and as treatment for local infections such as thrush.

The new azoles; voriconazole which is regarded as treatment of choice for proven or probable aspergillosis, and posaconazole, increasingly used as prophylaxis against invasive fungal infection in certain high risk neutropenic patients, both have excellent bioavailability after oral administration. Both drugs have good effect against the most common candida species with the possible exception of *C. glabrata*, which is an emerging pathogen in Sweden and now constitutes approximately 20% of all episodes of candidemia. *C.krusei* is always resistant.

The use of voriconazole is low in absolute numbers (1.76 DDD/ one million inhabitants and day), and the use decreased by 10% the last year. The total sale in prescriptions is three times higher (5.7 DDD/ one million inhabitants and day), and the absolute majority of voriconazole therapy is initiated and monitored by hospital physicians, so it is probably more correct to confer those data to hospital use rather than primary health care use. The amount of voriconazole on prescription is unchanged compared to last year.

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

Posaconazole can also be given orally, as a suspension, but in Sweden it is only licensed as second line therapy for invasive fungal infection refractory to the first line treatment and as prophylaxis, so it is mainly used as prophylaxis in haematologic units. The total amount is still low 2.2 DDD/ one million inhabitants and day, and 5.0 DDD/ one million inhabitants and day are used in outpatients settings (sale on prescriptions). As for voriconazole it is probably more correct to confer all data to hospital use.

Since 2005 there has been a small but steady increase in the use of the echinocandins. In 2013 the use increased by 8.5%, making the total amount 7.0 DDD/ one million inhabitants and day, and the group now constitutes 12% of all systemic antifungals used in hospitals. Caspofungin which has been available in Sweden since 2002 has seen its marketshare diminish for every year. It now constitutes 60% of the echinocandins down from 78% in 2012. Anidulafungin increased its share from 18% to 30% last year. The third member of the group micafungin that for the first time appeared in the statistics last year now constitutes 10% of the total echinocandin use, figure 1.27. Many of the counties with tertiary care hospitals have largely increased their use of both anidulafungin and micafungin at the expense of caspofungin. The echinocandins have a fungicide effect against candida species and a fungiostatic effect against *Aspergillus fumigatus*. Therefore those agents are increasingly used as first line therapy for patient with febrile neutropenia when antibiotics alone have not been successful and when there is a suspicion of infection with yeasts or mold. Both indications and side effects differ a little between the different agents but the antifungal spectrum is similar.

FIGURE 1.27. Sale of different echinocandins in hospital care 2008-2013, DDD/one million inhabitants and day

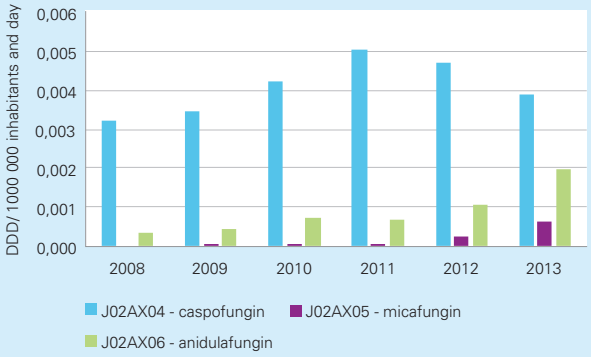
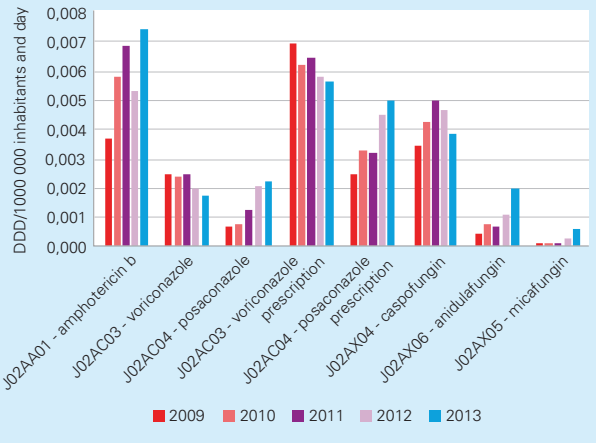


FIGURE 1.28. Sale of broad spectrum antifungals in hospital care, 2009-2013, DDD/one million inhabitants and day



Amphotericin B has for a long time been considered the golden standard for treatment of invasive fungal infection due to its broad spectrum and well documented effect against most yeasts and molds. However the tolerability is a problem. Side effects are common with nephrotoxicity and electrolyte imbalance as the most severe. Therefore amphotericin B is now mostly used in its liposomal form, which improves tolerability. The amount use has differed greatly between years, probably reflecting an extended use in single patients. In the year 2012 the use decreased by 24%, only to be followed by a 40% increase last year, figure 1.28. Some counties report a considerable increase in their use of amphotericin B while other counties haven´t use a single dose.

During the last years there have been many reports of a shift in the distribution of candida species, with an increase in non albicans species, especially *C. glabrata*, whose sensitivity to the azoles is debated. Two European centers have also reported the emergence of voriconazole resistance in *Aspergillus fumigatus* during azoletherapy (Howard S.J. et al., 2009).

An increased awareness and monitoring of developing resistance to antifungal drugs is warranted.

In outpatient care

79% of all systemically administrated antifungal drugs are sold on prescription. The majority of those prescriptions took place in primary health care. The most commonly prescribed drug is fluconazole (79%), mainly for mucocutaneal infections.

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

Data comparing sales of antimycotic drugs between different countries are rare but recently ESAC published comparative data from different European countries, showing that the Swedish figures of sale are comparably low (European Centre for Disease Prevention and Control, 2014).

Use of antimicrobials for animals

Statistics on total sales of antimicrobials for use in animals in Sweden are available since 1980. For a review of data from 1980-2000, see SVARM 2000. Data are derived from sales statistics and represent an approximation of the real use of antimicrobials, assuming that the amount sold is also used during the observation period. Details on data source and inclusion criteria are given in Background material and references.

Trends in animal populations

Changes in the numbers of animals may affect trends in statistics on use of antimicrobials. The number of pigs slaughtered has decreased by 14% in five years, while the number of broilers was 13% higher in 2013 than in 2009. The number of dairy cows has decreased by 3% in five years. The number of horses was 349 000 in 2010. The number of dogs was 784 000 in 2012 and 729 000 in 2006. Further details on animal numbers are found in Background material and references.

Completeness of data

Before July 2009, all Swedish pharmacies belonged to a state owned co-operation. Since, the market has been reregulated and today there are many pharmacies competing on the market. All pharmacies are obliged to report their sales to the Swedish eHealth Authority.

Concerns have been raised that after the reregulation, the statistics on sales of veterinary medical products with a general marketing authorisation in Sweden is less complete than before 2010, in particular for drugs authorised for animals. The competent authority will investigate these claims. No estimate of the magnitude of the problem was available at the time of the analyses underlying the SWEDRES-SVARM report. SVA therefore attempted to produce such an estimate for the sales of antimicrobials.

Sales from pharmacies to animal owners are to be reported to the eHealth Authority instantaneously and the transfer of data is automatic. Sales to veterinarians for use in veterinary practice are to be reported on a monthly basis. It is assumed that the lack of completeness relates to the latter type of sales. About 68% and 21% of reported sales from pharmacies during 2013 expressed in kg active substance were products for injection and for oral medication of individual animals, respectively. Of these two product types, 57% and 21%, respectively, was sold for use in veterinary practice. Products for oral medication of groups of animals are almost always sold to animal owners and sales of intramammary products constitute only 1% of the total sales in kg active substance. Thus, a problem with lack of completeness would mainly affect the statistics on sales of injectable products.

Of the total sales of injectable products, the ten products with highest sales from pharmacies during 2013, in kg active substance, were selected and the marketing authorisation holders were contacted. Information on sales to pharmacies for all marketed product-package types of the selected products was collected as number of packages. Number of packages sold and amount of active substance sold from wholesalers to pharmacies was compared to the sales from pharmacies to veterinarians and animal owners. The sales from wholesalers to pharmacies were 11% higher than the sales from pharmacies. The difference varied between classes; for benzylpenicillin it was 12%, for tetracyclines 5% and for trimethoprim-sulphonamides it was 4%.

The observed lack of completeness affects products for injection with general marketing authorisation in Sweden. Other types of products are less likely to be affected. Based on this assumption, the overall difference in total sales to and from pharmacies was calculated to 7%. The figure is uncertain as the difference varied between classes of antimicrobials, and there may be some lack of completeness for certain other products.

TABLE 1.9. Yearly sales of antimicrobial drugs for veterinary use expressed as kg active substance and percent injectable products in 2013 per class.

ATCvet code	Antimicrobial class	2004	2005	2006	2007	2008	2009	2010	2011[b]	2012	2013	Percent injectables 2013
QJ01AA, QG01A	Tetracyclines	1 329	1 562	1 516	1 853	1 649	1 174	1 115	1 073	881	935	45%
QJ01BA	Amphenicols									<1	3	100%
QJ01CE, -R, QJ51	Benzylpenicillin[a]	7 814	7 571	7 860	7 582	7 758	7 721	7 546	6 696	6 362	5 952	99%
QJ01CA, QJ01CR	Aminopenicillins	875	911	920	927	938	1 068	907	723	649	645	20%
QJ01D	Cephalosporins	928	1 009	1 217	954	820	738	575	498	410	330	1%
QA07AA, QJ01G, -R, QJ51R	Aminoglycosides and polymixins	606	62	750	718	643	609	557	503	483	341	31%
QA07AB, QJ01E	Sulphonamides	2 462	2 535	2 543	2 427	2 303	2 128	1 998	1 867	1 813	1 707	42%
QJ01E	Trimethoprim & derivatives	406	437	450	438	416	379	357	338	329	320	45%
QJ01F	Macrolides & lincosamides	1 095	1 080	1 254	1 520	1 096	988	739	648	632	564	17%
QJ01MA	Fluoroquinolones	187	184	195	180	169	164	148	120	106	52	55%
QJ01XX92, - 94	Pleuromutilins	387	338	459	506	572	398	174	140	99	126	13%
Total		**16 089**	**16 389**	**17 164**	**17 106**	**16 364**	**15 368**	**14 117**	**12 606**	**11 763**	**10 975**	**69%**

[a] Also includes small amounts of penicillinase stable penicillins; [b] For some classes data on sales of products sold with special licence may be incomplete for 2011 (indicated in red).

Most of the trends identified in the data presented below have been observed before 2010 and there are known explanations relating to *e.g.* changes in prescribing behaviour or improved animal health that support the view that there is a true decrease although the magnitude in recent years cannot be determined. The exception is sales of benzylpenicillin where sales have decreased from 2010. This trend is also corroborated by data from other sources indicating a true decrease (see Comments on trends by animal species, Dairy cows). However, from 2010 and onwards the magnitude of the changes cannot be assessed for classes where injectable products are a major part.

Taken together, the lack of completeness of data from 2010 should be kept in mind when interpreting the data from recent years. Overall, the difference between true sales and those presented below may be 5-10% for 2013. The lack of completeness is likely to mainly affect classes where injectable products are the major part and not those where oral medication of individuals or groups dominate.

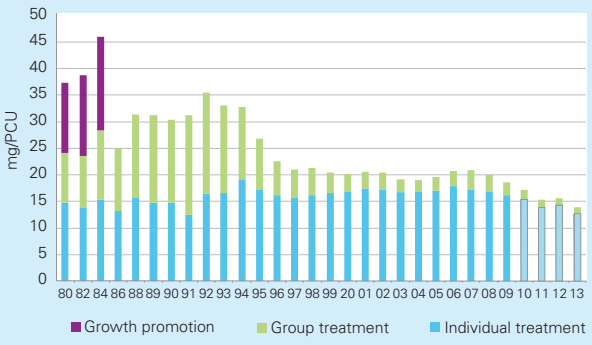
Overall sales

The total yearly sales of antimicrobials over the last decade are presented in Table 1.9. Given the problems with lack of completeness discussed above, the percentage injectables of the total amount sold of each class is also presented. The potencies of different antimicrobials are not equal and therefore each class should be evaluated separately. Also, the above mentioned uncertainty about completeness of data should be kept in mind when interpreting data from the last three years.

Of the total sales expressed as kg active substance, about 90% are products formulated for treatment of individual animals (injectables, tablets, intramammaries) and about 10% for treatment of groups or flocks (premixes, oral powders, solutions for in water medication).

To correct for changes in the numbers of animals over time, the population correction unit (PCU) described in a recent publication from the European Medicines Agency was applied (EMA, 2011). The PCU is a purely technical term representing an approximation of the summed live-weight of the major animal populations, excluding companion animals. In Figure 1.29, the total sales of antimicrobials for animals (including sales for companion animals) from 1980 are presented as mg active substance per PCU. The overall sales have decreased by more than 60% compared to the average figures for 1980-1984 (i.e. before the Swedish ban on growth promoting antimicrobials in 1986). This is explained both by the removal of growth promoting antimicrobials in 1986 and

FIGURE 1.29. Sales of antimicrobials for animals expressed as mg per population correction unit (PCU)[a].



[a] Data on injectable products for years 2010-2013 are uncertain because of lack of completeness. This is indicated by a paler colour for antimicrobials for individual treatment.

by a major gradual decrease from the mid 90s of the sales of veterinary products for medication via feed or water (group medication).The decrease from 2009 as presented in Figure 1.29 is 25% and the estimated overall lack of completeness in 2013 is 5-10% (see Completeness of data). Thus, there is most likely a true decrease also in recent years but its magnitude is uncertain.

In Table 1.10, the sales of antimicrobial products formulated for injection are presented. Trends from 2010-2013 are uncertain as there is a lack of completeness in data (See Completeness of data).

In January 2013, a regulation limiting veterinarians' right to prescribe fluoroquinolones and third and fourth generation cephalosporins entered into force (SJVFS 2013:42). These antimicrobials may only be prescribed for animals if a microbiological investigation shows that alternative choices cannot be expected to be effective. Exceptions are for example acute life threatening infections. The magnitude of the effect of the regulation cannot be assessed directly from the sales of fluoroquinolones. However, the decrease in sales of these antimicrobials is larger than the estimated lack of completeness. Further, an increase in the amounts sold of trimethoprim-sulphonamides from 2012 to 2013 probably reflects a change to this class in situations when fluoroquinolones would have been used before the regulation.

In Table 1.11, the sales of products formulated for oral medication of individual animals are presented. For this category, the completeness of data is likely to be very high and trends can be assessed. For all classes except trimethoprim-sulphonamides and aminoglycosides, this category of antimicrobials is tablets sold for companion animals. The aminoglycosides also include products authorised for farm animals while the trimethoprim-sulphonamides are mostly products for horses.

TABLE 1.10. Yearly sales of antimicrobial drugs formulated for injection[a].

ATCvet code	Antimicrobial class	2006	2007	2008	2009	2010	2011[b]	2012	2013
QJ01AA	Tetracyclines	564	588	557	527	492	471	422	424
QJ01BA	Amphenicols							0	3
QJ01CE, -R, QJ51	Benzylpenicillin	7 778	7 505	7 674	7 641	7 492	6 627	6 290	5 901
QJ01CA, QJ01CR	Aminopenicillins	134	142	143	152	144	146	143	131
QJ01DD	Cephalosporins	26	26	25	21	13	13	8	4
QJ01G, -R,	Aminoglycosides	345	343	318	301	272	246	210	104
QJ01E	Trimethoprim & sulphonamides	804	685	691	669	685	667	699	857
QJ01FA	Macrolides	241	216	136	118	101	95	95	95
QJ01MA	Fluoroquinolones	132	125	118	113	105	83	69	29
QJ01XX92, - 94	Pleuromutilins	39	36	36	28	17	13	14	17
Total		**10 064**	**9 666**	**9 699**	**9 568**	**9 322**	**8 362**	**7 950**	**7 565**

[a] Figures from 2010-2013 are uncertain because of an overall lack of completeness of around 11%; [b] For some classes data on sales of products sold with special licence may be incomplete for 2011 (indicated in red).

TABLE 1.11. Yearly sales of antimicrobial drugs formulated for oral medication of individual animals.

ATCvet code	Antimicrobial class	2006	2007	2008	2009	2010	2011	2012	2013
QJ01AA	Tetracyclines	45	44	47	48	46	49	50	47
QJ01CA, QJ01CR	Aminopenicillins	775	756	681	650	598	541	501	500
QJ01DB	Cephalosporins	1 186	924	792	714	562	484	402	325
QA07AA	Aminoglycosides	131	126	131	118	109	98	102	77
QA07AB, QJ01E	Trimethoprim & sulphonamides	2 189	2 179	2 028	1 838	1 670	1 539	1 442	1 169
QJ01FF	Lincosamides	176	194	216	214	210	192	178	164
QJ01MA	Fluoroquinolones	59	52	46	46	39	35	32	22
Total		**4 559**	**4 276**	**3 941**	**3 630**	**3 234**	**2 938**	**2 706**	**2 304**

TABLE 1.12. Yearly sales of antimicrobial drugs authorised for group treatment and ionophoric anticoccidials sold expressed as kg active substance.

ATCvet code	Antimicrobial class	1984	2004	2005	2006	2007	2008	2009	2010	2011[a]	2012	2013
QA07A	Intestinal anti-infectives			163	170	158	106	107	119	77	75	76
QJ01A	Tetracyclines	12 300	712	934	903	1 217	1 040	594	575	552	408	463
QJ01C	Penicillins incl. aminopenicillins				11	28	111	266	164	36	5	13
QJ01F	Macrolides & lincosamides	607	713	680	837	1 107	744	657	427	361	359	305
QJ01MA	Fluoroquinolones		7	5	5	3	5	5	4	2	6	1
QJ01MQ	Quinoxalinesb	9 900										
QJ01XX91	Streptogramins[b]	8 800										
QJ01XX92, -94	Pleuromutilins		355	309	420	471	536	370	157	127	85	109
QP51AA	Nitroimidazoles	1 440										
	Feed additives[c]	700										
Total		**33 747**	**1 787**	**2 091**	**2 346**	**2 984**	**2 543**	**1 999**	**1 447**	**1 154**	**937**	**968**
QP51AH	Ionophoric antibiotics (coccidiostats)[d]	7 900	10 486	11 095	12 335	12 527	13 376	12 471	15 325	14 693	NA[e]	NA[e]

[a] For some classes, data on sales of products sold with special licence may be incomplete for 2011 (indicated in red). Drugs with special licence prescription include colistin, tetracyclines, aminopenicillins and small quantities of benzylpenicillin; [b] Years 1980-1984 sold as feed additives, thereafter on veterinary prescription at therapeutic dosages until 1997; [c] Feed additives other than quinoxalines and streptogramins: avoparcin, bacitracin, nitrovin, oleandomycin and spiramycin; [d] Figures are from the Feed Control of the Board of Agriculture (www.sjv.se); [e] Not available at the time of publication.

The sales of fluoroquinolones have decreased gradually since 2007 (-58%) and by 31% since 2012. The latter more pronounced decrease is probably a reflection of the regulation limiting veterinarians' right to prescribe fluoroquinolones mentioned above.

Major downward trends are noted for almost all classes. For further comments see Comments on trends by animal species, Horses and Dogs.

Data on sales of antimicrobials formulated for medication of groups of animals are given in Table 1.12. Data for 1984 are given as historical reference. As for products for oral medication of individual animals, completeness is likely to be very high. Today, the sales of products for medication of groups of animals are less than 10% of what it was on average before 1986 (counting the sum of veterinary medicines and growth promoters). Products for medication of groups of animals are mainly sold for treatment of pigs. For further comments see Comments on trends by animal species, Pigs.

Comments on trends by animal species

Dairy cows

Växa Sweden publishes a yearly report related to the livestock organizations' work to improve animal health and welfare in dairy cows (Växa Sverige, 2013). For statistics on incidence of antimicrobial treatments of dairy cows enrolled in the Swedish milk recording scheme, data are retrieved from a database with veterinary reported disease events and treatments (Jansson Mörk, 2010).

According to Växa Sweden (2013), the by far most common indication for treatment of dairy cattle is mastitis; around 70% of all recorded treatments of cows. In Sweden, mastitis is generally treated systemically and any changes in treatment incidence, treatment length or choice of antimicrobial for this condition will have a noticeable influence on the statistics on sales of antimicrobials. The reported incidence of treatment of clinical mastitis in dairy cows has decreased over the last five years; from 13.49 to 11.66 per 100 completed/interrupted lactations in 2009 and 2012, respectively. Treatment with penicillin was by far the most common (86%).

Pigs

Antimicrobials for pigs are mostly sold on prescription by pharmacies to the animal owner. Data are therefore not likely to be affected by the lack of completeness discussed above (see Completeness of data).

In 2009 and 2013 the sales of antimicrobials for pigs were 3 780 and 2 913 kg active substance, respectively, or 14.5 and 12.4 mg/kg slaughtered pig (-14% in 5 years). Of the total sales in kg active substance, 70% were products for injection, and of those 58% were products containing penicillin. The sales of fluoroquinolones for pigs were 12 and 5 kg in 2012 and 2013, respectively. The sales of third generation cephalosporins were insignificant (0.01 kg).

In Sweden, products formulated for group medication are mostly used for pigs (Table 1.12). There has been an overall decrease by 52% of sales of such products for pigs since 2009. The sales of pleuromutilins have decreased since the mid 90s and were 68% lower in 2013 than in 2009. The main indication for pleuromutilins (tiamulin, valnemulin) is swine dysentery. Efforts to control the disease through *e.g.* eradication from affected farms and a certification programme have resulted in a decreased need to treat swine dysentery, reflected in overall declining sales figures. The increase from 2012 to 2013 reflects problems with swine dysentery in one large heard. The continued drop in sales of macrolides for group medication (Table 1.12; 53% lower in 2013 than in 2009) is likely to reflect improved knowledge on how to man-

age problems with concomitant infections in herds with post-weaning multisystemic wasting syndrome and the introduction of vaccination strategies.

Poultry

Antimicrobials are rarely used for treatment of bacterial diseases in commercially reared *Gallus gallus*. Localized outbreaks can therefore have a major influence on the sales in a specific year. Over the last five years, the yearly sales of fluoroquinolones for slaughter chickens and hens have been below or much below 1.5 kg. Cephalosporins are never used.

From 2011, the Swedish poultry meat association requests all treatments of broilers, parents and grandparents to be reported as part of the Poultry health control programme. According to the reports, a total of four of 3 133 broiler flocks (0.13%) were treated with either phenoxymethylpenicillin or amoxicillin. This corresponds to 0.08 mg active substance/kg slaughtered chicken. In addition to this, 8 flocks of parent or grandparent birds were treated with either phenoxymethylpenicillin or amoxicillin. These figures are well in line with the sales statistics, keeping in mind that all the quantity sold will not be used.

Coccidiostats of the ionophore group are used as feed additives to control coccidiosis in the production of chickens for slaughter and for turkeys. Since the late 80s, narasin is by far the most widely applied substance for broilers.

Horses

Around two thirds of the sales of trimethoprim-sulphonamides are products for oral use in horses (paste or powder). The sales of such products increased steadily until 2006 but from 2010, there has been a decrease by 41%. About 80% of the sales of this type of products are for use in veterinary practice which implies that the trend cannot be explained by lack of completeness of data. Since 2010, the number of mares covered and number of foals born has decreased (Anonymous, 2012). Among the indications for trimethoprim-sulphonamides in horses are reproductive disorders and various conditions in foals. Thus, it is probable that the decrease in sales of trimethoprim-sulphonamides is explained by the lower number of mares covered and a lower number of foals born.

The sales of other antimicrobials for horses is difficult to estimate, as they are frequently administered by the veterinarian in connection with an examination, either in ambulatory practice or in clinics or hospitals.

Dogs

Data on outpatient sales of veterinary antimicrobials for dogs have a high degree of completeness. Sales decreased by 637 kg since 2009. The most prominent reduction is of first generation cephalosporins (380 kg or 60% of the reduction). During the same time, the population of dogs has increased by approximately one percent per year.

In 2006, the total sales of antimicrobials for oral use in dogs, both veterinary antimicrobials and those authorised for use in humans, corresponded to 563 packages per 1000 dogs. Since then, the sales have decreased to 305 packages per 1000 dogs (-46%). The most prominent changes relative to 2006 are noted for cephalosporins (-77%), aminopenicillins with clavulanic acid (-56%), and fluorquinolones (-67%).

As described in SVARM 2008, the emergence of infections with multiresistant methicillin resistant *Staphylococcus pseudintermedius* and methicillin resistant *S. aureus* triggered a number of national and local initiatives. This has most likely led to changes in prescribers' behaviour, which in turn explains the downward trends in sales of antimicrobials for dogs.

Comparison of antimicrobial use in human and veterinary medicine

Data included and calculations

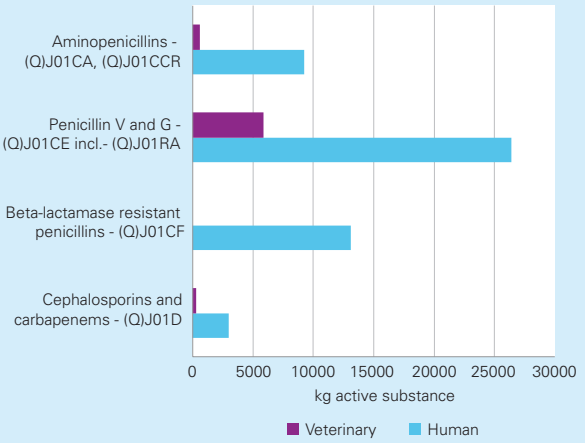
The figures on total amount of antimicrobials sold for systemic use of antimicrobials to humans (ATC group J01 excluding methenamine and JA07AA oral glycopeptides; out-patient and hospital sales) were retrieved as defined daily doses and calculated to kg active substance. Figures on sales of antimicrobials for use in animals (QJ01 and QJA07AA, total sales) are those presented in "Use of antimicrobials for animals". Sales for aquaculture were not included, nor were sales of drugs authorized for human use but sold for animals. The contribution of such sales to the total volumes is minor. It was assumed that the amounts sold were also used.

To estimate the body mass of the human population, data on population numbers by age were multiplied with the corresponding average body weights from studies made by Statistics Sweden. For animal body mass, the method for calculation of population correction unit was used (EMA 2011). This unit roughly corresponds to the total body mass of major animal populations, excluding dogs and cats.

Comparison of use in tonnes active substance

In total, 62.5 and 10.8 tonnes of antimicrobials in included ATC classes were sold for use in human and veterinary medicine, respectively. It should be noted that there is a lack of completeness of 5-10% of the sales of antimicrobials for animals (See Completeness of data in use of antimicrobials for animals). Figure 1.30 displays the sales of beta-lactam antibiotics. These substances are by far the most used antimicrobials in both human and veterinary medicine and also represent the largest amounts measured as kilograms. Penicillins represent most of the amount in kg active substance of antibiotics for both humans and animals; approximately 80 and 60% respectively. The substances shown in Figure 1.31 are sold in smaller quantities (n.b. the difference in indexation of the x-axis between the figures), but given their chemical and pharmacological properties, their impact on the emergence of antibiotic resistance and the environment is probably more pronounced than that of the penicillins. In the figures, only antimicrobials sold in a total quantity exceeding 1000 kg during 2013 are included. The only class where use in animals outweighs human use is trimethoprim-sulphonamides, of which two thirds are sold for horses.

FIGURE 1.30. Amount of beta-lactam antibiotics in human and veterinary medicine, kg active substance, 2013. Please note the difference in indexation of the x-axis between figures 1.30 and 1.31.



Comparison of use expressed as mg substance per kg body mass

When measuring the total antibiotic use in relation to estimated kg body mass in 2013, the sales were 99.1 and 13.8 mg per kg body mass in human and veterinary medicine, respectively. In Figure 1.32 a comparison of sales of antimicrobials for use in humans and animals are shown expressed as mg per kg body mass. Only classes where the total sales exceeded 1000 kg active substance are shown. Data on the total use does not take the heterogeneity of the likelihood of exposure within the population into account. This is especially true for data on sales for animals, as certain substances may only or mainly be sold for use in one particular animal species. This means that the selective pressure in a particular subset of the population (i.e. a particular animal species) can be far larger than in the total population. Nevertheless, in Figure 1.32 the largest difference is noted for the fluoroquinolones where use in humans is 72 times higher than in animals.

FIGURE 1.31. Amount of fluoroquinolones, macrolides, lincosamides, trimethoprim and suphonamides, and tetracyclins in human and veterinary medicine, kg active substance, 2013. Please note the difference in indexation of the x-axis between Figure 1.30 and 1.31.

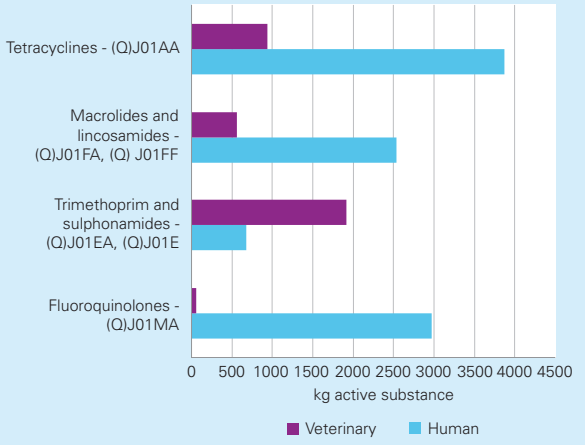
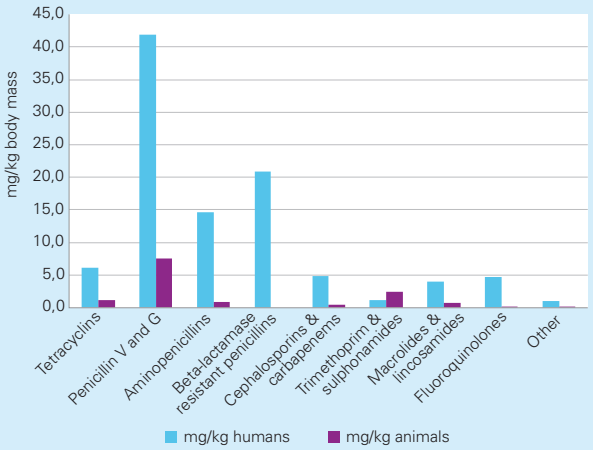


FIGURE 1.32. Use of antimicrobials in humans and animals expressed as mg active substance per kg body mass in 2013.



Antimicrobial resistance

Notifiable diseases

Four bacterial species are included in the Swedish Communicable Disease Act by virtue of their specific resistance mechanisms. These are *Staphylococcus aureus* with resistance to methicillin and other betalactam antibiotics (MRSA), *Streptococcus pneumoniae* with reduced susceptibility or resistance to penicillin (PNSP), *Enterococcus faecalis* and *E. faecium* with resistance to vancomycin (VRE), and bacteria belonging to the family Enterobacteriaceae carrying ESBLs of three different types. As in previous years, the reports of ESBLs have outnumbered the other three species manifold.

In animals, all methicillin resistant coagulase-positive staphylococci are notifiable, thus including MRSA and *Staphylococcus pseudintermedius* (MRSP). Also notifiable in animals is $ESBL_{CARBA}$-producing Enterobacteriaceae. In the monitoring, specific attention is also paid to the occurrence of other ESBL-producing Enterobacteriaceae and VRE.

In the following each of these bacterial pathogens are described.

ESBL-producing Enterobacteriaceae

ESBL-producing Enterobacteriaceae in humans

Background

In February 2007 ESBL-producing Enterobacteriaceae became notifiable by clinical laboratories according to the Communicable Disease Act. As no clinical data is available, information on ESBL cases is restricted to data on age, gender and cultured material. In 2009, a supplement to the 2007 action plan on containment of resistance caused by ESBL-producing bacteria was published, in which the definition of ESBL was broadened. Valid from 2010, the definition of an ESBL included not only classical ESBLs (=$ESBL_A$), which are inhibited by clavulanic acid, but also plasmid-mediated AmpC-betalactamases (= $ESBL_M$) and metallo-betalactamases / carbapenemases (= $ESBL_{CARBA}$). In March 2012 the notifications of bacteria with $ESBL_{CARBA}$ were extended to include both a laboratory and a clinical report, coupled to a demand for contact tracing by the local authorities. An updated version of the action plan was published in 2013.

Notifications of ESBL-producing bacteria according to the Communicable Disease Act

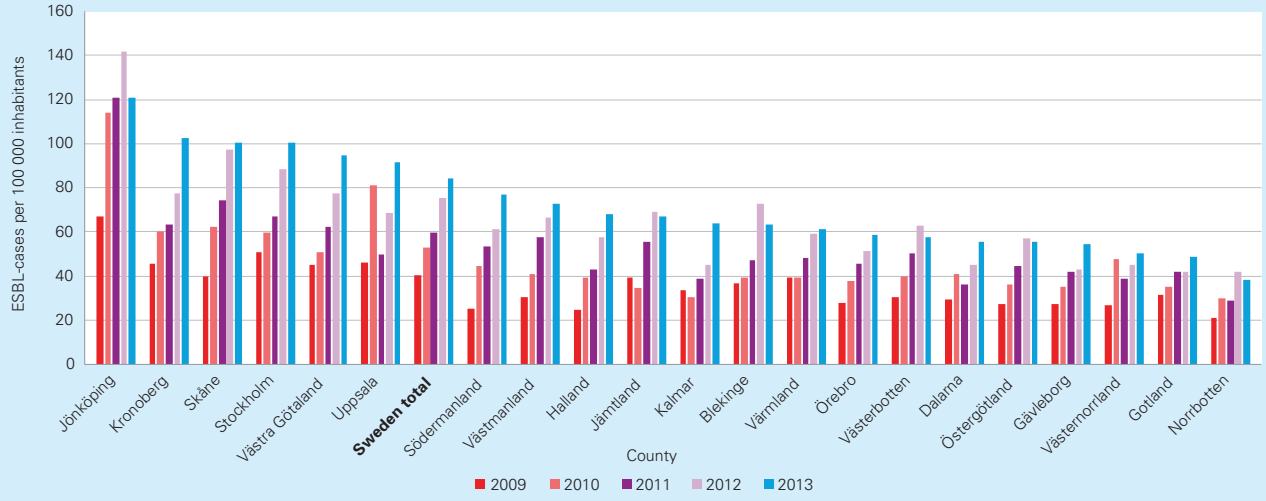
A total of 8131 cases were notified in 2013, an increase with 13% compared to 2012. Since 2007 the number of cases has increased continuously each year with 13-33%. An increased incidence was seen in 16 out of 21 Swedish counties, with the highest incidence found in Jönköping county (121 cases per 100 000 inhabitants; Figure 2.1). The average national incidence was 84 cases per 100 000 inhabitants. In part the large

TABLE 2.1. Distribution of species among cases of ESBL-producing Enterobacteriaceae 2013.

Species	Number of cases
Escherichia coli	7479
Klebsiella pneumoniae	615
Proteus mirabilis	61
Citrobacter species	32
Salmonella species	14
Shigella species	13
Enterobacteriaceae (not specified or species not reported)	167*
Total number reported	**8381****

* Distinction between an ESBL and a chromosomally mediated AmpC was not made for these bacteria
**In 250 patients two or more ESBL-producing species were reported resulting in [a] higher number of isolates than number of cases reported.

FIGURE 2.1. The incidence (cases per 100 000 inhabitants) of ESBL-producing Enterobacteriaceae in Swedish counties 2009-2013, arranged according to incidence figures 2013.

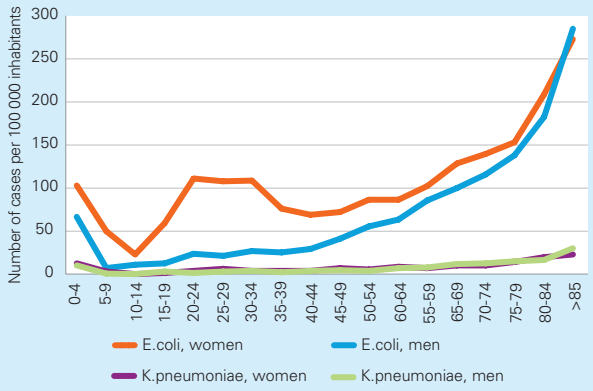


variation in incidence between counties could be explained by different sceening and contact tracing practices.

The most commonly reported species was *Escherichia coli* with 89% of all cases, followed by *Klebsiella pneumoniae* with 7% (Table 2.1). Fourteen cases of *Salmonella* species and 13 *Shigella* species with ESBL were reported in 2013.

ESBL-producing bacteria were most often found in urine samples (59%). The second most common source was fecal samples with 18%. Isolates from rectum and wound samples constituted 9% and 2%, respectively, and blood isolates 4% of the cases. Invasive infections with ESBL-producing bacteria, all in blood, were notified in 402 persons during 2013, as compared to 390 persons in 2013. Among these, 333 were new cases for 2013 and 69 were known carriers of ESBL, notified during the previous years. For details on the frequencies of antibiotic resistance among clinical samples, especially blood and urine samples, please see below in chapter: Resistance in clinical isolates from humans.

FIGURE 2.2. Age and gender distribution of *E.coli* and *K. pneumoniae* ESBL cases 2013.



The incidence in age groups and gender differed between species (Figure 2.2). ESBL-producing *E. coli* were derived from women in 65% of all *E. coli* cases. They had a median age of 52 years compared to 62 years for men. The *K. pneumoniae* ESBL cases were more equally distributed between sexes, with median ages of 58 years for women and 62 years for men.

Enterobacteriaceae with carbapenemases (ESBL$_{CARBA}$)

Enterobacteriaceae producing carbapenemases (ESBL$_{CARBA}$) were made notifiable by both physicians and laboratories from the 15th of March 2012. Before this date Enterobacteriaceae with an ESBL$_{CARBA}$ had been notified from the laboratories only and additional information about the cases had been gathered on a voluntary basis.

The rationale behind the strengthened notification was that infections caused by isolates with ESBL$_{CARBA}$, pose an even greater threat because they limit the treatment options even further. ESBL$_{CARBA}$ of clinical importance belong to one of three kinds, either KPC (*K. pneumoniae* Carbapenemase), MBLs (Metallo-betalactamases, i.e. NDM and VIM) or certain OXA-enzymes. In Sweden, all enzymes with carbapenemase activity are characterized as ESBL$_{CARBA}$ (Giske et al., 2009).

The total number of new cases with an ESBL$_{CARBA}$- producing Enterobacteriaceae in 2013 was 39, compared to 21 new cases in 2012. In 2013, cases were reported from 13 Swedish counties with more than half of the cases being reported from Stockholm and Västra Götaland counties. Twenty-nine cases were reported as acquired abroad and nine cases were reported as domestic (Figure 2.3). Twenty-four of the imported cases were detected through targeted screening after hospitalization abroad, and five cases due to clinical symptoms. For the domestic cases, six cases were detected by clinical symptoms and three were found by contact tracing. The way of acquisition for the domestic cases were by household contacts (2 cases) or hospital related (1 case), but for six cases there was no information of acquisition. For one patient no country of acquisition could be given. This case was detected through contact tracing.

The ESBL$_{CARBA}$-producing Enterobacteriaceae were detected in fecal/rectal samples (20), urine (10), wound (3), respiratory samples (3), blood (2), and one unknown specimen type. The cases were equally distributed between the sexes and the median ages were 46 and 47 years for women and men, respectively.

A total of 95 cases with ESBL$_{CARBA}$-producing Enterobacteriaceae were reported in Sweden 2007-2013. *K.pneumoniae* have dominated, but in 2012 isolates of *E. coli* accounted for half of the cases. Genes coding for carbapenem resistance have also been detected in several other species of Enterobacteriaceae (Figure 2.4). Four different types of ESBL$_{CARBA}$ have been identified so far, and the enzyme types OXA-48 and NDM continues to dominate in 2013. Both these types of enzymes appeared in *E. coli* and *K.pneumoniae* isolates and in most cases together with CTX-M (=ESBL$_A$) and/ or pAmpC CIT (=ESBL$_M$) enzymes. Countries from the Middle East were often mentioned in relation to OXA-48, and the Indian subcontinent and Eastern Europe in relation to NDM. All isolates with ESBL$_{CARBA}$ were multiresistant, leaving very few options for treatment.

FIGURE 2.3. Number of ESBL$_{CARBA}$ cases annually notified in Sweden 2007-2013. In two cases 2011 the same resistance gene was detected in both *E.coli* and *K.pneumoniae*.

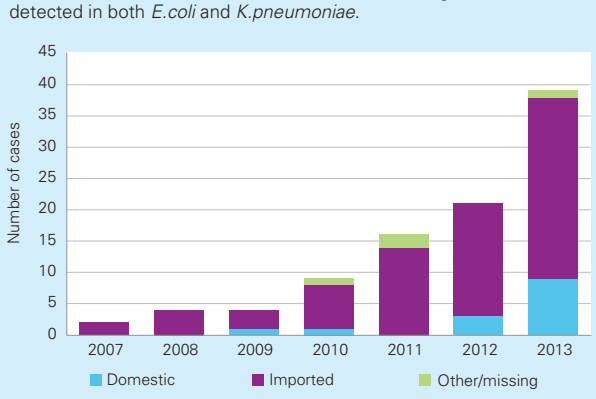
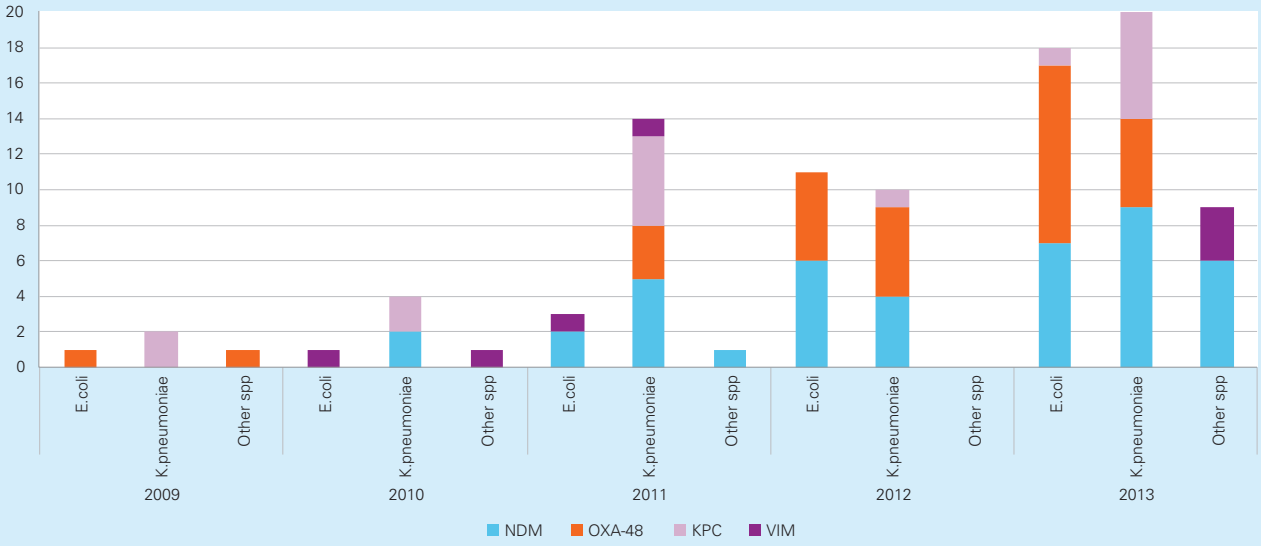


FIGURE 2.4. Number of cases and types of $ESBL_{CARBA}$ in Enterobacteriaceae in Sweden 2009-2013. In samples from two persons two different enzyme types were detected in the same isolate, and in samples from five persons the same enzyme type was detected in more than one bacterial species.



ESBL-producing Enterobacteriaceae in animals

Farm animals

In SVARM, active screening for ESBL-producing *E. coli* in healthy farm animals using samples collected at slaughter for the studies of indicator bacteria has been performed since 2008. During 2013, colon samples from healthy calves (n=202), caecal samples from healthy broilers (n=100) and healthy turkeys (n=55) as well as samples of broiler meat (n=59) were screened for *E. coli* resistant to expanded-spectrum cephalosporins (ESC). Isolates with reduced susceptibility were further investigated by molecular methods.

$ESBL_A$ or $ESBL_M$, *i.e.* classical ESBLs and plasmid-mediated AmpC, respectively, were detected in 1 (<1%) of the samples from calves, in 40 (40%) of the caecal samples from broilers and 30 (51%) of the samples of broiler meat, but in none of the caecal samples from turkeys.

The isolate from calves carried the gene $bla_{CTX\text{-}M\text{-}15}$ ($ESBL_A$) whereas two of the isolates from broilers carried the gene $bla_{TEM\text{-}52}$ ($ESBL_A$) and 38 isolates a gene of the CIT-group ($ESBL_M$). This is the first time that $bla_{TEM\text{-}52}$ has been found in *E. coli* from broilers in Sweden. All isolates from broiler meat carried a gene of the CIT-group. The gene belonging to the CIT-group in isolates from broilers and broiler meat has not been sequenced, but historically such isolates have always carried the gene $bla_{CMY\text{-}2}$.

All isolates with $ESBL_A$ or $ESBL_M$ from calves, broilers, and turkeys were susceptible to meropenem (MIC 0.008 – 0.064 mg/L).

The proportions of faecal samples positive for $ESBL_A$ or $ESBL_M$ in the most recent screenings of various animal species in Sweden are shown in Table 2.2. The proportion of samples from broilers positive for $ESBL_A$ or $ESBL_M$ in 2013 was somewhat lower but comparable to data from previous years.

Furthermore, 2 clinical isolates of *E. coli* from farm animals with phenotypic resistance to ESCs were submitted to SVA for further analysis during 2013. One of the isolates was from a dairy cow with mastitis and carried the gene $bla_{CTX\text{-}M\text{-}27}$. The other isolate came from a broiler and carried the gene $bla_{CMY\text{-}2}$.

Companion animals and horses

During 2013, a total of 37 isolates of Enterobacteriaceae with phenotypic resistance to ESCs from cats (n=2), dogs (n=22) and horses (n=13) were analysed at SVA. The majority was isolated from wounds or from the urogenital tract. Twenty three of the isolates (32%) were confirmed to produce $ESBL_A$ or $ESBL_M$ and are presented in Table 2.3 together with isolates from previous years.

TABLE 2.2. Recent screening studies for *E. coli* with $ESBL_A$ or $ESBL_M$ in healthy individuals of different animal species.

Animal species	Broilers	Calves	Dogs	Horses	Laying hens	Pigs	Turkeys
Year	2013	2013	2012	2010	2012	2011	2013
Number of samples	100	202	84	431	69	184	55
Percent (%) $ESBL_A$	2	<1	0	1	4	2	0
Percent (%) $ESBL_M$	38	0	1	0	9	0	0

TABLE 2.3. Clinical isolates of different bacterial species of Enterobacteriacae, producing $ESBL_A$ or $ESBL_M$ enzymes, from companion animals and horses 2008-2013.

Animal species	$ESBL_A$ or $ESBL_M$	Bacterial species	2008	2009	2010	2011	2012	2013
Cats	CTX-M-14	*Kluyvera* spp.				1		
	CTX-M-15	*Escherichia coli*			1			
	CTX-M-15	*Klebsiella pneumoniae*			1	1		
	CMY-2	*Escherichia coli*		1[a]	1			
	unknown	*Escherichia coli*				1		
Dogs	CTX-M-1	*Escherichia coli*			1		1	1
	CTX-M-2	*Escherichia coli*				1		
	CTX-M-3	*Enterobacter* spp.						1
	CTX-M-3	*Escherichia coli*						2
	CTX-M-9	*Escherichia coli*				1	2	1
	CTX-M-15	*Enterobacter* spp.		1	2	1	2	1
	CTX-M-15	*Escherichia coli*	1			2	3	2
	CTX-M-15	*Klebsiella pneumoniae*		1				
	CTX-M-27	*Escherichia coli*				3		1
	CMY-2	*Escherichia coli*			1	9	4	5
	CMY-2	*Proteus mirabillis*				1		
	unknown	*Escherichia coli*		1	1			
Horses	SHV-12	*Citrobacter braakii*			1			
	SHV-12	*Enterobacter* spp.		1	3	5	3	3
	SHV-12	*Escherichia coli*	2		2	2		
	SHV-12	*Escherichia hermanii*			1			
	SHV-12	*Klebsiella oxytoca*						2
	CTX-M-1	*Enterobacter* spp.						1
	CTX-M-1	*Escherichia coli*		2	9	8	3	3
	CTX-M-1	*Serratia odorifera*			1			
	CTX-M-14	*Escherichia coli*				1		
	CTX-M-15	*Escherichia coli*		1	1			
	CTX-M-15	*Klebsiella pneumoniae*		1				
	unknown	*Escherichia coli*			1			
	unknown	*Klebsiella pneumoniae*			5			

[a] The gene belongs to the CIT-group, but it has not been sequenced and it is therefore uncertain if the enzyme is CMY-2.

Zoonotic aspects on ESBL-producing Enterobacteriaceae

The European Food Safety Authority (EFSA) has concluded that there is indirect evidence for transmission of Enterobacteriaceae with $ESBL_A$ or $ESBL_M$, and their corresponding genes, between farm animals and humans, most likely through contaminated food (EFSA, 2011). The possibility for direct transfer to people handling animals should also be kept in mind.

Available data show that ESBL-producing bacteria are rare in animals in Sweden with the exception of poultry where *E. coli* with $ESBL_M$ resistance is found in a large proportion of birds. The majority of isolates from humans in Sweden is of the $ESBL_A$ type and only 5-8 % were of the $ESBL_M$ type (SWEDRES-SVARM 2012). Furthermore, a recent Swedish study investigating the potential overlap between human clinical isolates and isolates from healthy broilers concluded that the overlap was limited and restricted to similar plasmids, and that no closely related *E. coli* carrying $ESBL_M$ isolates were identified (Börjesson *et al*., 2013).

Accordingly, transmission of Enterobacteriaceae with $ESBL_A$ or $ESBL_M$ between animals and humans is therefore probably not imminent in Sweden. Nevertheless, continued vigilance towards development of reservoirs of ESBL-producing Enterobacteriaceae in animals is warranted.

Gram-negative ESBL-producing bacteria in perspective - humans and animals

Bacteria belonging to the family Enterobacteriaceae carrying genes coding for Extended Spectrum Beta-Lactamases (ESBL) have become the most serious threat to modern medicine in the last decades. In Sweden such bacteria are notifiable in humans and are also closely surveyed in animals.

A simple, yet useful, definition of the rapidly growing number of enzymes summarized as ESBLs is:

1. Beta-lactamases giving rise to phenotypic resistance against cefotaxime and/or ceftazidime (and other so called third generation cephalosporins) and/or carbapenems (e.g. imipenem and meropenem).

2. The gene coding for the beta-lactamase is transferable between strains of the same species or between different species within the family Enterobacteriaceae.

A detailed description of these enzymes and how to detect and characterize them in the laboratory according to the Swedish regulations can be found in the report "ESBL-producerande tarmbakterier. Kunskapsunderlag med förslag till handläggning för att begränsa spridningen av Enterobacteriaceae med ESBL" (http://www.folkhalsomyndigheten.se/pagefiles/12921/ESBL-producerande%20tarmbakterier.pdf).

Global situation

The first reports of gram negative bacteria, especially *Klebsiella pneumoniae* and *Escherichia coli*, expressing resistance to third generation cephalosporins, appeared already in the early 1980s. It was eventually understood that the enzymes conferring this resistance were variants of the well-known plasmid-mediated beta-lactamases TEM and SHV. One or several point-mutations in the genes led to amino acid shifts, which in turn resulted in higher affinity between enzymes and cephalosporins and thereby more effective hydrolysis of the third generation cephalosporins. A previously unknown plasmid-mediated beta-lactamase was named CTX-M and was identified in the early 1990s. This enzyme, coded by genes carried on plasmids soon evolved to become the dominating type of $ESBL_A$. The genes were often carried together with other resistance genes affecting other kinds of antibiotics such as aminoglycosides, tetracyclines and trimethoprim-sulfa. Not only did the plasmids, through horizontal transfer, spread between different strains of Enterobacteriaceae, but also did they infect virulent and successful strains of certain lineages of *E. coli* (e.g. ST131), thereby causing epidemics of such ESBL-producing strains both in healthcare and in the community. In *K. pneumoniae*, other successful lineages resulted in a similar evolution, but these were mainly restricted to the healthcare system.

Globally, the ESBL-producing and often multi-resistant bacteria seems to be dominating on every continent and in every country, and the situation in Sweden is just a mere reflection of the situation around the world. It is also highly probable that new resistance mechanisms, being described in the scientific literature, most often emanate from a foreign country, despite the fact that one new carbapenemase, later named New Delhi metallo-betalactamase (NDM, a $ESBL_{CARBA}$ according to the current Swedish nomenclature), was detected in a patient in Sweden 2008.

Recent research on ESBL-producing bacteria in humans in Sweden

The highly standardized methodology for susceptibility testing in clinical laboratories in Sweden, and the various surveillance systems employed (described in every SWEDRES-SVARM report), ascertain a high probability of detecting and correctly interpreting bacteria as susceptible or resistant. Research activities in the area of antimicrobial resistance and especially ESBL-producing bacteria have been frequent in recent years and have led to several doctoral thesis being defended. Their titles and short summaries are presented below.

Enterobacteriaceae producing extended-spectrum beta-lactamases was defended by Birgitta Lytsy at Uppsala University 2010. She described the first large hospital outbreak of an ESBL-producing ($bla_{CTX\text{-}M\text{-}15}$) and multi-resistant *K. pneumoniae* in Sweden, and also identified risk factors for the acquisition of the outbreak strain in urine cultures. She could also show that the simultaneous increase in ESBL-producing *E. coli* was not secondary to the *K. pneumoniae* outbreak strain.

Extended-spectrum beta-lactamase-producing Enterobacteriaceae: Epidemiology, risk factors, and duration of carriage was defended by Johan Tham at Lund University 2012. He studied the rapid increase in ESBL-producing Enterobacteriaceae, mainly *E. coli*, in the hospital and the community. A high prevalence of fecal carriage of ESBL-producing bacteria in patients who had contracted travellers´diarrhoea after visiting high-risk areas such as Egypt or India was shown. The duration of carriage was also studied, and one fourth of the patients were still carriers after 3-8 months, and one tenth still after three years. The total prevalence of ESBL-producing bacteria in the study population had more than doubled between

2008 and 2010, more so in hospitalized patients than in patients in primary care.

Multidrug-resistant *Escherichia coli* and *Klebsiella pneumoniae:* Treatment, Selection and international spread was defended by Thomas Tängdén at Uppsala University 2012. In a prospective study he could show that ESBL-producing *E. coli* spread through international travel, and twenty-four of 100 Swedes travelling outside Northern Europe acquired ESBL-producing *E. coli* in the intestinal flora. To minimize selection of ESBL-producing *K. pneumoniae* during a hospital outbreak (see also thesis by Birgitta Lytsy), an antibiotic intervention was performed in 2006 with the primary aim to reduce consumption of parenteral cephalosporins. An immediate and radical reduction of cephalosporins was also demonstrated. Time-kill experiments on the antibacterial effects of antibiotic combinations against four carbapenemase-producing strains of *K. pneumoniae* were performed. Double and triple combinations of aztreonam, fosfomycin, meropenem, rifampin and colistin at clinically relevant static concentrations were effective despite bacteria being resistant to the individual drugs, indicating an unexplored potential of antibiotic combination therapy for multidrug-resistant *K. pneumoniae*.

Plasmid-mediated antibiotic resistance – with focus on extended spectrum beta-lactamases (ESBL) was defended by Alma Brolund at Karolinska Institutet 2013. Her studies focused on methods for epidemiological typing of both bacterial strains and plasmids in order to get a better understanding of plasmid dissemination and its role in transferring and spreading resistance genes. Nationwide collections of human ESBL-producing *E. coli* from 2007 to 2011 were used, and it was found that both bacterial strain types (ST131 dominated) and ESBL-genotypes ($bla_{CTX\text{-}M\text{-}15}$ dominated) were stable over the five-year period. Next generation sequencing (NGS) was used as a new plasmid typing approach. The investigated strains often carried several plasmids and multi-replicon plasmids of IncF-type.

Recent research on ESBL-producing bacteria in animals in Sweden

Enterobacteriaceae producing classical extended-spectrum beta-lactamases ($ESBL_A$) or transferable AmpC beta-lactamases ($ESBL_M$) has in recent years also emerged among animals (current Swedish nomenclature). The first findings among animals in Sweden were *E. coli* isolated in 2007 from intestinal content of healthy broilers which in retrospect were confirmed as $ESBL_M$

TABLE. Results of screening for ESBL-producing *Escherichia coli* in healthy animals and meat in SVARM

Animal species	Matrix	Year	No. of samples	No. samples with $ESBL_A$	No. samples with $ESBL_M$	Beta-lactamase					
						CTX-M-1	CTX-M-3	CTX-M-15	TEM-52	SHV	CMY-2
Pigs	Intestine	2008	452	0	0						
Pigs	Meat	2008	50	0	0						
Calves	Intestine	2009	256	0	0						
Broilers	Intestine	2010	200	12	56	12					56
Broilers	Meat	2010	100	4	40	4					40
Horses	Faeces	2010	431	6						6	
Pigs	Intestine	2011	184	3	0		1	1	1		
Pigs	Meat	2011	100	0	0						
Broilers	Intestine	2011	100	3	51	3					51
Broilers	Intestine	2012	200	0	97						97[a]
Broilers	Meat	2012	97	0	40						40[a]
Laying hens	Intestine	2012	69	3	6	3					6
Calves	Intestine	2012	742	5	4	1		4			4
Dogs	Faeces	2012	84		1						1[a]
Broilers	Intestine	2013	100	2	38				2		38[a]
Broilers	Meat	2013	59		30						30[a]
Calves	Intestine	2013	202	1	0			1			
Turkeys	Intestine	2013	55	0	0						

[a] CIT-group, all isolates from broilers or broiler meat with a CIT-group enzyme in previous years possessed the gene $bla_{CMY\text{-}2}$.

(bla_{CMY-2}). The following year $ESBL_A$ was confirmed in clinical isolates of *E. coli* from a dog ($bla_{CTX-M-15}$) and a horse (bla_{SHV-12}).

Vigilance towards ESBL-producing and cephalosporin-resistant bacteria from animals in Sweden increased substantially after these findings. The main reason for this is the potential impact on public health if animals become reservoirs of resistant bacteria and resistance genes transferrable to humans. Reservoirs among farm animals are particularly worrisome due to the risk of food borne transmission. Cephalosporin resistance is of concern also from an animal health perspective, since it undermines the therapeutic arsenal available in veterinary medicine.

Studies in Sweden related to ESBL resistance in bacteria from animals include estimating the prevalence in animal populations and in food. In addition, studies designed to elucidate specific issues and knowledge gaps have been performed. Activities 2008-2013 are shortly described below.

ESBL resistance in clinical isolates from animals

Monitoring ESBL resistance in clinical isolates is mostly passive and based on observations at diagnostic laboratories of phenotypes indicating ESBL resistance. Laboratories are advised to submit such isolates to SVA for further phenotypic and genotypic typing but this is not mandatory and compliance is unknown.

It is therefore not possible to accurately estimate the prevalence of ESBL resistance in clinical isolates from animals. The small number of isolates confirmed since 2008, however, indicates that such resistance so far is not a major problem in animal health care (see Table 2.3).

ESBL-producing bacteria in healthy animals and meat

In SVARM, active monitoring of ESBL-producing *E. coli* in faecal samples from healthy farm animals was introduced in 2008. In addition, healthy horses and dogs as well as samples of meat have been screened using the same methodology.

The studies so far performed show that bacteria with ESBL resistance are uncommon among healthy animals in Sweden (Table). Exceptions are broilers and laying hens where $ESBL_M$ is common. Use of antimicrobials in broilers and laying hens is extremely uncommon in Sweden and cephalopsorins are never used. Most likely the high prevalence is due to introduction of resistant bacteria via poultry imported for breeding purposes.

Spread of ESBL-producing *E. coli* in broiler production by imported breeding stock

In 2010 to 2011, paper linings from boxes in which imported grandparent broiler flocks were transported to Sweden were screened for ESBL-producing *E. coli*. One positive grandparent flock and its progeny were sampled longitudinally through the production pyramid. The relationship of isolates was investigated using MLVA. ESBL-producing *E. coli* carrying bla_{CMY-2} was found in six out of eight imported grandparent flocks. One clone of *E. coli* carrying bla_{CMY-2} was found in flocks of imported grandparents and in all levels of the production pyramid. The findings indicate that introduction through imported breeding stock is one explanation for the high proportion of Swedish broilers colonized with ESBL-producing *E. coli* (Nilsson et al., 2014).

Similarity of *E. coli* with bla_{CMY-2} from broilers and humans

In 2010, 22 isolates of bla_{CMY-2} carrying *E. coli* from intestinal content of Swedish broilers and 72 contemporary human clinical isolates were characterised by molecular methods.

Apart from carrying the bla_{CMY-2} gene, human and broiler isolates were distinct from each other with regard to MLST and PFGE. In addition, all broiler isolates, but only 26% of the human isolates, carried bla_{CMY-2} on an incK plasmid. Moreover, only a minority (6%) of ESBL-producing clinical isolates from humans in Sweden is of the $ESBL_M$ type (SWEDRES-SVARM 2012). This shows that in Sweden there s a limited overlap between isolates of *E. coli* producing ESBL and pAmpC in Sweden from humans and broilers (Börjesson et al., 2013).

Occurrence of ESBL-producing *E. coli* in imported meat

The prevalence of ESBL-producing *E. coli* was investigated in 518 samples of imported meat from cattle, pigs and broilers in 2009-2011. *Escherichia coli* producing $ESBL_A$ or $ESBL_M$ were found in 0-8% of imported beef samples and in 2-13 % of imported pork samples. The highest prevalence was in South American broiler meat (95%), followed by European broiler meat (61 %) and Danish broiler meat (15%) (Egervärn et al., 2011).

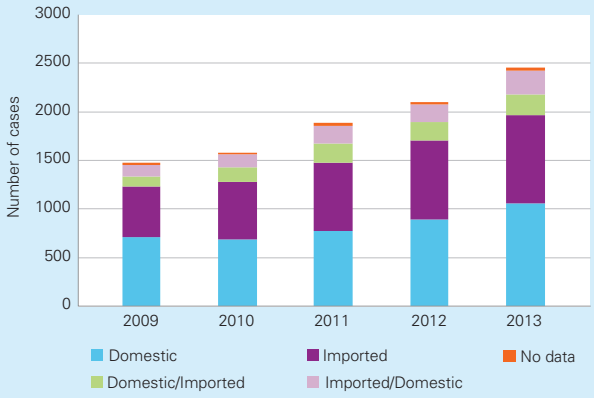
Methicillin resistant *Staphylococcus aureus* (MRSA)

MRSA in humans

Background

MRSA has been mandatory notifiable since the year 2000. Infection control programmes have been developed and implemented locally under supervision of the County Medical Officers (CMO) and infection control teams. These programmes are based on early case-finding through extensive screening of patients with risk factors and contact tracing combined with infection control measures such as isolation of MRSA positive cases and intensive campaigns on basic hygiene precautions. The following presentation is based on data collected in the national web-based notification system SmiNet. During the last seven years an active effort has been made to improve the quality of data and to collect missing data. The notifications have been reviewed and complemented with available relevant epidemiologic information from investigations around each case in collaboration with the CMOs.

FIGURE 2.5. Number of MRSA cases notified annually by country of infection, Sweden 2009-2013. "Domestic/Imported" and "Imported/Domestic" indicate several mentioned countries of infection with the most likely mentioned first.



Notifications of MRSA according to the Communicable Disease Act

In 2013 a total of 2454 cases of MRSA were notified, an increase by 357 cases (17%) compared to 2012 (Figure 2.5).

Nine of the Swedish counties, Jämtland, Jönköping, Kalmar, Skåne, Värmland, Gotland, Stockholm, Kronoberg and Västra Götaland, had a higher incidence than the average national incidence of 25 cases/100 000 inhabitants (Table 2.4).

In 2013, 43% (n=1054) of all reported MRSA cases were domestically acquired and 37% (n=915) were acquired abroad. Syria (95 cases), Iraq (74), Philippines (41), Thailand (36) and Afghanistan (34) made up the five most common countries for imported MRSA infection. For approximately 20 percent country of infection was unclear ("Domestic/Imported" and"Imported/Domestic").

TABLE 2.4. MRSA notifications according to the Communicable Disease Act 2009-2013 by county.

County	2009		2010		2011		2012		2013	
	No	Inc *	No	Inc*	No	Inc*	No	Inc*	No	Inc*
Blekinge	11	7.2	8	5.2	17	11.1	19	12,5	35	22,9
Dalarna	28	10.1	27	9.7	38	13.7	32	11,6	31	11,2
Gotland	6	10.5	5	8.7	9	15.7	10	17,5	17	29,7
Gävleborg	12	4.3	26	9.4	36	13.0	30	10,8	51	18,3
Halland	45	15.2	40	13.4	51	16.9	46	15,1	55	17,9
Jämtland	18	14.2	28	22.1	19	15.0	33	26,1	61	48,2
Jönköping	66	19.6	54	16,0	61	18.1	86	25,4	127	37,2
Kalmar	42	18.0	72	30.8	45	19.3	78	33,4	78	33,4
Kronoberg	26	14.2	23	12.5	40	21.7	40	21,5	54	28,9
Norrbotten	13	5.2	21	8.4	20	8.0	30	12,1	37	14,8
Skåne	284	23.1	313	25.2	369	29.5	380	30,1	391	30,7
Stockholm	375	18.6	412	20,0	502	24.0	595	28	628	29
Södermanland	23	8.5	30	11.1	34	12.5	31	11,3	50	18
Uppsala	33	9.9	41	12.2	42	12.4	79	23,1	73	21,1
Värmland	33	12.1	28	10.2	48	17.6	43	15,7	82	29,9
Västerbotten	28	10.8	39	15,0	20	8.0	18	6,9	36	13,8
Västernorrland	43	17.7	30	12.4	24	9.9	36	14,9	42	17,3
Västmanland	46	18.3	32	12.7	28	11.0	35	13,7	48	18,5
Västra Götaland	258	16.4	264	16.7	347	21.8	361	22,6	432	26,7
Örebro	45	16.1	40	14.3	44	15.6	55	19,4	54	18,9
Östergötland	45	10.5	47	10.9	71	16.5	60	13,8	72	16,4
Total	**1480**	**15.8**	**1580**	**16.8**	**1884**	**19.9**	**2097**	**21,9**	**2454**	**25,4**

*=Incidence (cases/100 000 inhabitants)

Among the domestic MRSA cases 2013, the incidence was highest in the age group 0-6 years, followed by the age group 80 years and older (Figure 2.6). The incidence of MRSA among the very old and the very young was substantially higher (≥ 24) than in the other age groups. In these groups the incidence had remained at a low but slightly increasing level, in 2013 reaching 8-11. Among children (0-6 years), the infants (0 years) were clearly overrepresented (Figure 2.7). Of 131 cases 51 (39%) were hospital related, 31 of these were part of neonatal outbreaks comprising four or more cases. Sixty-nine cases in this group were community aqcuired.

In 2013, 41% of the domestic cases were identified through contact tracing, 11% in targeted screening, and 47% during investigations of clinical symptoms (Figure 2.8 A). For imported cases the corresponding figures were 15%, 54%, and 29%, respectively (Figure 2.8 B). The majority of samples from investigations of clinical symptoms were wound samples (63%). Invasive MRSA infection was reported in 42 cases 2013 compared to 36 cases 2012. 31 of those were newly notified persons 2013 and 11 occurred in patients already known to carry MRSA.

Epidemiological classification of the acquisition of MRSA was based on information in the clinical notifications and from subsequent investigations by the CMOs, Figures 2.9, A and B. Community-acquired infections dominated among domestic cases 2013 and comprised 65% (n=687) of all domestic cases, Figure 2.9 A. Among the imported cases the proportion of community acquired infections was 45% (n=410), Figure 2.9 B. Hospital acquired MRSA was comparatively more common in imported cases, 30% (n=278), than among domestic cases, 13% (n=140). The number of domestic cases with hospital acquired MRSA had almost doubled, from 72 (2012) to 140 (2013). On the other hand, the number of domestic cases with MRSA acquired in healthcare/care outside hospital decreased to 87 in 2013 compared to 130 in 2012. In addition, the number of imported cases with MRSA acquired in healthcare/care outside hospital declined to 59 (6%), from 109 (12%) in 2012.

Outbreak investigations

During 2013 approximately 30 outbreaks (2-13 cases/outbreak) were reported in 14 different counties. These outbreaks comprised 125 cases, representing 5% of all cases of MRSA in 2013. The three most common *spa*-types were t002, t008 and t019. One third of the outbreaks were reported from healthcare institutions outside hospitals, whereas 55% were hospital outbreaks. Two of the outbreaks in 2013 were connected to sports.

Epidemiological typing of MRSA

The primary method used for epidemiological typing of the MRSA isolates sent to the Public Health Agency of Sweden

FIGURE 2.6. Incidence per age group of all notified domestic MRSA cases in Sweden 2009-2013.

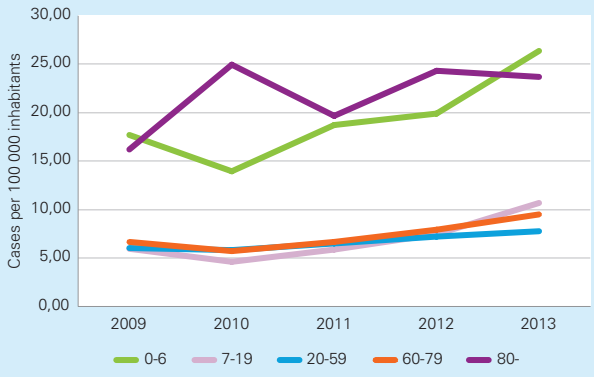


FIGURE 2.7. Incidence of notified domestic MRSA cases in the age group 0-6 years in Sweden 2009-2013.

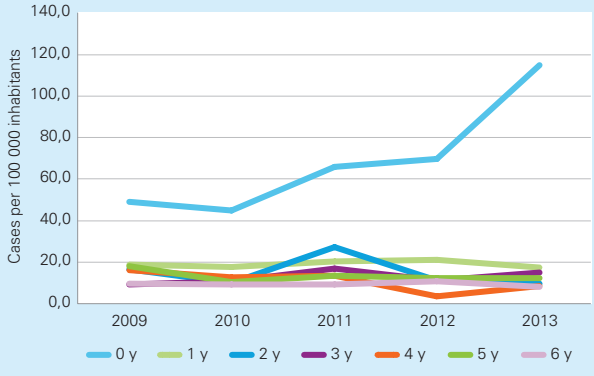
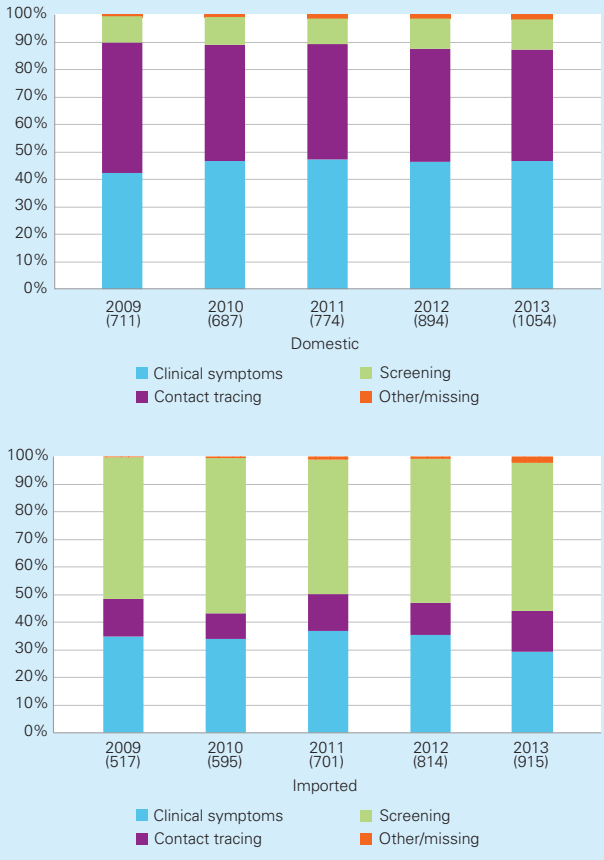
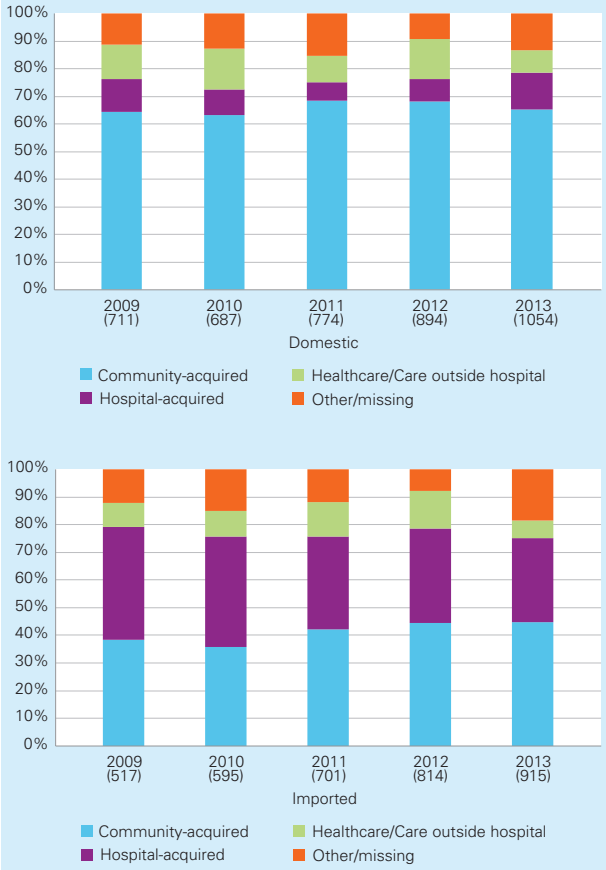


FIGURE 2.8, A AND B. The reasons for detection of domestic (A, top) and imported (B, bottom) MRSA cases in Sweden 2009-2013. Number of reported cases each year is shown in brackets.



is *spa*-typing. This method is DNA sequence based. It has a standardized, unambiguous and internationally well recognized nomenclature (http://spaserver.ridom.de/). In addition to *spa*-typing the PVL status, i.e., absence/presence of genes coding for PVL, is determined by PCR. PVL status is a useful epidemiological marker that differentiates MRSA variants within *spa*-types.

FIGURE 2.9, A AND B. Epidemiological classification of the acquisition of domestic (A, top) and imported (B, bottom) MRSA, Sweden 2009-2013. Number of reported cases each year is shown in brackets.



In 2013, *spa*-typing results were available for MRSA isolates from 2267 cases (92% of the notified cases). All but 13 of the isolates were typable. The total number of *spa*-types recorded among the 2254 typable isolates were 358. Of these isolates, 846 (37%) were PVL-positive, compared to 34% in 2012. The ten most common MRSA variants seen during 2013 were t008, PVL-pos (n=154), t223, PVL-neg (n=137), t002, PVL-neg (n=118), t044, PVL-pos (n=113), t019, PVL-pos (n=87), t127, PVL-neg (n=76), t304, PVL-neg (n=54), t002, PVL-pos (n=48), t437 PVL-pos (n=36), t386, PVL-neg (n=32) and t688, PVL-neg (n=32). The ten most common *spa*-types in 2009-2013 are listed in Table 2.5. Five *spa*-types have been among the top ten since 2009. These are t008, t002, t044, t019 and t437. In 2013, 1015 cases (41%) had an MRSA with a top ten *spa*-type. New *spa*-types for 2013 on the list were t386 and t688, both ranked number ten. *spa*-type t304 (46 cases) was new among the top ten in 2012 and was seen in 59 cases in 2013. Three of the top ten *spa*-types in 2009 were not seen among the top ten in 2013. They were t032, t037 and t015. One of these types, t015, had been seen every year from 2009 to 2012, but not in 2013.

TABLE 2.6. The ten most common *spa*-types among MRSA from domestic and imported cases in 2013. Number of notifications per *spa*-type and percent PVL-positive isolates are shown.

Domestic			Imported		
***spa*-type**	**No.**	**PVL-pos (%)**	***spa*-type**	**No.**	**PVL-pos (%)**
t002	90	32	t008	66	91
t008	86	87	t223	57	4
t044	47	98	t002	46	22
t127	47	30	t127	46	28
t223	46	0	t019	39	95
t019	37	95	t044	37	89
t304	28	11	t304	28	7
t015	23	0	t037	19	16
t790	18	0	t437	19	74
t437	17	65	t690	18	33
t690	17	59			

TABLE 2.5. The ten most common *spa*-types among MRSA from notified cases in 2009 - 2013. Number of notifications per *spa*-type and percent PVL-positive isolates are shown for 2012 and 2013.

2009	2010	2011	2012			2013		
***spa*-type**	***spa*-type**	***spa*-type**	***spa*-type**	**No.**	**PVL-pos (%)**	***spa*-type**	**No.**	**PVL-pos (%)**
t008	t008	t008	t002	176	36	t008	176	88
t044	t002	t002	t008	132	83	t002	166	29
t002	t044	t019	t019	107	100	t223	139	1
t019	t019	t044	t223	105	1	t044	121	93
t015	t223	t223	t044	81	95	t127	104	27
t437	t437	t127	t127	68	1	t019	93	94
t127	t127	t437	t437	56	52	t304	59	8
t223	t032	t690	t015	55	0	t437	47	77
t032	t015	t015	t304	46	4	t690	46	46
t037	t021	t790	t690	38	58	t386	32	0
						t688	32	0

In Table 2.6 the top ten *spa*-types seen among MRSA isolated from domestic or imported cases in 2013 is shown. Nine of these *spa*-types were present in both groups; t002, t008, t044, t127, t223, t019, t304, t437 and t690. Two *spa*-types were seen only among the MRSA from domestic cases (t015 and t790), and one *spa*-type (t037) was found only among the isolates from imported cases.

MRSA in animals

In Sweden, MRSA in animals was first verified in 2006 and was made notifiable in 2008. During 2013, eight new cases of MRSA were detected; five dogs, one cat, one horse and one dairy cow. Up to and including 2013 a total of 60 cases in animals have been reported (Tables 2.7 and 2.8). Most cases were detected in passive monitoring when animals with clinical infections were sampled. From such samples, isolates of *S. aureus* with resistance to oxacillin were further analysed with confirmatory tests. Screening studies for active monitoring have been performed in pigs, cattle, horses and dogs during different years.

Farm animals

In pigs, there was no active monitoring of MRSA in 2013 and no clinical isolates were detected. Screening studies have been performed four times in pigs since 2006 with only one positive sample from pigs at slaughter in 2010. The latest screening was performed in nucleus and multiplying herds in 2011.

In dairy cattle, active monitoring of selected isolates of beta-lactamase producing *S. aureus* has been ongoing since 2010 and 570 isolates have been tested up to and including 2013. In this monitoring, four isolates of PVL-negative MRSA with *mecC* of *spa*-types t524 and t9111 were detected in 2010-2011 (Unnerstad et al., 2013) and one in 2013 of *spa*-type t843. During the second half of 2013, 500 isolates with-

TABLE 2.7. Isolates of methicillin resistant *Staphylococcus aureus* (MRSA) in Swedish horses, pigs and cows 2007-2013. Shaded areas indicate MIC above EUCAST cut-off values.

Animal species	Year	Clinical background	Antimicrobial													*spa*-type	*mec*-gene
			Oxa[a]	Fox	Pen	Cet	Cli	Ery	Tet	Fus	Gen	Kan	Cip	Tmp	Chl		
Horse	2007	nasal screening	>16	-	>4	1	≤0.25	0.5	64	0.5	>64	>32	1	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	1	≤0.25	0.5	32	0.5	64	>32	1	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	2	≤0.25	1	32	1	>64	>32	1	>32	8	t011	*mecA*
Horse	2008	post-op wound	16	>16	>4	2	≤0.25	1	32	0.5	>64	>32	0.5	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	2	≤0.25	0.5	32	0.25	>64	>32	0.5	>32	8	t011	*mecA*
Horse	2008	nasal screening	>16	16	>4	2	≤0.25	1	32	0.5	64	>32	0.5	>32	8	t011	*mecA*
Horse	2008	post-op wound	>16	>16	>4	2	≤0.25	1	64	1	>64	>32	1	>32	16	t011	*mecA*
Horse	2008	post-op wound	2	>16	4	4	≤0.25	≤0.25	32	0.12	4	32	0.25	>32	4	t011	*mecA*
Horse	2009	wound	16	>16	>4	>8	≤0.25	0.5	64	0.25	16	>32	0.25	>32	8	t011	*mecA*
Horse	2009	post-op wound	16	>16	4	1	≤0.25	0.5	32	0.25	64	>32	1	>32	8	t011	*mecA*
Horse	2010	post-op wound	>16	>16	>4	8	0.5	2	64	1	>64	>32	1	>32	16	t011	*mecA*
Horse	2010	post-op wound	>16	>16	>4	4	≤0.25	1	32	0.5	>64	>32	0.5	>32	8	t064	*mecA*
Horse	2010	post-op wound	>16	>16	>4	8	≤0.25	0.5	64	0.25	64	>32	0.25	>32	8	t011	*mecA*
Horse	2010	wound	>16	>16	>4	4	≤0.25	0.5	32	0.5	>64	>32	0.25	>32	8	t011	*mecA*
Horse	2010	post-op wound	>16	>16	>4	2	≤0.25	1	32	0.5	16	>32	0.25	>32	8	t064	*mecA*
Horse	2010	post-op wound	>16	-	>4	4	≤0.25	0.5	64	0.25	>64	>32	0.25	>32	8	t011	*mecA*
Horse	2011	post-op wound	16	>16	>4	1	≤0.25	≤0.25	32	0.12	32	>32	0.25	>32	4	t011	*mecA*
Horse	2011	skin infection	>16	>16	>4	2	≤0.25	≤0.25	64	0.5	≤0.5	4	0.25	1	8	t011	*mecA*
Horse	2012	wound	>16	>16	>4	8	1	1	64	0.25	>64	>32	0.5	>32	8	t011	*mecA*
Horse	2012	wound	16	-	>4	1	≤0.25	0.5	32	0.25	32	>32	0.25	>32	4	t011	*mecA*
Horse	2013	post-op abscess	>16	4	>4	>8	≤0.25	1	64	1	>64	>32	1	>32	16	t011	*mecA*
Pig	2010	nasal screening	>16	>16	>4	>8	0.5	1	64	0.5	>64	>32	0.25	>32	16	t011	*mecA*
Cow	2010	milk screening	4	16	2	1	≤0.25	≤0.25	≤0.5	0.25	≤0.5	2	0.5	2	8	t524	*mecC*
Cow	2010	milk screening	4	16	1	1	≤0.25	0.5	≤0.5	0.5	≤0.5	2	0.25	1	4	t524	*mecC*
Cow	2010	milk screening	16	>16	>4	4	≤0.25	0.5	≤0.5	0.25	≤0.5	2	0.5	2	8	t524	*mecC*
Cow	2011	milk screening	2	>16	2	2	≤0.25	0.5	≤0.5	0.12	≤0.5	4	0.25	1	8	t9111	*mecC*
Cow	2012	milk screening	>16	>16	2	0.5	≤0.25	0.5	≤0.5	0.25	≤0.5	2	0.25	2	8	t002	*mecA*
Cow	2012	milk	>16	16	>4	1	≤0.25	1	≤0.5	0.5	1	8	0.5	2	8	t002	*mecA*
Cow	2013	milk screening	1	8	0.5	0.5	≤0.25	1	≤0.5	0.5	≤0.5	4	0.5	2	8	t843	*mecC*

[a] tested with 2% NaCl.

out beta-lactamase production were part of the monitoring as well, without any findings of MRSA. PVL-positive MRSA of *spa*-type t002 was isolated from milk and body samples of cattle on a dairy farm in 2012 and 2013 (see below).

Companion animals and horses

In dogs, cats and horses, there was no active monitoring of MRSA during 2013. A screening in dogs was performed in 2012 without detection of MRSA. Screening studies in horses have been performed twice, in 2007 and 2010, with only one positive sample in 2007. In 2013, MRSA was detected in clinical samples, mostly from wound infections, from five dogs, one cat and one horse.

Since MRSA was first detected in 2006, *spa*-type t032 has dominated in companion animals (Grönlund Andersson et al., 2014), and *spa*-type t011, CC398, in horses. Most isolates from horses were from clinical cases with postoperative wound infections (Table 2.7), and all isolates from both companion animals and horses have been PVL-negative.

Zoonotic aspects on MRSA

Zoonotic transmission of MRSA occurs by direct or indirect contacts, making farmers, animal owners, veterinarians and other persons in close contact with animals the population at risk. MRSA is reported globally in farm animals, companion animals and horses. During the last ten years, the zoonotic aspects on MRSA in farm animals, mostly in pigs but also in veal calves, broilers and dairy cows, has widened due to spread of the livestock-associated MRSA CC398 in many countries.

TABLE 2.8. Isolates of methicillin resistant *Staphylococcus aureus* (MRSA) in Swedish dogs and cats 2006-2013. Shaded areas indicate MIC above EUCAST cut-off values.

Animal species	Year	Clinical background	Antimicrobial													*spa*-type	*mec*-gene
			Oxa[a]	Fox	Pen	Cet	Cli	Ery	Tet	Fus	Gen	Kan	Cip	Tmp	Chl		
Dog	2006	post-op wound	>16	>16	>4	8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2006	post-op wound	>16	>16	>4	8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2006	post-op wound	>16	8	>4	>8	≤0.25	0.5	≤0.5	0.25	1	4	>4	2	8	t032	*mecA*
Dog	2007	post-op wound	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.5	≤0.5	4	>4	2	8	t032	*mecA*
Dog	2007	abscess	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2007	post-op wound	>16	>16	>4	>8	0.5	0.5	2	-	1	2	>4	2	4	t032	*mecA*
Dog	2007	post-op wound	>16	16	>4	8	≤0.25	0.5	≤0.5	0.25	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2007	unknown	>16	16	>4	>8	≤0.25	0.5	≤0.5	0.25	≤0.5	4	>4	2	8	t032	*mecA*
Dog	2008	wound	>16	>16	>4	>8	≤0.25	1	≤0.5	0.25	1	2	>4	2	8	t032	*mecA*
Dog	2008	unknown	>16	>16	>4	>8	≤0.25	≤0.25	≤0.5	0.5	1	2	>4	1	8	t032	*mecA*
Dog	2008	unknown	>16	>16	>4	>8	≤0.25	1	≤0.5	0.25	1	2	>4	2	8	t032	*mecA*
Dog	2008	unknown	>16	>16	>4	>8	0.5	>32	≤0.5	0.5	32	>32	>4	>32	16	t127	*mecA*
Dog	2009	post-op wound	8	>16	>4	>8	≤0.25	0.5	≤0.5	0.25	≤0.5	2	>4	2	8	t032	*mecA*
Dog	2009	wound	>16	>16	>4	>8	0.5	1	1	0.5	1	4	>4	4	16	t032	*mecA*
Dog	2010	wound	>16	>16	>4	>8	>32	>32	≤0.5	0.5	1	>32	>4	2	16	t002	*mecA*
Dog	2010	ear	8	-	>4	>8	≤0.25	0.5	≤0.5	0.5	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2010	unknown	>16	16	>4	8	≤0.25	>32	≤0.5	0.5	≤0.5	2	>4	8	4	t020	*mecA*
Dog	2010	skin	16	16	>4	1	≤0.25	≤0.25	≤0.5	8	1	2	0.5	2	8	t002	*mecA*
Dog	2013	wound	4	>16	>4	1	≤0.25	>32	16	0.25	2	>32	0.25	2	8	t127	*mecA*
Dog	2013	wound	16	>16	>4	2	≤0.25	1	≤0.5	0.5	≤0.5	2	0.5	4	8	t304	*mecA*
Dog	2013	wound	>16	>16	>4	2	≤0.25	1	≤0.5	0.25	≤0.5	4	0.5	2	8	t127	*mecA*
Dog	2013	unknown	>16	>16	>4	>8	0.5	1	1	1	1	4	>4	4	8	t032	*mecA*
Dog	2013	wound	16	>16	>4	2	≤0.25	0.5	≤0.5	0.5	≤0.5	2	0.5	>32	8	t223	*mecA*
Cat	2009	urine	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.25	≤0.5	0.5	>4	4	4	t032	*mecA*
Cat	2009	unknown	>16	>16	>4	>8	≤0.25	0.5	≤0.5	0.5	1	1	>4	2	8	t032	*mecA*
Cat	2010	ear	>16	-	>4	>8	≤0.25	0.5	≤0.5	1	≤0.5	2	>4	1	8	t032	*mecA*
Cat	2010	nose	>16	16	>4	>8	≤0.25	≤0.25	≤0.5	0.25	≤0.5	1	>4	1	8	t032	*mecA*
Cat	2011	skin infection	>16	>16	>4	>8	≤0.25	≤0.25	≤0.5	0.25	≤0.5	2	>4	1	8	t022	*mecA*
Cat	2012	wound	>16	>16	>4	>8	≤0.25	≤0.25	≤0.5	0.25	≤0.5	4	>4	2	8	t032	*mecA*
Cat	2012	wound	>16	>16	>4	>8	0.5	1	1	1	1	4	>4	2	16	t032	*mecA*
Cat[b]	2013	wound															

[a] tested with 2% NaCl; [b] Isolate not available for laboratory analyses.

MRSA CC398

Internationally, the livestock-associated MRSA CC398 dominates in farm animals and can be of importance for the overall human MRSA burden in countries with low prevalence of MRSA in humans (EFSA, 2009). In countries with high prevalence of MRSA CC398 in pigs, the pig population constitutes a reservoir of MRSA with continuous transmission to people in close contact with pigs. In the latest screening study MRSA was not detected in Swedish pigs, indicating a favourable situation. However, continuous monitoring is of importance as the situation can change rapidly, for example through import of live animals. MRSA CC398 also occurs among horses and *spa*-type t011, belonging to CC398, is by far the most common type among Swedish horses.

Four PVL-negative MRSA CC398-associated *spa*-types (t034, t011, t571 and t108) were seen among 49 human cases in 2006-2013. The two dominating *spa*-types were t034 (n=25) and t011 (n=19). Nine of the 49 cases were from 2013, five with *spa*-type t034 and four with t011. The epidemiological information on these cases is however scarce.

MRSA with *mecC*

Isolates of MRSA with *mecC* were first reported internationally from dairy cows and humans in 2011 (García-Álvarez et al., 2011, Shore et al., 2011, Ito et al., 2012). Such MRSA isolates were detected in milk from Swedish dairy cows sampled in 2010, 2011 and 2013 and were of *spa*-types t524, t9111 and t843. Two of these *spa*-types, t9111 and t843, have also been found in human cases. MRSA with *mecC* have been found in 51 human cases 2011-2013. The two most common *spa*-types seen among the human isolates were t843 (13 cases) and t373 (11 cases).

MRSA in dairy cattle

Staphylococcus aureus is a common cause of mastitis in dairy cows and the udder may constitute a reservoir. For example during milking, close contact between farmer and dairy cows may give good opportunities for transmission from human to cow, or vice versa.

Suspected transmission between human and cattle was detected on a dairy farm in 2012. Initiated by the detection of PVL-positive MRSA of *spa*-type t002 in a dairy farmer, all cattle on the farm were sampled. Milk samples from lactating cows and body samples from nostrils and groin from other cattle were taken initially. MRSA of the same *spa*-type as in the farmer was detected in milk samples from several cows and one nasal swab. Since MRSA of this *spa*-type is common among humans in Sweden, it is likely that transmission has occurred from the farmer to cows.

Hygienic measures were implemented on the farm in order to reduce the risk of transmission and several of the MRSA-positive cows were culled. This reduced the number of colonized or infected animals, but MRSA was still detected in milk from dairy cows, in the nostrils of five heifers and perineum of one bull at a second sampling about ten months later.

MRSA in companion animals

MRSA isolated from dogs and cats often belong to *spa*-types seen in MRSA from humans. This supports the view that humans often constitute the source of MRSA in companion animals (EFSA 2009, CVMP, 2009). The most common *spa*-type among Swedish dogs and cats has been t032. This type was one of the ten most common *spa*-types among human MRSA isolates in Sweden up to 2011. In 2013 it was only found in 18 isolates.

Conclusion

The prevalence of MRSA in Sweden is still low both in humans and in animals. If the favourable situation in animals is preserved, a reservoir of MRSA in animals with risk of spread from animals to humans can be prevented. Infection control and caution in trade of live animals are important strategies for preventing introduction and spread of MRSA in animal populations. Cautions to prevent transmission from humans to animals are also of importance, since human types of MRSA may be established also in animal populations.

Methicillin resistant *Staphylococcus pseudintermedius* (MRSP)

MRSP in animals

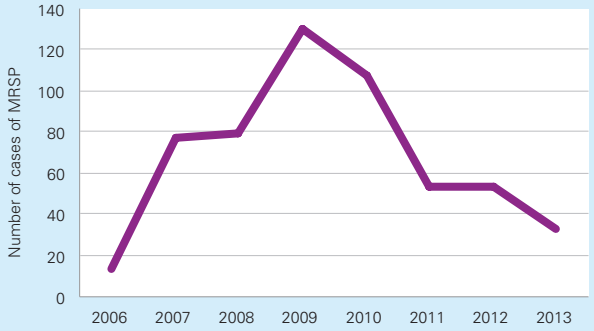
Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) was first isolated in Sweden from a healthy dog in a screening for MRSA in 2006. In 2008, methicillin-resistant coagulase positive staphylococci (including MRSP) isolated from animals in Sweden became notifiable.

From 2006 a large increase in the numbers of MRSP cases was observed, the numbers peaked in 2009 with 130 cases (Figure 2.10). However, since 2010 the number of cases has dropped yearly with only 33 cases notified in 2013. Whether this reflects a true reduction in the number of animals infected with MRSP is uncertain. The drop appears primarily be due to a decreasing occurrence of the European clone ST71-J-t02-II-III.

One explanation for the observed decrease could be the insight among veterinary practitioners in recent years on the importance of preventing spread of MRSP and on the prudent use of antimicrobials. For instance, in many animal clinics and hospitals, infection control programmes have been implemented with focus on strict hand hygiene routines. In addition, veterinarians with special interest in dermatology have agreed on an antimicrobial policy for treatment of dogs with dermatological disorders. Over the years MRSP has mostly been isolated from dogs, but also from a few cats and horses. In 2013 all cases, except one involving a cat, were from dogs.

In 2013, 27 of the 33 notified MRSP isolates were available at SVA for further epidemiological typing and extended antimicrobial susceptibility testing. In 58% of the cases the origin of isolates was unknown, but 19% were from wounds,

FIGURE 2.10. The number of cases with methicillin resistant *Staphylococcus pseudintermedius* in Sweden notified to the Swedish Board of Agriculture 2008-2013. In 2006-2007 the numbers represent the isolates that were sent to SVA and confirmed as *mecA*-positive.



19% from skin including ears and the remaining isolates from miscellaneous sampling sites. The majority of MRSP isolates (52%) belonged to the *spa*-type t02 carrying SCCmec II/III. Of the remaining isolates 11% belonged to t06-SCCmec II/III, 4% to t06-SCCmec V, 7% to t10 with a non-typeable (NT) SCCmec, and 22% were NT with *spa*-typing carrying either a SCCmec IV or II/III.

Based on PFGE and *spa*-typing of all isolates and on MLST on a subset, 63% of the isolates belonged to the European clone ST71-J-t02-II-III described by Perreten et al. (2010). Remarkable was that 3 of these isolates were non-typeable using *spa*-typing, but all belonged to ST71. In addition, 4 isolates being t02-SCCmec II/III did not show close relatedness to the ST71-J-t02-II-III clone based on PFGE and one of these isolates was typed to as a new ST not related to ST71.

All isolates were defined as multiresistant, but 89% were susceptible to fusidic acid, 78% to tetracycline, and 70% to chloramphenicol. The isolates belonging to the ST71-J-t02-II-III clone were all susceptible to tetracycline and fusidic acid, 65% were susceptible to chloramphenicol, and 35% to kanamycin. The remaining isolates showed variable antimicrobial susceptibility patterns. The isolates carrying the SCCmec II/III were described to have a MIC >16 mg/L for oxacillin, both when tested with or without NaCl, and a MIC ≥8 mg/L for cephalothin. However, the isolates carrying other SCCmec types had a wide range of MICs, 0.5-16 mg/L, of oxacillin and generally low MICs, below cut-off, 0.25-4 mg/L of cephalothin. Cefoxitin MICs varied from 0.5 to 16 mg/L.

Zoonotic aspects on MRSP

Staphylococcus pseudintermedius is generally not considered to be a human pathogen, but there are several reports of MRSP infections in humans with a varying degree of severity. Furthermore, in 2011 an outbreak of MRSP belonging to the ST71-J-t02-II-III clone was described among patients at Uppsala University hospital without any established animal-human contact (Starlander et al., 2011). The highest risk of getting an infection with MRSP is most likely through dog bites, but MRSP carriage is unusual among healthy dogs in Sweden (SWEDRES-SVARM 2012).

Vancomycin resistant *Enterococcus faecalis* and *Enterococcus faecium* (VRE)

VRE in humans

Background

Vancomycin resistant enterococci (VRE) are important causes of nosocomial infections in many parts of the world, usually involving high-risk populations such as immunocompromised and intensive care patients. Like MRSA, VRE were made notifiable according to the Swedish Communicable Disease Act in the year 2000 and since 2004 contact tracing is mandatory. The following presentation is based on data collected in the national web-based notification system SmiNet. During the last seven years an active effort has been made to improve the quality of data and to collect missing data. The notifications have been reviewed and complemented with available relevant epidemiologic information from investigations around each case in collaboration with the CMOs.

Notifications of VRE according to the Communicable Disease Act

From 2000 to 2006 only low numbers (18-35 per year) of VRE-cases were reported in Sweden. In 2007, reports came from Stockholm County about an increase in the number of VRE-cases, and the total yearly count was 53 cases (Table 2.9, Figure 2.11). This was the beginning of an outbreak that would last until 2011, when it was finally declared to have come to an end in the affected counties. The outbreak has been described in SWEDRES 2011 and elsewhere (Söderblom et al., 2010). The total number of cases with a strain of *Enterococcus faecium* with *vanB* belonging to this outbreak was 872. The next large outbreak occurred in Västernorrland County and lasted 2010-2011 with an estimated number of 100 cases. It was caused by another strain of *E. faecium* still with a *vanB* gene. In 2012 at least two outbreaks caused by two different strains of *E. faecium* with *vanA* genes contributed to the increase in this type of VRE. These outbreaks occurred in Jönköping and Halland counties, respectively, and led to extensive infection control measures to limit and eradicate the outbreak strains (SMI Newsletter 2013).

During 2013 a total of 227 cases were reported, an increase by 49% compared to 2012 (Table 2.9). This largely due to one major hospital outbreak in Gävleborg. VRE cases were reported from 15 of the 21 Swedish counties. The average national incidence of VRE was 2.4 with higher than average incidence figures in Gävleborg (33.1), Kronoberg (3.7) and Västra Götaland (2.6) counties. Of all cases, 165 (73%)

TABLE 2.9. VRE-notifications according to the Communicable Disease Act 2006-2013 by species and van-gene.

Species and R-gene	2006	2007	2008	2009	2010	2011	2012	2013
E. faecium vanA	9	12	96	61	63	39	97	93
E. faecium vanB	3	38	505	326	135	70	26	126
E. faecalis vanA	2	2	4	6	3	8	5	1
E. faecalis vanB					1	2		
E. faecium, not specified R-gene	10	1	12	9	12	3	24	7
Total	**24**	**53**	**617**	**402**	**214**	**122**	**152**	**227***

*In one case in 2013 a strain of *E. faecium* with both vanA and vanB gene was detected.

were reported as domestic (Figure 2.11), and of those 151 were healthcare related. In 61 cases (27%) VRE had been acquired abroad. The most common countries for imported VRE infection were Serbia (8 cases), Bosnia-Hercegovina (7), Iran (6) and Greece (5). Fifty-six (92%) of the imported cases were healthcare related.

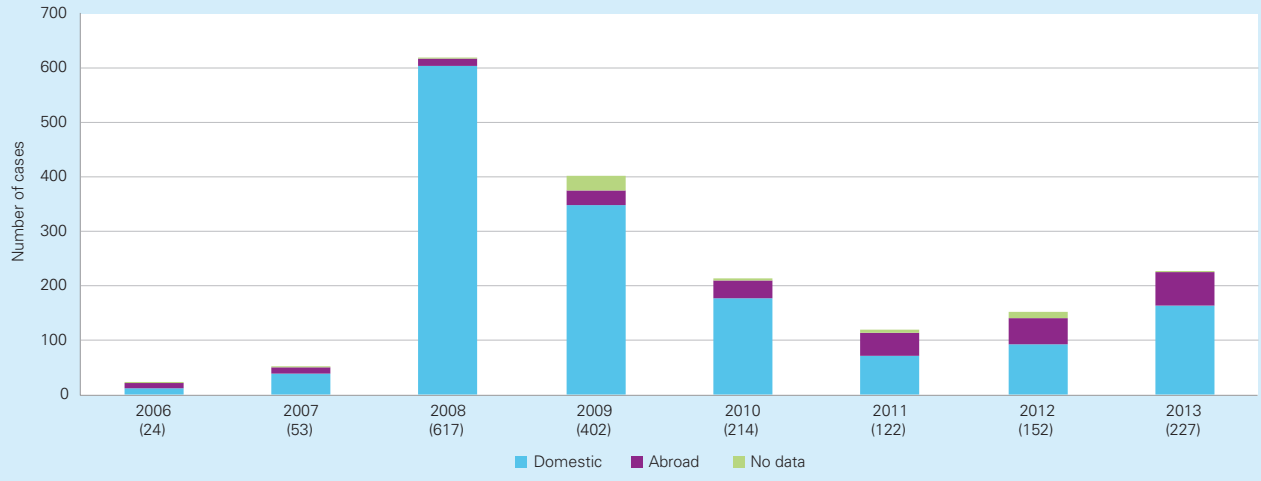
The domestic VRE cases were detected through contact tracing (77%), screening (12%) or clinical symptoms (15%). The majority of the imported cases (95%) were detected through screening, 3% due to clinical symptoms and none due to contact tracing. Accordingly a majority of the isolates (83%) in the first laboratory notifications were from feces and rectum, and only 1% from urine samples. More cases were notified from men (56%) than from women (44%), with the median age for women 74 years and for men 70 years. The median age was lower for imported (65 years) than for domestic cases.

In 2013, 226 cases were *E. faecium* and 1 case *E. faecalis*. In contrast to 2012, the dominating resistance gene 2013 was once again *vanB* (Table 2.9). Invasive VRE infection was reported in three cases in 2013. Two of those were newly notified persons and one occurred in a patient already known to carry VRE.

Epidemiological typing of VRE in outbreaks

For enterococci PFGE is still used as the standard typing method. Isolates from notified cases in all counties from 2007 and onwards have been analysed, and comparisons with isolates from previous years have also been performed. From this national strain collection and PFGE database it has been shown that the *E. faecium* with *vanB* gene causing the outbreak situation 2007-2010 had not been detected before 2007. This strain was named SE-EfmB-0701 to indicate species (Efm), resistance gene (B), year of detection (07) and a serial number (01). Several smaller outbreaks in Sweden during 2000 – 2006 had been caused by strains of different PFGE-types, and they were given names retrospectively. The extensive outbreak 2010-2011 in Västernorrland County was

FIGURE 2.11. Number of VRE cases annually notified in Sweden 2006-2013 by country of infection. Numbers of isolates are shown in brackets.



caused by a strain with the PFGE-type SE-EfmB-1001. In 2012 the first extensive outbreaks caused by *vanA*-producing *E. faecium* occurred in Jönköping (SE-EfmA-1203), Halland (SE-EfmA-1204) and Stockholm counties (several types) with a total of around 50 cases. (SMI Nyhetsbrev 2012).
In 2013, ten outbreaks of *E. faecium* were reported from six counties; six outbreaks with *vanA* gene and four with *vanB* gene. The six *vanA* outbreaks affected 2-3 patients each, and three *vanB* outbreaks affected 8-18 patients. The largest outbreak occurred in Gävleborg county during the autumn and winter 2013, and at the end of the year 85 cases had been reported from this outbreak caused by a strain typed as SE-EfmB-1308. All outbreaks were healthcare related, but according to the epidemiological typing they were caused by different strains, and there were no reasons to suspect connections between the affected counties.

The regular typing of VRE from all new cases makes the national PFGE database useful in identifying outbreak strains among the relatively large number of isolates with so called "unique" PFGE patterns.

VRE in animals

No specific screening for VRE was performed in SVARM 2013. However, in the monitoring of indicator bacteria from healthy animals all isolates of *Enterococcus faecalis* and *Enterococcus faecium* are tested for susceptibility to vancomycin. In 2013, samples from calves were investigated and no resistant isolates were detected. See section Resistance in indicator bacteria from animals for details.

Historically, vancomycin resistant *E. faecium* with the *vanA* gene has been isolated from intestinal content of healthy broilers but not from other farm animals studied in SVARM. For further information regarding VRE in broilers see SVARM 2011; *Vancomycin resistant enterococci (VRE) in Swedish broiler production – a summary*.

Zoonotic aspects on VRE

Previous data from SVARM have shown that *E. faecium* with the *vanA* gene is present among Swedish broilers. There is a potential risk for transfer of VRE to humans. However, most human VRE cases in Sweden are healthcare associated and have mainly been caused by *E. faecium* with *vanB* gene, although the number of cases with *E. faecium* with *vanA* gene have increased dramatically since 2008 (Table 2.9). Also, it has been shown by PFGE that the VRE found in Swedish broilers have never been identified among human isolates. Accordingly, there are no indications that the presence of VRE in broilers in Sweden has affected the situation in Swedish healthcare.

Streptococcus pneumoniae with reduced susceptibility to penicillin (PNSP)

PNSP in humans

Background

Streptococcus pneumoniae with reduced susceptibility to penicillin (PNSP, defined as MIC ≥ 0.5 mg/L) became notifiable according to the Communicable Disease Act in 1996. In May 2012, a revised case definition was introduced, stating that only PNSP with MIC of penicillin > 1 mg/L were now notifiable and the identified cases subjected to contact tracing. However, all pneumococcal isolates with MIC ≥ 0.5 mg/L are still collected by the Public Health Agency of Sweden for serotyping.

Notifications according to the Communicable Disease Act

In 2013 a total of 53 PNSP cases were reported in Sweden. Forty-seven percent of the cases had been infected domestically and 25% of the cases in a foreign country. For the remaining 15 cases (28%) no country of acquisition was given.

The incidence of PNSP in Sweden 2013 was 0.5 cases per 100 000 inhabitants. The majority of PNSP cases (30 % in 2013), independent of year observed, were found in the age group 0-4 years. There was no difference in the proportion of the reported cases with regard to sex.

PNSP were reported from 15 of 21 Swedish counties, with Stockholm (18 cases) and Skåne (9 cases) accounting for 50% of all notifications. The remaining 13 counties reported 1-7 cases each.

PNSP, were most often found in cultures from the nasopharynx. In 28 cases the detection of PNSP was due to clinical infection, and in 6 cases due to targeted screening. In the remaining cases another reason for sampling was stated (7) or the information was missing (12).

Serotype distribution

In 2013, 2 cases of invasive PNSP infection, with bacteria isolated from blood were reported (MIC> 1 mg/L). These were of serotypes 9V and 19F. For all cases of PNSP with MIC > 0.5 mg/L (216 isolates serotyped so far) the most common serotypes were in descending order: 19F (21%), 35B (14%), 19A (12%), non-typabale (NT) (11%), 3 (7%), 14 and 6B (6% each), 9V (5%) and 23F (3%).

Outbreaks of resistant bacteria in health care

Hospitals have long been considered key environments for the spread of antibiotic resistant bacteria. There is a need for a close monitoring of such transmission, as cross infection in hospitals can be prevented with good hand hygiene, other hygiene measures, and prudent antibiotic use. In comparison it is harder to introduce effective measures against the spread of antibiotic resistance in the community. The higher vulnerability in hospital patients compared to the general population is another reason for more comprehensive surveillance and programs for preventive actions in hospitals.

Since the late 1990ties a number of major outbreaks of resistant bacteria in hospitals have been reported in Sweden. Increased cross infection with MRSA was first recognized in Västra Götaland, followed by MRSA in Stockholm, *Klebsiella pneumoniae* with ESBL in Uppsala, and a common *vanB* VRE strain in Stockholm, Varberg, and Västerås. All these outbreaks were successfully stopped by intense case finding, appointment of a central steering groups to handle the outbreaks, and enhanced compliance to hand hygiene and other basic hygiene measures. Additionally, in the management of some outbreaks, there was an emphasis on improved cleaning and disinfection, as well as prudent use of antibiotics.

Unfortunately new outbreaks in health care continue to be reported despite that the preventive measures are well described, commonly known, and should be universally applied within health care. It is acknowledged that not all health care related infections are preventable. It is however unreasonable with larger outbreaks especially over any extended periods of time.

Outbreaks of resistant bacteria during 2013

The following outbreaks have been communicated to the Public Health Agency of Sweden. There is as yet to be established a comprehensive scheme for outbreak surveillance. Thus, there is most likely an underreporting of outbreaks.

During 2013 approximately 30 outbreaks with MRSA (2-13 cases/outbreak) were reported in 14 different counties. These outbreaks comprised approximately 125 cases, representing 5% of all cases in 2013. One third of the outbreaks were reported from healthcare institutions outside hospitals, whereas 55% were hospital outbreaks. Two of the outbreaks in 2013 were connected to sports.

Nine outbreaks of VRE in hospitals have been reported. One of the outbreaks, in Gävleborg, has continued in 2014 and now comprises over 200 cases.

For ESBL three outbreaks in hospitals have been reported, all these occurred in neonatal wards.

In addition to these mandatory reportable bacteria two other outbreaks in hospitals have been communicated. The first concerned five patients in a burns unit carrying multiresistant, carbapenem resistant *Acinetobacter baumannii*. The second occurred in a haematology ward and comprised two fatal cases with carbapenem resistant *Pseudomonas aeruginosa*.

Questionnaire to neonatal wards

During December 2013 The National Board of Health and Welfare asked for reports of any outbreaks or cross infections in neonatal units in Sweden during 2012 and 2013. All 36 wards in Sweden responded.

There had been no outbreaks in 17 of the units during these years, in 2012 there were 16 outbreaks in 10 units, and in 2013 there were 20 outbreaks in 16 units.

The types of bacteria causing these outbreaks were: *E. coli* ESBL (11), *S. marcescens* (4), *K. pneumoniae* ESBL (3), *E. cloacae* (1), MRSA (11), tobramycinresistant *S. aureus* (4), and *S. aureus* (1).

National resources for future preventive work

Outbreaks in hospitals continue to be reported. Thus, intensified preventive efforts are needed, both specifically in neonatal care and in general within all medical specialties. Caregivers need to consider if local surveillance is at the right level, if the level of staffing is adequate, if single rooms are available, if cleaning and disinfection routines are appropriate. Of course, the level of compliance to hand hygiene and other essential hygiene routines need to be considered. The current antibiotic policy, and the antibiotic consumption also need to be taken into account, as antibiotic use will drive the spread of resistance.

There are several resources available at the national level for this continued work

- Epidemiological typing and characterization of antibiotic-resistant bacteria, as well as advice on typing methods are available at The Public Health Agency of Sweden.
- Report from The National Board of Health and Welfare on planning and preparation for outbreaks of communicable disease, 2012
- http://www.socialstyrelsen.se/publikationer2012/2012-12-5
- Report from The Public Health Agency of Sweden on vancomycin resistant enterococci, 2011.

- http://www.folkhalsomyndigheten.se/pagefiles/13630/Vankomycinreistenta_enterokocker-VRE.pdf
- Report from The Public Health Agency of Sweden on ESBL-producing enteric bacteria, 2013.
- http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/ESBL-producerande-tarmbakterier/
- Report from The National Board of Health and Welfare on cross infection in neonatal care in Sweden, 2011.
- http://www.socialstyrelsen.se/publikationer2011/2011-5-25
- Recommendation for the treatment of neonatal sepsis, 2013.
- http://www.lakemedelsverket.se/upload/om-lakemedelsverket/publikationer/information-fran-lakemedelsverket/2013/Rev%20130806_Info%20fr%C3%A5n%20LV%20nr%203_2013_webb.pdf
- A model for improvement of hand hygiene published by The Public Health Agency of Sweden and The Swedish Association of Local Authorities and Regions, 2012.
- http://www.folkhalsomyndigheten.se/publicerat-material/informationsmaterial/rena-hander-raddar-liv/

Zoonotic pathogens

Zoonoses are diseases and infections that can be naturally transmitted between animals and humans. Antimicrobial resistance in zoonotic bacteria such as *Salmonella* and *Campylobacter* from animals is therefore of direct public health concern.

Salmonella

Salmonella from human clinical specimens

Infection with *Salmonella* in humans is a notifiable disease in Sweden, and the focus has been on epidemiological typing in order to facilitate contact tracing. Antibiotic susceptibility testing on isolates derived from fecal cultures has only been monitored locally by a few laboratories. Since a majority of the *Salmonella* strains isolated in Sweden originate from persons who were infected when travelling abroad, it has been anticipated that their resistance patterns most probably reflect the situation at their geographical origin.

Blood culture isolates of *Salmonella* are always tested, and in 2013, as in 2012, we used the complete data sets of positive blood cultures from ten laboratories (see background information) as one source of information on antibiotic susceptibility in *Salmonella*. In 2013, 65 isolates of *Salmonella* were found among a total of 18 367 blood cultures. The most common serovars were *S.* Enteritidis (17), *S.* Typhi (12), *S.* Typhimurium (4), *S.* Dublin, *S.* Panama, *S.* Paratyphi A, *S.* Saintpaul, (2 each), (Table 3.1). The remaining 24 isolates were reported as *S.* other. Only nine of the cases were reported as travel associated with Thailand, Turkey, Africa (north or central regions), and India being the countries/regions mentioned.

TABLE 3.1. *Salmonella* from blood cultures in Sweden 2013. Data collected from 10 laboratories, covering approximately 55% of the Swedish population.

Salmonella serovar	No. of isolates	No. of Cip-R[a]	No. of Tsu-R[a]	Countries reported
S. Enteritidis	17	1		Turkey
S. Typhi	12	11	3	India
S. Typhimurium	4	1		
S. Dublin	2			Africa
S. Panama	2		1	Thailand
S. Paratyphi A	2	2		
S. Saintpaul	2			India
S. other serovars	24	4	6	
Total	**65**	**19**	**10**	

[a] Cip-R = ciprofloxacin resistant; Tsu-R = trimethoprim-sulfa resistant

Susceptibility testing by disk diffusion and application of NordicAST breakpoints was performed by local clinical laboratories. No isolate was resistant to cefotaxime. Resistance to trimethoprim-sulphametoxazole was found in 10 isolates (15%) and resistance to ciprofloxacin in as many as 19 (29%). Typically, all but one of *S.* Typhi were resistant to ciprofloxacin (MICs 0.25-32 mg/L), and both *S.* Paratyphi A (MICs 0.25-1 mg/L). Ciprofloxacin resistance was also found in single isolates of other serovars (Table 3.1).

Salmonella in animals

Findings of *Salmonella* in animals are notifiable in Sweden. In SVARM, antimicrobial susceptibility is determined in one isolate from each warm-blooded animal species (wild and domesticated) involved in a notified incident. In incidents involving more than one serovar, one isolate of each serovar is tested. Isolates obtained in the salmonella surveillance programme from samples collected at slaughter are also included.

In SWEDRES-SVARM 2013, isolates from incidents notified in 2013 are included but also isolates from incidents previously notified but still under restrictions in 2013. For details on methodology see Materials and methods, resistance in bacteria from animals.

All animals 2013

Altogether, 86 isolates were tested of which 47 were *S.* Typhimurium and of these one isolate was of the monophasic serovar O 4,5:i:- (Table 3.2). Distributions of MICs and resistance in all isolates are presented in Table 3.3 and for the subset *S.* Typhimurium in Table 3.4. The majority of isolates (74%) were susceptible to all antimicrobials tested, but 22 isolates were resistant to at least one substance, and three isolates (3%) were multiresistant.

The three multiresistant isolates were all *S.* Typhimurium (Table 3.5). Two isolates were from cattle and one isolate from a dog. One of the isolates from cattle was resistant to ampicillin, streptomycin, sulphonamide and tetracycline and in addition to quinolones *i.e.* ciprofloxacin and nalidixic acid. The other cattle isolate was resistant to ampicillin, streptomycin and sulphonamide. Both these resistance phenotypes are rare in *Salmonella* from animals in Sweden (Table 3.6) but have been found in *Salmonella* from different farm animals in EU (EFSA, 2012). The third multiresistant isolate was from a dog and was resistant to ampicillin, streptomycin, sulphonamide and tetracycline. This phenotype has been observed in previous incidents in cattle, pigs and poultry in Sweden (Table 3.6).

TABLE 3.2. Number of *Salmonella enterica* isolates tested for antimicrobial susceptibility, 2013.

Serovar	Cattle	Pigs	Poultry	Horses	Dogs	Cats	Wild birds	Wild mammals	Total
S. Brandenburg					1				**1**
S. Dublin	7								**7**
S. enterica subsp. (I)					1		3		**4**
S. enterica subsp. diarizonae (III)							1	2	**3**
S. Enteritidis				1				6	**7**
S. Fulica							1		**1**
S. Infantis	1	1			1				**3**
S. Konstanz								1	**1**
S. Mbandaka	10								**10**
S. Newport								1	**1**
S. Reading					1				**1**
S. Typhimurium	4	7	2	1	1	10	16	5	**46**
S. Typhimurium (monphasic 4,5:i:-)	1								**1**
Total	**23**	**8**	**2**	**2**	**5**	**10**	**21**	**15**	**86**
Percent of total	27%	9%	2%	2%	6%	12%	24%	17%	

Farm animals 2000-2013

From a public health perspective resistance in *Salmonella* from farm animals is of greater concern than resistance in isolates from wild animals or pets. This is because bacteria from animals raised for food production can contaminate carcasses at slaughter and thereby be transmitted to humans through the food chain.

In the period 2000-2013, isolates from the vast majority of notified incidents in farm animals were tested in SVARM, in total 599 isolates. About half of the isolates, 295 (49%), were *S.* Typhimurium and of these 40% were from pigs, 32% from cattle, 27% from poultry and 2% from sheep.

The majority (74%) of the *S.* Typhimurium isolates have been susceptible to all antimicrobials tested and only 30 (7%) were multiresistant (Table 3.6). The most common resistance traits were ampicillin, streptomycin, tetracycline, sulphonamide, chloramphenicol and florfenicol (Fig 3.1). Resistance to third generation cephalosporins has not been found and resistance to ciprofloxacin has been confirmed in only two isolates. Six isolates (2%) of other serovars than Typhimurium have been multiresistant.

The 30 multiresistant isolates of *S.* Typhimurium in the period 2000-13 were from 28 separate incidents of which 17 involved cattle, 6 pigs, 2 poultry and 1 incident involved both

TABLE 3.3. Distribution of MICs and resistance (%) in *Salmonella enterica* (n=86) from all animals, 2013.

Antimicrobial	Resistance %	Distribution (%) of MICs (mg/L)																	
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	3								96.5								3.5			
Ceftazidime	0							16.3	64.0	19.8										
Cefotaxime	0			7.0	9.3	73.3	10.5													
Chloramphenicol	0									30.2	64.0	5.8								
Ciprofloxacin	3		2.3	3.5	90.7	2.3			1.2											
Colistin	1							37.2	40.7	20.9	1.2									
Florfenicol	0										97.7	2.3								
Gentamicin	0							45.3	46.5	8.1										
Kanamycin	0											98.8	1.2							
Nalidixic acid	1									14.0	76.7	8.1		1.2						
Streptomycin	22										3.5	1.2	73.3	18.6			1.2	2.3		
Sulphamethoxazole	3											1.2	2.3	10.5	65.1	15.1	2.3			3.5
Tetracycline	3								91.9	4.7					1.2	2.3				
Trimethoprim	0					1.2	27.9	68.6	2.3											

TABLE 3.4. Distribution of MICs and resistance (%) in *Salmonella* Typhimurium (n=47) from all animals, 2013.

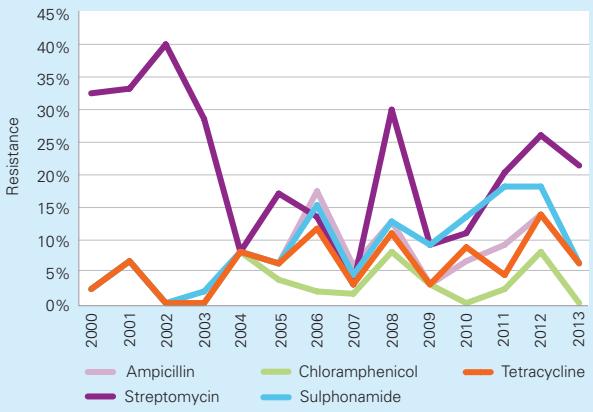
Antimicrobial	Resistance %	Distribution (%) of MICs (mg/L)																	
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	6								93.6								6.4			
Ceftazidime	0							4.3	91.5	4.3										
Cefotaxime	0						8.5	85.1	6.4											
Chloramphenicol	0									34.0	63.8	2.1								
Ciprofloxacin	2					97.9			2.1											
Colistin	2							21.3	59.6	17.0	2.1									
Florfenicol	0										97.9	2.1								
Gentamicin	0							51.1	44.7	4.3										
Kanamycin	0											100								
Nalidixic acid	2									12.8	83.0	2.1		2.1						
Streptomycin	21										2.1		76.6	14.9			2.1	4.3		
Sulphamethoxazole	6													4.3	59.6	25.5	4.3			6.4
Tetracycline	6								89.4	4.3					2.1	4.3				
Trimethoprim	0							25.5	74.5											

TABLE 3.5. MICs (mg/L) in *Salmonella enterica* resistant to three or more antimicrobials, 2013. Shaded fields indicate resistance.

Source	Serovar	Amp	Caz	Ctx	Cip	Nal	Chl	Flo	Col	Gen	Kan	Str	Sul	Tet	Tmp
Cattle	*S.* Typhimurium	>128	1	0.25	1	32	4	≤4	≤0.5	1	8	>256	>1024	128	0.5
Dogs	*S.* Typhimurium	>128	0.5	0.12	0.06	8	4	≤4	≤0.5	2	8	>256	>1024	128	0.25
Cattle	*S.* Typhimurium (monphasic 4,5:i:-)	>128	0.5	0.12	0.06	4	4	≤4	2	1	8	256	>1024	≤1	0.25

pigs and cattle. Of the remaining incidents, one was in sheep and one in ducks in a hobby flock. Three incidents in 2004 involving cattle were epidemiologically linked through trade of calves. An epidemiological link was also suspected between four incidents 2007-2008 involving cattle, pigs and sheep. There are no known links between the other incidents.

FIGURE 3.1. Resistance (%) in *Salmonella* Typhimurium from all animals, 2000-2013. The number of isolates each year varies (n=31-85).



Nine incidents of monophasic *S.* Typhimurium I (O 4,5,12:i-/O 4,5:i:- / O 4:i:-) have been confirmed in farm animals since this variant was first found in Swedish animals in 2006 (Table 3.6). Three incidents involved cattle, three incidents pigs, one incident ducks, and one incident involved both cattle and poultry. In five incidents isolates have had the resistance phenotype ampicillin, streptomycin, sulphonamide and tetracycline (Table 3.6). Monophasic *S.* Typhimurium has also been isolated from three dogs and a wild bird. Epidemiological links have been confirmed between some of the incidents of monophasic *Salmonella*.

Zoonotic aspects on *Salmonella*

Occurrence of *Salmonella* among farm animals as well as among other animals is low in Sweden and few incidents involve multiresistant strains. Notably, resistance to ESCs has never been found and resistance to fluoroquinolones is rare. Thus, the overall situation in Sweden is favorable. This is largely due to the effective strategies in the Swedish salmonella control programme initiated in the 1950-ies.

Compiled data on occurrence and susceptibility of *Salmonella* from humans in Sweden is largely lacking. It is therefore not possible to comprehensively relate the situation in Swedish animals to the situation in humans. However,

TABLE 3.6. Resistance phenotypes of *Salmonella* Typhimurium (n=295) from incidents in farm animals, 2000-2013. All isolates were tested for susceptibility to ampicillin, florfenicol, gentamicin, chloramphenicol, nalidixic acid, streptomycin, sulphamethoxazole, tetracycline, trimethoprim and to ceftiofur or cefotaxime.

		Phagetype																						
Phenotype	**Source**	**1**	**7**	**9**	**10**	**12**	**15a**	**39**	**40**	**41**	**99**	**104**	**110b**	**120**	**125**	**126**	**146**	**193**	**195**	**NST**	**NST (U277)**	**NT**	**Not typed**	**Monophasic**	**Sum**
AmpStrSulTetNalChlFlo	**Pigs**											1													**1**
AmpStrSulTetChlFlo	**Cattle**											6		1									2		**9**
AmpStrSulTetChlFlo	**Pigs**											4											1		**5**
AmpStrSulTetChlFlo	**Sheep**											1													**1**
AmpStrSulTetChl	**Cattle**											1													**1**
AmpStrSulTetNal	**Cattle**																						1		**1**
AmpStrSulTet	**Cattle**													1								2		2	**5**
AmpStrSulTet	**Pigs**																							1	**1**
AmpStrSulTet	**Poultry**																					1		2	**3**
AmpStrSul	**Cattle**													1										1	**2**
StrSulTet	**Cattle**																			1					**1**
AmpSul	**Cattle**											2													**2**
AmpSul	**Pigs**											1													**1**
StrGen	**Cattle**									1															**1**
StrGen	**Pigs**								1																**1**
StrGen	**Poultry**									1															**1**
StrSul	**Pigs**																							2	**2**
StrSul	**Poultry**						2																		**2**
SulTm	**Cattle**																1			1					**2**
Amp	**Poultry**																			2					**2**
Gen	**Poultry**																			1					**1**
Nal	**Pigs**					1																			**1**
Str	**Cattle**											1		1		1				4			1		**8**
Str	**Pigs**								4	3		2		1						4		1	2		**17**
Str	**Poultry**									2										3					**5**
Tet	**Pigs**																						1		**1**
Susceptible	**Cattle**	4			2		1	1	1	6		2		5	1	1				26	1	1	9	1	**62**
Susceptible	**Pigs**	1	1			2			33	5	1	1		8					1	17	1	2	14		**87**
Susceptible	**Poultry**	1		1		1			5	1			1	2				1	1	42	1	4	4		**65**
Susceptible	**Sheep**	1																					3		**4**
Sum		**7**	**1**	**1**	**2**	**4**	**3**	**1**	**44**	**19**	**1**	**22**	**1**	**20**	**1**	**2**	**1**	**1**	**2**	**101**	**3**	**11**	**38**	**9**	**295**

of the most common serovars from human invasive infections in 2013 (Table 3.1) *S.* Typhi is a serovar that is not associated with animals. Also, the other serovars from human invasive infections, *e.g. S.* Enteritidis, are most rare in animals in Sweden.

Moreover, nearly one third of the human isolates from 2013 were resistant to ciprofloxacin. This high rate is in contrast to the rare findings of ciprofloxacin resistance in *Salmonella* from animals in Sweden. Taken together, this strongly suggests that *Salmonella* causing human invasive infections rarely originate from Swedish animals.

Campylobacter

Campylobacter in humans

Information on *Campylobacter* from humans was not available for 2013.

Campylobacter in animals

The isolates of *Campylobacter jejuni* tested are from colon content from healthy calves sampled at slaughter and broiler meat. For details on methodology see Materials and methods, resistance in bacteria from animals.

Cattle

Of the 109 isolates tested, 74 were susceptible to all six antimicrobials. Resistance to quinolones only (nalidixic acid n=2, nalidixic acid and ciprofloxacin n=20) was the most common phenotype (Table 3.7).

In comparison to 2001 fluoroquinolone resistance in isolates from yearling cattle has increased with 20 percentage units. Fluoroquinolones are used for treatment of cattle but to a limited extent. The main indication is mastitis in dairy cattle (Växa Sverige, 2013) further details are given in Use of antimicrobials for animals. Tetracycline resistance was detected in 6% of the isolates and has not been recorded in *C. jejuni* from cattle previous years.

Broiler meat

Of the 111 isolates tested, 88 were susceptible to all six antimicrobials. Resistance to quinolones only (n=19) was the most common phenotype (Table 3.8). In comparison with isolates from broilers sampled at slaughter, presented in SWEDRES-SVARM 2012, the resistance percentages are similar. The relatively high occurrence of fluoroquinolone resistance cannot be explained by use because fluoroquinolones are seldom used in broiler production in Sweden. Erythromycin resistance was detected in two isolates from broiler meat. Since the monitoring within SVARM started, no erythromycin resistance has been recorded for isolates from broilers sampled at slaughter.

Zoonotic aspects on *Campylobacter*

No data for *Campylobacter* from humans were available for 2013 but data for 2002-2011 were presented in SWEDRES 2011. However, comparisons to data for *Campylobacter* from animals is hampered because the human isolates are not separated by species or by infections acquired in Sweden or abroad. *Campylobacter* spp. isolates acquired within the country are expected to have a lower level of resistance.

In 2011 higher resistance percentages were reported for human isolates of *Campylobacter* spp. for fluoroquinolones (69%), tetracycline (37%) and erythromycin (7%) than for isolates of *C. jejuni* from cattle or broiler meat 2013. Notably, resistance to erythromycin, the drug of choice for treatment of human campylobacteriosis, was only found in two isolates from Swedish broiler meat. It can therefore be concluded that animals in Sweden are an unlikely source for *Campylobacter* infection with the high resistance levels seen in isolates from humans.

TABLE 3.7. Distribution of MICs and resistance (%) in *Campylobacter jejuni* from cattle, 2013. Resistance (%) for yearling cattle from SVARM 2001 and dairy cattle from SVARM 2006 are given for comparison.

Antimicrobial	Resistance (%)			Distribution (%) of MICs (mg/L)											
	2001	2006	2013												
	n=67	n=68	n=109	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ciprofloxacin	1[a]	7[a]	21	21.1	42.2	14.7	0.9				4.6	16.5			
Erythromycin	0	0	0				83.5	13.8	2.8						
Gentamicin	3	0	3		0.9	10.1	73.4	12.8	0.9				1.8		
Nalidixic acid	1	9	23						3.7	35.8	30.3	7.3	0.9	0.9	21.1
Streptomycin	NT	NT	5				7.3	45.9	35.8	6.4	0.9				3.7
Tetracycline	0	0	6		76.1	14.7	2.8			0.9			5.5		

[a] Enrofloxacin tested.

TABLE 3.8. Distribution of MICs and resistance (%) in *Campylobacter jejuni* from broiler meat, 2011-2013.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)											
	n=111	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ciprofloxacin	20	7.2	61.3	11.7				0.9	11.7	7.2			
Erythromycin	2				89.2	9.0							1.8
Gentamicin	0		1.8	18.0	75.7	4.5							
Nalidixic acid	20					0.9	0.9	47.7	27.0	3.6	0.9	0.9	18.0
Streptomycin	0				2.7	72.1	22.5	2.7					
Tetracycline	4		70.3	20.7	4.5	0.9				0.9	2.7		

Penicillin resistance in *Bacillus anthracis*

The bacterium *Bacillus anthracis* causes the disease anthrax, primarily in grazing animals but it can also infect other animals and humans. In the late nineteenth century *B. anthracis* was a model for Robert Koch as he formulated his postulates on bacterial pathogenicity. In more recent years, *B. anthracis* has become known as a potential bioterrorism agent. In the "2001 anthrax letter attack" five persons died from anthrax spores contained in letters addressed to American congress members and news media offices. *Bacillus anthracis* is found world-wide as dormant spores in the soil which is its natural reservoir. The spores can survive for several decades until they eventually get exposed and infect grazing animals. In Sweden, anthrax outbreaks were frequent during the first half of the 20th century but the disease then declined and now, only sporadic cases occur.

Bacillus anthracis is considered susceptible to penicillin but there are a few reports of resistant clinical human and animal isolates. Penicillin is the recommended first choice of treatment in animals during an anthrax outbreak (WHO, 2008).

During a Swedish anthrax outbreak in cattle in 2011, animals were put on penicillin treatment and moved to a new area, pending vaccination. This halted the aggressive progression of the outbreak but some animals died after the treatment. A new penicillin treatment was started but two fetuses were aborted during or after this second treatment. *Bacillus anthracis* was isolated from the animals and fetuses that had died and those isolated after the treatment had begun were shown to be resistant to penicillin.

Most *Bacillus* species have two beta-lactamase genes in their chromosome and have an inducible system of transcribing these genes thus producing beta-lactamases (Ross et al., 2009). However, in *B. anthracis* this induction is not functional and the bacterium cannot respond to beta-lactams. The transcription is believed to be regulated by a sigma factor and its anti-sigma factor (Ross et al., 2009). The sigma factor is a positive regulator and the anti-sigma factor is a negative feedback system.

The whole genome was sequenced for several of the isolates from the outbreak – representing both penicillin resistant and susceptible phenotypes. The genomes were then compared and the mutations that had lead to the resistance were identified. It was clear that the only mutations shared between resistant isolates were mutations in the anti-sigma factor gene. The mutations created premature stop codons that lead to incomplete anti-sigma factor proteins. Thus, the negative feedback system had been disabled leaving the positive sigma factor constantly on. This led to a constitutive high expression of the beta-lactamase genes.

The mutation rate was measured by whole genome sequencing of isolates after a certain amount of passages on blood agar plates. The resulting rate was comparable to a previously reported value (Vogler et al., 2002) thus indicating that the outbreak strain had a normal mutation rate. Taken together, these results indicate that when a large amount of bacteria is present in the animal, it is probable that a few of the individual genomes have acquired one of the several possible mutations that will disable the anti-sigma factor. When penicillin treatment is commenced, these few bacteria will become the sole survivors and re-colonize the animal until it dies from the disease.

Another interesting finding in this study was that a few isolates with penicillin resistance causing mutations had also acquired a counter-acting mutation in the sigma-factor. These isolates were, as expected, no longer resistant. This suggests that there is a benefit for the bacterium to turn off this system, when the selective pressure has been removed. This can certainly have implications for resistance determinations if some colonies on an agar plate harbor anti-sigma factor mutations and are resistant, and some have converted back to susceptibility.

The study showed that the beta-lactam resistance of *B. anthracis* was due to mutations in an anti-sigma factor gene on the chromosome leading to an incomplete protein product. The fact that all it takes is one random mutation in this gene means that it can happen for any *B. anthracis* outbreak but it also suggests that the bacterial load has to be high for this to occur. The fact that the bacterium can revert to a sensitive phenotype once the beta-lactam pressure is gone, should be borne in mind when determining the resistance *in vitro*.

The results of this study have been previously published in:

Ågren J, Finn M, Bengtsson B, Segerman B (2014) Microevolution during an Anthrax Outbreak Leading to Clonal Heterogeneity and Penicillin Resistance. *PLoS ONE* 9(2): e89112. doi:10.1371/journal.pone.0089112.

Clinical isolates from humans

Swedish surveillance of antimicrobial resistance is based on the routine testing of clinical samples in microbiology laboratories. In these laboratories the majority of tests for antibiotic susceptibility are performed using the standardized disk diffusion method. From 2011 and onwards all laboratories are following guidelines and breakpoints proposed by EUCAST for the standardized disk diffusion test (www.eucast.org). Commercially available tests for MIC determination are also used, and in recent years there has also been an increase in the use of automated methods for susceptibility testing and categorization.

Two sets of data are included in the surveillance programme. The first set is found under the heading **Isolates from blood cultures reported to ECDC/EARS-Net**. The data on susceptibility testing of consecutive invasive (blood) isolates are collected from twenty laboratories, together representing approximately 80% of the Swedish population. Results on seven important bacterial pathogens are requested by and reported to ECDC. These data form the Swedish part of EARS-Net, the European Antimicrobial Resistance Surveillance Network.

As part of the surveillance of bacteria from blood cultures, ten of these Swedish laboratories, with coverage of approximately 55% of the Swedish population, also deliver data on invasive isolates from all their positive blood cultures. This enables a further insight into clinically important bacterial species other than those reported to ECDC/EARS-Net. These results are presented under the heading **Resistance in other bacterial species from blood cultures**.

The second set of data in the surveillance programme can be described as point-prevalence studies of predefined bacteria and antibiotic combinations in which laboratories are able to report aggregated quantitative data (inhibition zones) via the web-based software ResNet. The methodology is further described in Background data and the results are found under the heading **The annual resistance surveillance and quality control programme (ResNet)**.

Isolates from blood cultures reported to ECDC/EARS-Net

Background

In 1998 when EARSS (the European Antimicrobial Resistance Surveillance System) started, two bacterial pathogens were included, *Staphylococcus aureus* representing hospital-related infections, and *Streptococcus pneumoniae* representing community-acquired infections. Data on both pathogens was however derived from cases with invasive disease (positive blood cultures). After three years the EARSS programme was ready to include new pathogens. The natural choice was to include *Escherichia coli*, which is by far the most common bacterial pathogen in invasive infections (not counting the normal skin flora bacterial species like CoNS), and also the two enterococcal species *E. faecalis* and *E. faecium*. A third step was taken in 2005 when *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were added, and by that time also most of the European countries were participating in EARSS.

EARSS turned into EARS-Net

The transition of the EARSS management from RIVM in the Netherlands to ECDC in Stockholm in 2010 did not change the focus of the surveillance system with regard to bacterial pathogens included, and in Sweden the coordination and validation of results from the 20 participating laboratories is still managed by SMI.

FIGURE 4.1. Yearly numbers of bloodstream infections by seven pathogens reported to EARS-Net from Sweden 2006-2013 (19 laboratories, covering approximately 80% of the population).

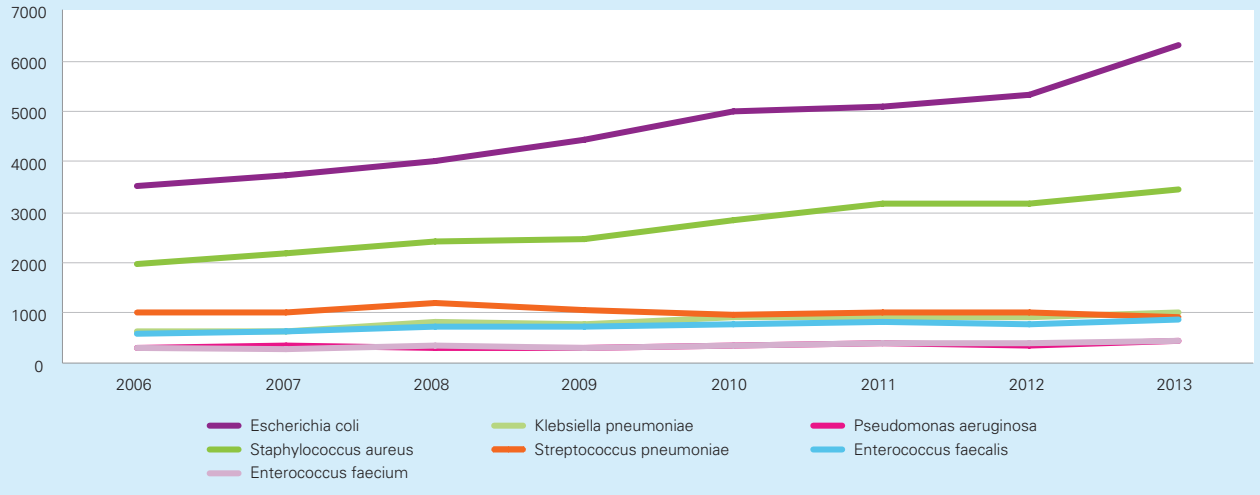
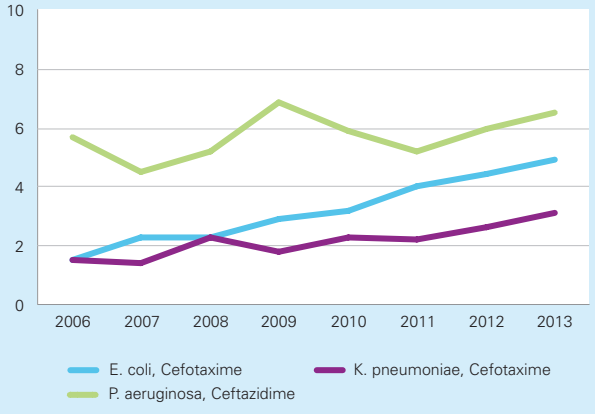


TABLE 4.1. Antimicrobial resistance in isolates from bloodstream infections of seven pathogens included in EARSS/EARS-Net surveillance during the years 2006-2013.

		2006		2007		2008		2009		2010		2011		2012		2013	
Species	**Antibiotic**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**
Escherichia coli	Ctx	3514	1.5	3745	2.3	4028	2.3	4423	2.9	4991	3.2	5066	4.0	5336	4.4	6323	4.9
	Imp/Mer		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0
	Gen/Tob		1.6		2.2		2.3		3.3		4.5		5.1		5.5		4.5
	Cip		11.1		13.3		14.4		13.7		14.0		10.4		9.9		9.9
Klebsiella pneumoniae	Ctx	610	1.5	649	1.4	826	2.3	755	1.8	908	2.3	934	2.2	933	2.6	1028	3.1
	Imp/Mer		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0
	Gen/Tob		0.3		1.1		1.1		1.0		2.0		2.1		2.1		2.0
	Cip		8.5		10.8		12.9		12.2		8.5		5.0		4.6		4.4
Pseudomonas aeruginosa	Caz	297	5.7	335	4.5	309	5.2	326	6.9	337	5.9	402	5.2	350	6.0	428	6.5
	Imp/Mer		4.7		7.1		4.0		7.7		6.7		7.2		6.9		6.3
	Gen/Tob		0.5		0		0		0		3.0		1.0		1.4		2.3
	Cip		7.7		10.4		7.6		10.1		10.1		7.0		9.1		7.9
Staphylococcus aureus	Oxa/Fox	1967	0.9	2163	0.5	2409	0.7	2457	1.0	2856	0.5	3143	0.8	3268	0.7	3442	1.2
	Van		0.0		0.0		0.0		0.0		0.0		0.0		0.0		0.0
Streptococcus pneumoniae	Pen (I+R)	993	2.1	1028	3.0	1213	2.0	1060	3.3	960	3.8	1019	3.5	992	5.0	909	6.6
	Ery		4.5		5.2		5.2		3.9		3.9		4.5		5.1		5.8
Enterococcus faecalis	Van	578	0.2	651	0	720	0	718	0	776	0	824	0	779	0	851	0.0
	Gen (HLAR)		20.0		16.1		20.1		18.6		15.2		16.6		14.1		13.3
Enterococcus faecium	Van	302	0.3	279	0	333	1.5	311	0.5	339	0.3	406	0	391	0	431	0
	Gen (HLAR)		11.9		14.4		24.8		24.1		21.8		22.0		18.4		20.4

A summary of the data reported from Sweden 2006-2013 is presented in Figure 4.1 in which numbers of isolates are shown, and in Table 4.1 where the proportions of resistance to certain antibiotics are included. The numbers of isolates of *E. coli* and *S. aureus* were much greater than the other pathogens, but they also showed increasing trends over the years, whereas the numbers of the other five pathogens were stable.

FIGURE 4.2. Proportion of resistance to third-generation cephalosporins in *E. coli, K. pneumoniae* and *P. aeruginosa*. Swedish data in EARS-Net 2006-2013 (19 laboratories, covering approximately 80% of population).



Results and comments

In general the proportions of resistance to clinically important antimicrobials were low, and this has been the typical situation for Sweden and its neighbouring Nordic countries all through the EARSS/EARS-Net history (www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/). However, increasing trends of resistance to third-generation cephalosporins are seen for both *E. coli* and *K. pneumoniae*. This increase is due to an increasing prevalence of ESBL-producing isolates, whereas the mechanism causing resistance to ceftazidime in *P. aeruginosa* has a non-ESBL explanation (Figure 4.2). In *E. coli* and *K. pneumoniae* the levels of cephalosporin resistance had reached 4.9% and 3.1%, respectively (Table 4.1). Reduced susceptibility and resistance to fluoroquinolones (I+R) seems to have stabilized on a level of approximately 10% in *E. coli* but approximately 5% in *K. pneumoniae*.

Among the grampositive bacteria the resistance rates had increased for both *S. aureus* and *S. pneumoniae*, with 1.2% MRSA and 6.6% nonsusceptibility to penicillin (I+R). This was the first year that MRSA exceeded 1%, and for PNSP

TABLE 4.2. Antimicrobial resistance in invasive isolates of Streptococcus pyogenes, Streptococcus agalactiae and Haemophilus influenzae during six years (2008-2013).

		2008 (n=11.115)[a]		2009 (n=11.416)		2010 (n=12.296)		2011 (n=16.969)		2012 (n=18.117)		2013 (n=18.367)	
Species	**Antibiotic**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**
Streptococcus pyogenes	Ery	196 (1.8)	0.5	134 (1.2)	2.2	118 (1.0)	1.7	188 (1.1)	3.2	257 (1.4)	2.3	297 (1.6)	4.0
	Tet		14.6		9.7		12.7		13.3		12.5		7.7
Streptococcus agalactiae	Ery	107 (1.0)	6.5	131 (1.1)	6.9	166 (1.4)	7.8	206 (1.2)	6.8	197 (1.1)	13.2	205 (1.1)	12.7
	Kli		6.5		3.8		5.4		5.8		13.7		9.3
Haemophilus influenzae	Amp	63 (0.6)	25.4	49 (0.4)	20.4	75 (0.6)	9.3	76 (0.5)	18.4	103 (0.6)	20.4	87 (0.5)	25
	Beta+ [b]		23.8		20.4		6.6		nd		8.7		6.9
	Ctx		nd		nd		nd		2.5		1.9		0
	Tsu		14.3		14.3		13.3		15.8		22.3		17.2

[a] Total number of positive blood cultures from ten laboratories.
[b] Beta+ = beta-lactamase producing strains.

6.6% I+R was the highest level noted in Sweden ever since the start of EARSS/EARS-Net. For the two enterococcal species there were no VRE reported, and high-level aminoglycoside resistance (HLAR) was found in 13-18%, similar to previous years.

Resistance in other bacterial species from blood cultures

Streptococcus pyogenes, *Streptococcus agalactiae* and *Haemophilus influenzae*

Data on all positive blood cultures were obtained from ten laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is at present 5 millions, thus representing more than 55% of the Swedish population. From these laboratories data for the pathogens specified by EARS-Net are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In previous SWEDRES reports (2008-2012) data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* were presented, and they are summarized in Table 4.2 together with the most recent data from 2013.

Invasive isolates of *S. pyogenes* (GAS) and *H. influenzae* are notifiable according to the Communicable Disease Act, but regardless of their antibiotic susceptibility. It is therefore of value to summarise this kind of information in the SWEDRES report. *S. agalactiae* (GBS) is not included in the Communicable Disease Act, but it is an important pathogen in the context of pregnancy and child birth.

The most important finding in the 2013 data when compared to previous years concerned the number of GAS infections. They had increased by 40 cases compared to 2012 to 297 in 2013 (1.6% of all positive blood cultures), reflecting the present situation in Sweden with high prevalence of severe cases of this disease (www.folkhalsomyndigheten.se). The proportions of GAS isolates with erythromycin resistance had increased to 4%, whereas tetracycline resistance had decreased from 12.5 to 7.7% (Table 4.2). Cultures with GBS and *Haemophilus influenzae* still constituted 1.1% and 0.5%, respectively, of all positive blood cultures, and their frequencies of resistance to relevant tested antibiotics had not changed dramatically over the years.

Salmonella

Antibiotic resistance in blood isolates of *Salmonella* were also retrieved from the database of the ten laboratories in 2012, and results are presented in the chapter Zoonotic pathogens.

The annual resistance surveillance and quality control programme (ResNet)

Background

One part of the national surveillance programme on antimicrobial resistance makes use of the web-based software ResNet to receive aggregated data from laboratories and to present them in the form of resistance frequencies in their respective geographical areas on a map of Sweden, and also as individual zone histogram graphs as a tool for internal quality assurance.

In 2013 six pathogens were included in the programme, and the results on these pathogens are presented and analysed in the following texts and graphs, now using a different graphical presentation from previous SWEDRES reports to illustrate trends. For *Escherichia coli* and *Staphylococcus aureus* in 2013, the aggregated data reports from laboratories were collected from outpatients and inpatients separately, and they were also given "bacterial names" indicating these different origins. This more detailed approach was chosen to evaluate possible differences between the two patient categories.

However, in the ResNet application, data from these two categories were also summarized under the original bacterial names *Escherichia coli* and *Staphylococcus aureus* in order to make use of the trend analysis function in ResNet.

Escherichia coli

Escherichia coli, mainly derived from urinary tract infections, have been included in the national surveillance programme regularly since 1996 and every year since 2002. Resistance to commonly prescribed oral antibiotics for treatment of urinary tract infections (UTI) has been tested every year. The number of isolates tested by each laboratory was increased from 100 to 200 from 2006 in order to increase the statistical validity of the data.

In 2013, 24 laboratories delivered data for outpatients and inpatients separately as requested. All laboratories used the recently introduced EUCAST methodology, and a total of 7680 isolates were included in the analysis (Figure 4.3).

The average resistances rates for all tested antibiotics were very similar between 2012 and 2013 and only slightly increasing for cefadroxil and ciprofloxacin (Figure 4.3). It should be noted that ciprofloxacin 5 µg is now the recommended disk for detecting fluoroquinolone resistance, and the resistance rate 8,8% represents resistance (R, not I+R as was the case when nalidixic acid was used) calculated from the zone breakpoint R < 19 mm correlating to the clinical MIC-breakpoint R > 1 mg/L.

Data for ampicillin and cefadroxil 2013, collected separately for outpatients and inpatients according to the definitions of healthcare sites where the samples were taken, is shown in Figure 4.4, A and B. Neither sets of data indicate any significant differences between the two patient categories, although local variations are seen. It is anticipated that results for ampicillin give an indication of the pool of resistance genes in the population, and that cefadroxil results indicate the presence of genes coding for ESBLs.

FIGURE 4.4, A AND B. Ampicillin (A) and cefadroxil (B) resistance rates in *Escherichia coli* from outpatients and inpatients in Swedish counties 2013.

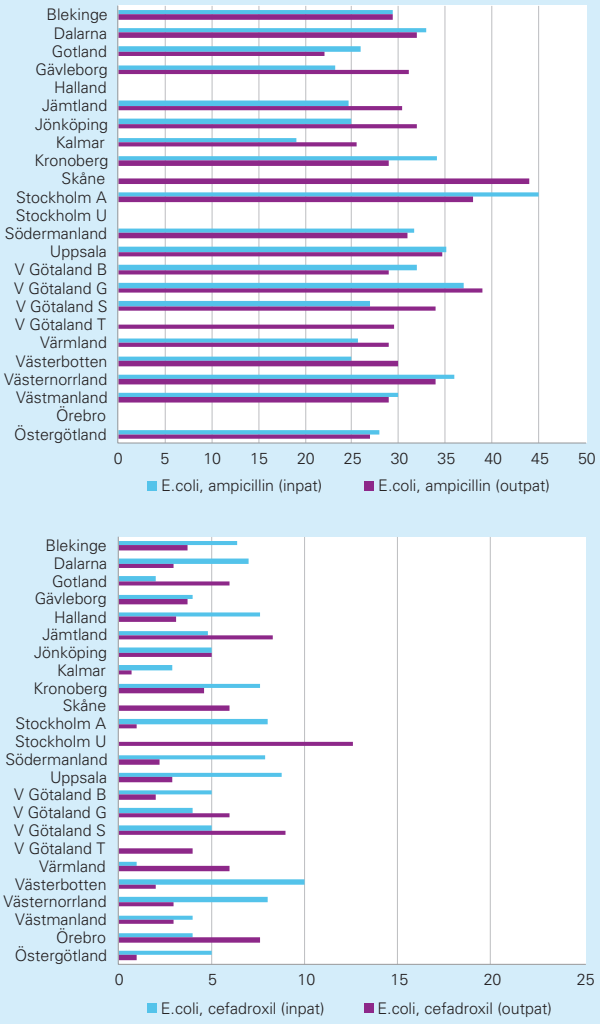
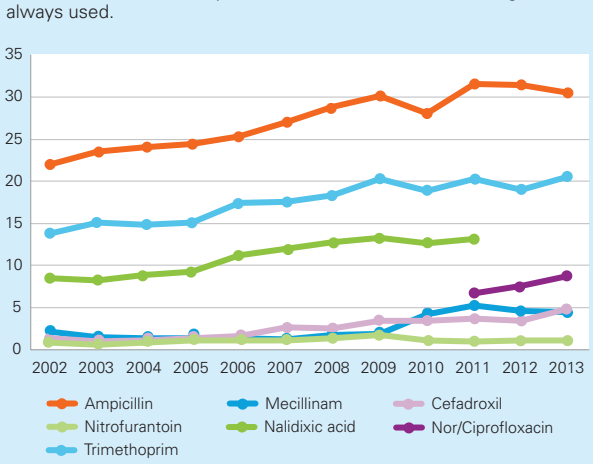


FIGURE 4.3. Resistance rates for UTI antibiotics in *Escherichia coli*, 2002-2013. Resistance (R) to fluoroquinolones was tested by nalidixic acid (screening for I+R) 2002-2011, and by ciprofloxacin from 2011 and onwards. Zone breakpoints relevant at the time of testing were always used.



Klebsiella pneumoniae

K. pneumoniae is one of the most important bacterial species from a hospital infection control point of view. Bacteria mainly derived from urine samples have been included in the surveillance programme since 2005. In 2013, 22 laboratories delivered data according to the recently introduced EUCAST methodology, and 2430 isolates were included in the analysis (Figure 4.5). The results indicate that the rates of resistance to all tested antibiotics were the same in 2012 and 2013.

Pseudomonas aeruginosa

Pseudomonas aeruginosa has been included in the surveillance programme on a yearly basis since 2006, but with the exception of 2008. Laboratories have been asked to test 100 consecutive isolates of *P. aeruginosa* with the exclusion of respiratory isolates. In 2013, 23 laboratories delivered data according to the recently introduced EUCAST methodology, and 2515 isolates were included in the analysis (Figure 4.6).

FIGURE 4.5. Resistance rates for UTI antibiotics in *Klebsiella pneumoniae,* 2005-2013. Resistance (R) to fluoroquinolones was tested by nalidixic acid (screening for I+R) 2005-2011, and by ciprofloxacin from 2011 and onwards. Zone breakpoints relevant at the time of testing were always used.

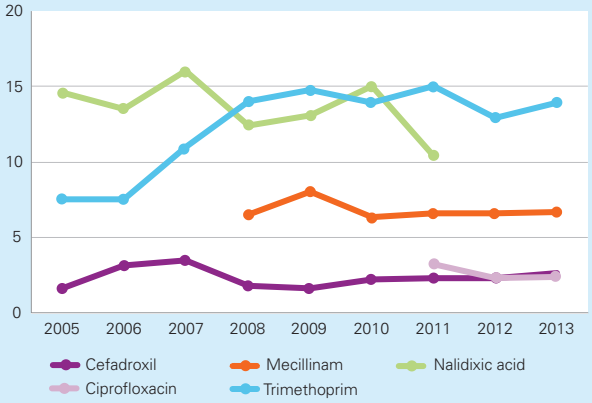
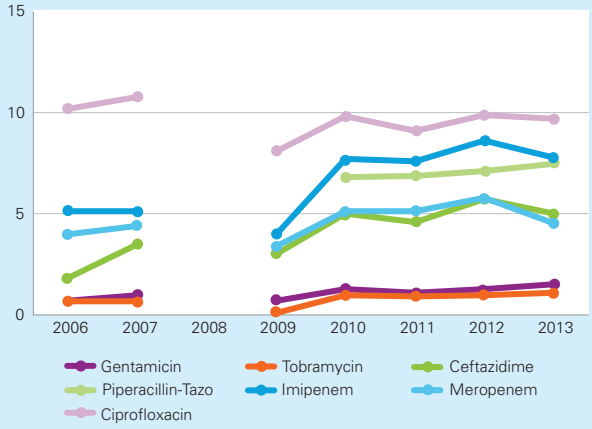


FIGURE 4.6. Resistance rates for four groups of antibiotics tested against *Pseudomonas aeruginosa,* 2006-2013 (no data collected in 2008). Zone breakpoints relevant at the time of testing were always used.



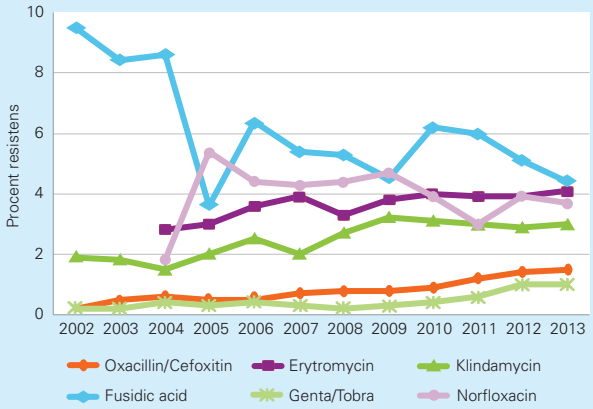
Aminoglycoside resistance (gentamicin and/or tobramycin tested) seemed stable around 1%. Four beta-lactam antibiotics were tested; one cephalosporin, one penicillin-inhibitor combination, and two carbapenems. For all of them, the rates of resistance have been stable since 2010. For the carbapenems, resistance to imipenem continues to be higher (7.8%) than to meropenem (4.5%) in 2013. Resistance to ciprofloxacin seems to have stabilized around 10%.

Staphylococcus aureus

Staphylococcus aureus from skin and soft tissue infections has been included in the annual surveillance programme since 2002. In 2013, 24 laboratories delivered data for outpatients and inpatients separately as requested. All laboratories used the recently introduced EUCAST methodology, and a total of 5980 isolates were included in the analysis (Figure 4.7).

The frequency of MRSA in skin and soft tissue infections (SSTI) (cefoxitin used as test compound) has increased slowly and reached an average value of 1.5% in 2013. The average

FIGURE 4.7. Resistance rates for *Staphylococcus aureus* from skin and soft tissue infections 2002-2013. In 2005 resistance rates were recorded in *S. aureus* infections from elderly (> 65 years) patients only.



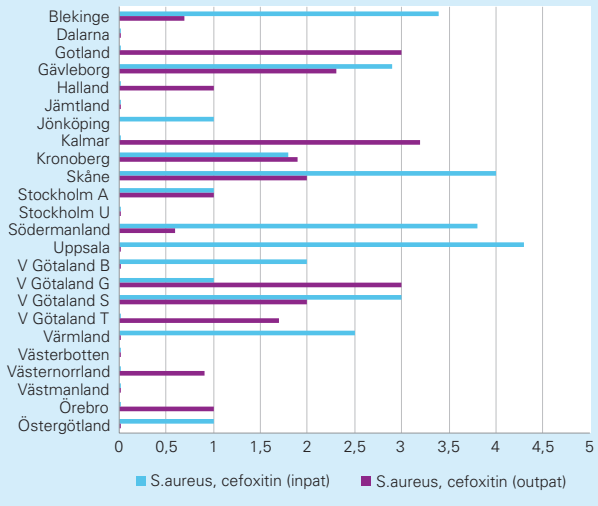
resistance rates for erythromycin, clindamycin, fusidic acid and norfloxacin were almost the same as in the previous 3 years. Resistance to aminoglycosides was still only 1%.

Data from each laboratory for cefoxitin in 2013, collected separately for outpatients and inpatients according to the definitions of healthcare sites where the samples were taken, is shown in Figure 4.8. The data show large variation within and between counties and should be interpreted with caution before the special conditions in each county are known.

Streptococcus pneumoniae

Isolates collected and tested in the surveillance programme were mainly derived from nasopharyngeal cultures. Most of the years a total of approximately 3000 consecutive isolates from all clinical laboratories have been tested for susceptibility to penicillin (by means of oxacillin 1 µg screen disk), erythromycin, clindamycin (since 2004), tetracycline, trimethoprim-sulfamethoxazole, and norfloxacin (since 2005,

FIGURE 4.8. Cefoxitin resistance rates (=MRSA) in *Staphylococcus aureus* from outpatients and inpatients in Swedish counties 2013.



used as indicator for fluoroquinolone resistance) using the disk diffusion method. In 2013, 24 laboratories delivered data according to the newly introduced EUCAST methodology, and 2539 isolates were included in the analysis. The national summary of the results, as retrieved from ResNet, are shown in Figure 4.9. During the first 15 years of surveillance there had been a slow increase in the rates of resistance for all tested antibiotics. However, since 2010 this successive increase has stopped, only to show a slight increase in rates of resistance in 2013 for all tested antibiotics.

Haemophilus influenzae

Haemophilus influenzae was re-introduced into the yearly surveillance programme on antibiotic resistance in 2008 after several years with no data collections (see previous SWEDRES reports). In 2013, 24 laboratories delivered data according to the new EUCAST methodology, and 2521 isolates were included in the analysis. In 2010 methodological changes were introduced (for description see www.nordicast.org) which made results for beta-lactam resistance more difficult to interpret, but by correlating beta-lactamase producing isolates to 6 mm only of penicillin G 1 unit disk, it was possible to get a percentage of the prevalence of this resistance mechanism (Figure 4.10). Other mechanisms of beta-lactam resistance were then assumed if zones of penicillin G 1 unit disk measured 7-11 mm, allowing for a rough estimation of the frequencies of BLNAR. By doing so the results since 2010 indicate a dramatic increase in BLNAR. However, disk diffusion results must always be verified by MIC determination, and useful interpretation tables for treatment options are issued and updated yearly by NordicAST.

In 2013 the high rates of resistance to trimethoprim-sulfamethoxazole did not increase further and remained at 24%. Tetracycline resistance in *Haemophilus influenzae* was still rare (1.3%) as was resistance to fluoroquinolones (1.2%), detected by the nalidixic acid screening disk.

FIGURE 4.9. Resistance rates for *Streptococcus pneumoniae* isolated from respiratory tract specimens 1994-2013.

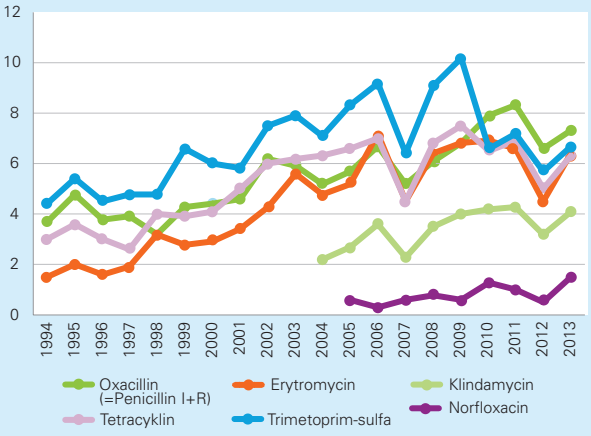
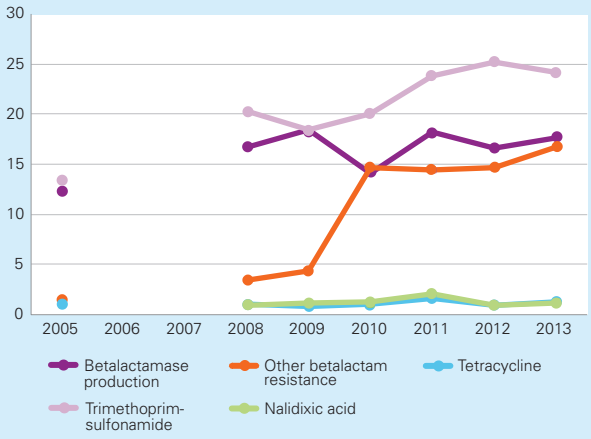


FIGURE 4.10. Resistance rates for *Haemophilus influenzae* isolated from respiratory tract specimens 2005-2013 ((no data collected in 2006-2007). In 2010-2013 beta-lactamase producing isolates were separated from isolates with other beta-lactam resistance mechanisms by use of penicillin G 1 unit disk using the following interpretation: 6 mm = beta-lactamase production, 7-11 mm = other beta-lactam resistance.



Clostridium difficile

The *Clostridium difficile* surveillance programme in Sweden

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

Distribution of resistant *Clostridium difficile* isolates in 2013

In the national surveillance programme 2013 a total of 458 isolates sent from all Swedish counties were characterised. No isolate was resistant to the current treatment options, metronidazole or vancomycin. The proportions of *C. difficile* isolates resistant to moxifloxacin, clindamycin, or erythromycin decreased in 2013 compared to 2012 (Table 4.3). There was also less geographical clustering of moxifloxacin-resistant isolates, especially for the types 012 and 046. The decreased numbers of these moxifloxacin-resistant types resulted in a relative increase of other types resistant to these antibiotics as compared to 2012. Despite the decrease, small clusters of type 017 and 231 were seen, suggesting minor outbreaks of such moxifloxacin-resistant isolates (Figure 4.11 and Table 4.3). There was an increase in the number of virulent type 027 compared to previous years (n=5). However, only 2/5 isolates were found to be moxifloxacin resistant.

Svebar - Swedish surveillance of antimicrobial resistance

The major part of the data used for surveillance of antimicrobial resistance in humans in Sweden is generated by clinical cultures performed to diagnose suspected infections. The reporting for surveillance of antimicrobial resistance is either mandatory for notifiable diseases or based on voluntary reports. Data reported in the EARS-Net and the ResNet systems are to a great extent handled manually, and collects only a fraction of the data generated at the local clinical microbiology laboratories.

The aims with Svebar are

- to automatically collect all results from clinical microbiology laboratories that are of relevance to antimicrobial resistance.
- to provide functions for early warnings for serious types of antimicrobial resistance.
- to support easy generation of reports, including reports of multiple resistance.
- to support centralized compilation of reports that can be used both at the local and national levels.
- to aid the process of national consensus regarding which types of resistance are to be considered serious.

Reporting to Svebar is voluntary, but all clinical microbiology laboratories in Sweden (25) have agreed to participate. Svebar is developed and owned by the Public Health Agency of Sweden. The data is owned by the individual, participating laboratories, and by agreement the Public Health Agency of Sweden is given the right to maintain the data and to use it for routine reports of antimicrobial susceptibility.

Currently (April 10, 2014) thirteen laboratories deliver data to Svebar, covering approximately 2/3 of the population. Since the start more than 3,1 million results have been reported.

Each local laboratory system generates a file every day containing all culture results from the last two weeks. The file is encrypted and sent automatically to Svebar, where it is imported to the system. A new file will thus contain more up-to-date results from thirteen days than the results stored the day before. These new results will replace the old data, and in this way both the preliminary results can be captured to generate early warnings, and the final more correct results will be the one stored in the database. The sample identification number is kept during the early warning phase, but is discarded when the results are finally stored.

For a set of results the following information is stored: local laboratory, sample date, species name, antibiotic + susceptibility result, patient age (year, month), analysis, sample type, requesting unit.

Different laboratories will use slightly different terms, both for antibiotics, species, sample types, and analysis. To solve this problem all terms are reviewed and approved before they can be imported to Svebar. In this process terms are either approved as new terms, made synonyms with a previously approved term, or discarded.

After the results have been imported they are scanned using early warning algorithms, and alarms are sent by e-mail to local laboratories and operators at the Public Health Agency of Sweden. Certain serious resistance types are discussed by phone for confirmation and to collect epidemiological information.

Early warning algorithms are either central, these are applied at all connected laboratories, or local, these are only applied at a certain local laboratory.

There are two different types of algorithms: Those that alert for isolates with a specific combination of species and type of antibiotic resistance, e.g. *E. faecium* resistant to vancomycin and/or teicoplanin, and algorithms that monitors the e.g. the percentage of *E. coli* resistant to ampicillin during the last 90 days, and reports the actual percentage for all laboratories above a selected cut-off (for example 30%).

There are three different methods to compile reports on antimicrobial resistance in Svebar:

A. by using the standard interface, where data from a selected time period can be shown, and further selected regarding species, sample type etc. This method is available both for the Public Health Agency of Sweden and the local laboratories.
B. by exporting data selected by method A. to file and using spreadsheet or statistical software for analysis. This method is also available both for the Public Health Agency of Sweden and the local laboratories.
C. by exporting data by directly accessing the database and further analyze it using spreadsheet or statistical software. This method is only available to the Public Health Agency of Sweden.

To date Svebar data has not been used to compile routine reports on antimicrobial resistance. The early warning feature is, however, in operation for all connected laboratories.

Antimicrobial resistance data from Svebar has been used in a report on urinary tract infection in men. Compared to collecting this data by sending separate files from all the laboratories in Sweden and merging the files manually, using Svebar is far easier.

Some future developing goals for Svebar:

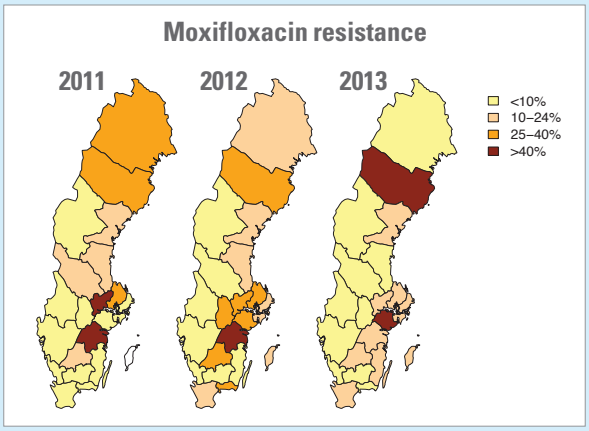
- using Svebar to collect national and local denominator data.
- use Svebar to collect data for EARS-Net and ResNet.
- develop automatic routines to generate reports from Svebar.
- develop trend monitoring that can generate alarms when baselines levels are exceeded.

TABLE 4.3. Distribution of MICs and resistance (%) in *Clostridium difficile* of different PCR ribotypes tested against erythromycin, clindamycin and moxifloxacin, Sweden 2013 (n=458).

Antimicrobial	PCR ribotype	Resistance 2013 (%)	Resistance 2012 (%)	Distribution (no. of strains) per MIC (mg/L)												
				0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Clindamycin	012	75	94						2	2						12
	017	79	88							2	1		1			10
	046	53	76					1	3	3						8
	231	100	94													8
	Other	42	5					42	102	132	60	13	4			24
	Total	**15**	**18**			**2**	**26**	**43**	**107**	**139**	**61**	**13**	**5**			**62**
Erythromycin	012	75	91				2	2		1		1	2	1		7
	017	79	100					2	1			1			1	9
	046	46	76				2	2	3						1	7
	231	100	94									1	1	2		4
	Other	51	7	2	1	60	116	139	47	5				1		35
	Total	**16**	**21**	**2**	**1**	**60**	**120**	**145**	**51**	**6**		**3**	**3**	**4**	**2**	**62**
Moxifloxacin	012	63	91					3	3							10
	017	59	75					1	2	4						10
	046	27	43				2	5	3	1						4
	231	100	94													8
	Other	46	6		1	6	80	217	69	1	5					23
	Total	**14**	**18**		**1**	**6**	**82**	**226**	**77**	**6**	**5**					**55**

Shaded areas indicate resistance based on ECOFFs proposed for C. *difficile:* clindamycin R > 16, erythromycin R > 8 and moxifloxacin R > 8 mg/L.

FIGURE 4.11. Proportion of *Clostridium difficile* isolates with resistance to moxifloxacin per county 2011-2013.



Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable infection and in 2013, 1114 cases (11.6 cases per 100,000 inhabitants) of gonococcal infections were reported. Most of the cases were identified in the three largest counties of Sweden, which comprise the cities Stockholm, Gothenburg, and Malmö, respectively. Clinical isolates are in the present report described from the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Public Health Agency of Sweden [previously Swedish Institute for Communicable Disease Control, SMI]), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, Örebro; Department of Laboratory Medicine, Medical Microbiology, Skåne University Hospital, Malmö; and Department of Clinical Microbiology, Karolinska University Hospital, Stockholm. In 2013, in total *N. gonorrhoeae* strains from 967 of the notified cases were fully characterised at these laboratories, representing 87% of the notified cases.

Antimicrobial susceptibility testing was performed according to standardized and quality assured methodology using Etest for MIC determination of ceftriaxone, cefixime, azithromycin, spectinomycin, ciprofloxacin, and ampicillin. The used SIR criteria have been determined by The Swedish Reference Group for Antibiotics (SRGA) and The European Committee on Antimicrobial Susceptibility Testing (EUCAST). Production of beta-lactamase was examined by nitrocefin discs.

The results for 2013 are compared with those from 2006 to 2012 in Table 4.4. Briefly, the levels of resistance to antimicrobials previously used as first-line treatment for gonorrhoea (penicillins and ciprofloxacin) remain high. The level of resistance to azithromycin also remains high (>10% since 2010), however, no high-level resistance to azithromycin

TABLE 4.4. Antibiotic resistance rates (%) and beta-lactamase production of Swedish *Neisseria gonorrhoeae* strains 2006-2013

	2006 (n=352)	**2007** (n=406)	**2008** (n=447)	**2009** (n=384)	**2010** (n=618)	**2011** (n=805)	**2012** (n=877)	**2013** (n=967)
Betalactamase positive	30	30	28	44	29	23	23	18
Ampicillin	30	30	28	44	31	24	23	18
Cefixime	0	<1	1	5	6	8	10	4
Ceftriaxone	0	0	<1	0	2	2	1	<1 (0.3)
Azithromycin	5	7	13	6	12	11	10	13
Ciprofloxacin	61	70	63	75	56	55	62	53
Spectinomycin	0	0	0	0	0	0	0	0

(MIC>256 mg/L) was found in 2013. Notably, the azithromycin resistance has during the recent years been substantially higher in Stockholm, which may reflect an overuse of azithromycin in antimicrobial monotherapy of gonorrhoea and/or other sexually transmitted infections, in particular, urogenital chlamydial infections. In 2013, the resistance to cefixime decreased for the first time during the last decade and also the resistance to ceftriaxone declined. This is exceedingly promising because ceftriaxone is the last remaining option for empirical antimicrobial monotherapy of gonorrhoea. Similar decreases in the resistance to these extended-spectrum cephalosporins have been indicated in additional European countries. The reasons for this decline is still unknown, however, most probably the European recommendations to replace cefixime with ceftriaxone (in a dose of 500 mg) in the first-line treatment, and ideally use ceftriaxone in combination with azithromycin have been very effective. No gonococcal isolates resistant to spectinomycin has yet been detected in Sweden. However, the availability of spectinomycin is limited (in Sweden as well as in most countries globally), and it is not suitable for treatment of pharyngeal gonorrhoea.

Neisseria meningitidis

Notifications according to the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease, and in 2013 a total of 74 clinical cases (0.76 cases per 100,000 inhabitants) of the disease were reported. All together 67 clinical invasive isolates from blood, cerebrospinal fluid or puncture (one per patient) were analysed at the Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Public Health Agency of Sweden [previously Swedish Institute for Communicable Disease Control, SMI]), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital.

Antimicrobial susceptibility testing was performed according to standardized and quality assured methodology using Etest for determinations of MICs of penicillin G, cefotaxime, meropenem, chloramphenicol, ciprofloxacin and rifampicin. Production of beta-lactamase was examined by nitrocefin discs.

Eighteen (27%) isolates had reduced susceptibility to penicillin G (MIC>0.064 mg/L). All isolates (100%) were susceptible to cefotaxime (MICs <0.002-0.032 mg/L), meropenem (MICs <0.002-0.032 mg/L), chloramphenicol (MICs 0.125-2 mg/L), ciprofloxacin (MICs 0.002-0.008 mg/L), and rifampicin (MICs 0.002-0.125 mg/L). None of the isolates produced beta-lactamase.

Mycobacterium tuberculosis

During 2013 in total 655 cases of tuberculosis (TB) were reported compared to 645 cases during 2012 which is a very small increase.

The number and proportion of culture confirmed cases were 522 (80 %) compared to 503 (78 %) in 2012. *Mycobacterium tuberculosis* was identified in all 522 cases and there was no *Mycobacterium africanum* or *Mycobacterium bovis* diagnosed this year. The proportions of cases diagnosed with isoniazid resistant TB in 2013 were 8.4 % (n=44) and MDR 1.5 % (n=8) out of which two were XDR-TB.

Isolates of *M. tuberculosis* resistant to at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) were identified in 56 patients corresponding to 10.7 % of the 522 with culture confirmed TB (Table 4.5). As always the most common resistance found was against isoniazid. Among the cases born in Sweden 5 % (3/60) of the ones with culture confirmed diagnosis had resistant TB and one of these had MDR-TB. All three had unique typing results and were most likely infected outside Sweden. We have had very few with MDR-TB among TB cases born in Sweden.

Around 85 % of the TB patients in Sweden are born in another country. In this group 11.5 % (53/462) had some kind of resistant TB and seven of those 53 had MDR- or XDR-TB.

For 22 of the 522 we have information on previous treatment for TB after 1950 since when effective medication has been available. Out of these 22 cases 10 % (2/22) had resistant strains and both were cases of XDR-TB. It is likely that more have received treatment earlier but there is no data on this.

Among the 7 cases with MDR/XDR-TB whom was not of Swedish origin the majority (5/7) came to Sweden 2012 or later. In total seven of the eight cases had pulmonary manifestations and among them three were smear positive.

Genetic typing with MIRU-VNTR (Mycobacterial Interspersed Repetitive Units - Variable Numbers of Tandem Repeat) has been performed on 506 of the 522 isolates so far. This is done to help detect clusters which could indicate ongoing spread in Sweden. Of all 655 reported cases, 66 are considered to have been infected in Sweden and the connection with the index case is confirmed by typing in 50 % of these cases. Among culture confirmed cases thought to have been infected in Sweden where the index is not confirmed, the majority were elderly who most likely were infected in their youth.

The proportion of patients with *M. tuberculosis* resistant against isoniazid has decreased slightly in 2013 and we have seen less cases of MDR-TB. Unfortunately both in 2012 and in 2013 we have had two XDR-TB cases which is a serious sign of the increasing problem with resistant TB worldwide.

TABLE 4.5. Drug resistant tuberculosis in Sweden 2005-2013.

Year of diagnosis	2005		2006		2007		2008		2009		2010		2011		2012		2013	
Culture confirmed *M. tuberculosis*	448		395		361		434		510		523		473		498		522	
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**	**No**	**%**
Any resistance	52	11.6	43	10.9	49	13.6	57	13.1	58	11.4	68	13	73	15.4	60	12	56	10.7
Isoniazid	46	10.3	38	9.6	46	12.7	51	11.8	51	10	57	10.9	57	12	49	9.8	44	8.4
Rifampicin	5	1.1	6	1.5	15	4.2	15	3.5	14	2.7	20	3.8	19	4	15	3	10	1.9
Ethambutol	3	0.7	1	0.3	7	1.9	6	1.4	7	1.4	12	2.3	10	2.1	12	2.4	8	1.5
Pyrazinamid	6	1.3	6	1.5	11	3	18	4.1	15	2.9	20	3.8	27	5.7	23	4.6	14	2.7
Isoniazid + rifampicin (MDR)	4	0.9	3	0.8	15	4.2	14	3.2	13	2.5	18	3.4	17	3.6	14	2.8	8	1.5

Clinical isolates from animals

Isolates tested are from clinical submission of samples to SVA, if not otherwise stated. For many samples, information on the indication for sampling was not available but the vast majority of submissions were likely from diseased animals. Therefore, data are probably biased towards samples from treated animals or from herds where antimicrobial treatment is common. Any assessment of trends is based on the assumption that this bias is inherent throughout the observation period.

In SVARM, isolates are, when possible, classified as susceptible or resistant by ECOFFs issued by EUCAST (see Guidance for readers for details). This classifies isolates with acquired reduced susceptibility as resistant, which is relevant for monitoring purposes, but it should be understood that this not always implies clinical resistance.

Pigs

Escherichia coli

Isolates of *Escherichia coli* are from clinical submissions of samples from the gastro-intestinal tract. In general only *E. coli* isolates that harbour genes coding for virulence factors are tested for susceptibility at SVA. The presence of genes coding for the following proteins are determined by PCR: enterotoxin (LT), heat-stable enterotoxin a and b (STa and STb), verocytotoxin (VT2e) and adhesion factors F4, F5, F6, F18 and F41. Isolates with at least one of these genes are generally tested for antimicrobial susceptibility. However, isolates may be susceptibility tested regardless of presence of virulence factors.

As in previous years, resistance to ampicillin, streptomycin, tetracycline or trimethoprim-sulphamethoxazole was most commonly occurring (Table 5.1). Resistance to ampicillin and to trimethoprim-sulphamethoxazole has increased considerably compared to previous years (Figure 5.1). Multiresistance occurred in 38% of the isolates in 2013 which is higher than previous years (24% in 2012, 25% in 2011, 15% in 2010, 19% in 2009 and 14% in 2008). The reason for this increase is uncertain. According to new legislation in 2013, susceptibility testing is generally required before fluoroquinolones are allowed for prescription in animals. Due to this, sampling may be biased towards isolates from herds with therapeutic failure with trimethoprim-sulphonamides, since fluoroquinolones may be an alternative for treatment of *E. coli* diarrhoea. Co-resistance to trimethoprim-sulphonamides and other antimicrobials is common.

The combination of resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole was the most common trait in 2013, as in previous years, occurring in 60% of the multiresistant isolates. Nine percent of all isolates were resistant to four antimicrobials. One isolate was resistant to five antimicrobials.

FIGURE 5.1. Resistance (%) in clinical isolates of *Escherichia coli* from pigs 1992-2013. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract. The number of isolates each year varies (n=74-482).

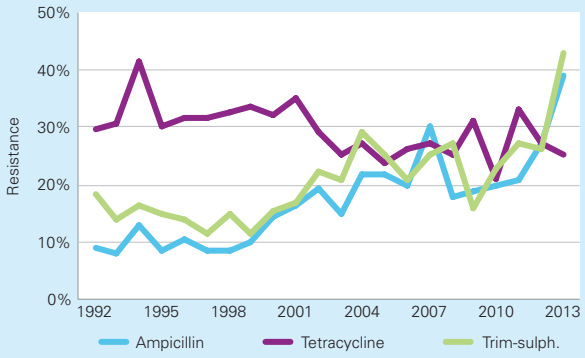


TABLE 5.1. Distribution of MICs and resistance (%) in *Escherichia coli* from pigs 2013. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2013 n=142	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	39				10.2	44.9	5.5		39.4		
Ceftiofur	0		32.3	59.1	8.7						
Enrofloxacin	9	91.3	1.6	4.7	0.8	1.6					
Florfenicol	0					3.1	52.0	41.7	3.1		
Gentamicin	0					95.3	4.7				
Neomycin	7						89.0	3.9		0.8	6.3
Streptomycin	41						12.6	19.7	26.8	4.7	36.2
Tetracycline	25				23.6	44.1	7.1		25.2		
Trim-Sulph.[a]	43			55.9	1.6			42.5			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole).

Brachyspira hyodysenteriae

Isolates of *Brachyspira hyodysenteriae* are from clinical submissions of faecal samples. Analysis of antimicrobial susceptibility data from isolates of *B. hyodysenteriae* from Sweden 1990-2010 has resulted in a proposal for ECOFFs for the antimicrobials tested at SVA (Pringle et al., 2012). In Table 5.2 these ECOFFs are used and historical data have been adjusted. With the new ECOFF >0.25 mg/L for tiamulin, some isolates are classified as resistant or with decreased susceptibility. However, with the previously used clinical breakpoint >2 mg/L, no isolate was classified as resistant. The ECOFF for tylosin (>16 mg/L) has not been changed compared to previous years and more than half of the isolates are resistant.

Brachyspira pilosicoli

Isolates of *Brachyspira pilosicoli* are from clinical submissions of faecal samples. ECOFFs for *B. pilosicoli* are not available for the antimicrobials tested. As guide for the choice of antimicrobial for treatment of spirochaetal diarrhoea, a clinical breakpoint for tiamulin of >2 mg/L and for tylosin of >16 mg/L are used at SVA. With these breakpoints, 12% of the isolates are resistant to tiamulin and 60% to tylosin (Table 5.3). If the same ECOFF as for *B. hyodysenteriae* is used, 28% of the isolates are resistant to tiamulin. Only tiamulin and tylosin are currently licensed for treatment of spirochaetal diarrhoea in pigs in Sweden and isolates with high MICs of both these substances are detected.

Actinobacillus pleuropneumoniae

Isolates of *Actinobacillus pleuropneumoniae* are from post mortem investigations of lungs or from lung samples taken at slaughterhouses within the monitoring programme SVARMpat (See In focus: SVARMpat). The resistance situation is favourable and almost no resistance is detected (Table 5.4). However, since pneumonia caused by *A. pleuropneumoniae* is an important disease in Swedish pig production, sampling and susceptibility testing is desirable if emerging resistance is to be detected early.

Pasteurella spp.

Most isolates of *Pasteurella* spp. are from post mortem investigations of lungs or from lung samples taken at slaughterhouses within the monitoring programme SVARMpat. Some isolates are from nasal swabs collected within a control programme for atrophic rhinitis in nucleus and multiplying herds. Isolates from the control programme are likely from healthy pigs, whereas isolates from lung samples are most likely from pigs with respiratory disease. Antimicrobial resistance is rare among isolates of *Pasteurella* spp. (Table 5.5).

TABLE 5.2. Resistance (%) in *Brachyspira hyodysenteriae* from pigs 2005-2013 and distribution of MICs for isolates from 2009-2013. Clinical isolates from faecal samples.

Antimicrobial	Resistance (%)			Distribution (%) of MICs (mg/L)													
	2005-06 n=54[a]	2007-08 n=38[b]	2009-13 n=55[c]	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline	9	3	4			10.9	72.7	12.7		3.6							
Tiamulin	7	18	5		45.5	34.5	14.5	3.6	1.8								
Tylosin	81	76	55								25.5	18.2	1.8			1.8	52.7
Tylvalosin	-	93[d]	53				1.8	20.0	25.5	3.6	9.1	23.6	12.7		3.6		
Valnemulin	0	18	2	87.3	10.9			1.8									

[a]29 isolates 2005, 25 isolates 2006; [b]23 isolates 2007, 15 isolates 2008; [c]24 isolates 2009, 9 isolates 2010, 7 isolates 2011, 7 isolates 2012, 8 isolates 2013; [d]15 isolates tested.

TABLE 5.3 Distribution of MICs for *Brachyspira pilosicoli* from pigs 2005-2013, n=276. Clinical isolates from faecal samples.

Antimicrobial	Distribution (%) of MICs (mg/L)													
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline			37.0	50.4	4.7	2.9	4.7	0.4						
Tiamulin		32.2	27.2	12.3	8.3	6.5	1.8	0.4	2.2	9.1				
Tylosin							5.1	19.7	10.9	3.6	4.7	3.6	5.4	46.7
Tylvalosin[a]					11.5	23.9	24.8	5.3	1.8	4.4	15.0	13.3		
Valnemulin	44.9	21.0	6.2	9.1	6.9	4.3	2.2	1.4	4.0					

[a]113 isolates tested.

TABLE 5.4. Distribution of MICs and resistance (%) in *Actinobacillus pleuropneumoniae* from pigs 2005-2013. Clinical isolates from post mortem investigations of lungs. The number of isolates each year varies (n=16-57).

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)														
	2005-2013 n=289	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ampicillin	0						100									
Chloramphenicol	0								100							
Ciprofloxacin	0	1.4	65.4	33.2												
Florfenicol	0									100						
Gentamicin	0							0.3	5.9	80.6	13.1					
Nalidixic acid	0							2.8	57.1	40.1						
Penicillin	0			0.3	4.8	66.8	28.0									
Streptomycin	2								0.3		2.1	43.9	51.6	2.1		
Tetracycline	0							99.7	0.3							
Trimethoprim	0				18.0	58.8	19.4	2.8	1.0							

TABLE 5.5. Distribution of MICs and resistance (%) in *Pasteurella* spp. from pigs 2005-2013. Clinical isolates from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)													
	2005-2013 n=233	≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ampicillin	0								100							
Chloramphenicol	0[a]									100						
Ciprofloxacin	0[a]	21.6	58.8	18.6	1.0											
Enrofloxacin	0[b]					98.5	1.5									
Florfenicol	1[c]										98.7	1.3				
Gentamicin	1									76.0	20.2	3.0	0.4	0.4		
Nalidixic acid	0[a]								50.5	40.2	8.2		1.0			
Penicillin	0					49.8	45.1	5.2								
Streptomycin	5										2.6	46.4	33.5	12.4	5.2	
Tetracycline	0								98.7	1.3						
Trim/Sulph	2[d]							95.8	0.8	0.8	0.8	1.7				

[a] 97 isolates tested; [b] 136 isolates tested; [c] 229 isolates tested, [d]119 isolates tested, concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole).

Cattle

Escherichia coli from faecal samples

Isolates of *E. coli* are from the gastro-intestinal tract of calves. Due to low number of isolates in 2013 (30 isolates), the results from 2012 and 2013 are combined. Most of the isolates are probably from calves no more than a few weeks old, *i.e.* during a period when resistance in enteric bacteria often is high in cattle. However, in the 30 isolates from 2013 resistance is higher than previous years with resistance to ampicillin and tetracycline of 67% and 90%, respectively (not shown in Table 5.6). Multiresistance occurred in 70% of the isolates from 2013, compared to 50% in 2012 and 40% in 2007-2011. The reason for this increase is not known. However, a biased material, due to sampling in herds with therapeutic failure and to new legislation that proclaims susceptibility testing, could have influenced the results. The low number of tested strains in 2013 makes drawing conclusions hazardous.

In 2012, there were differences in resistance between isolates from samples investigated at SVA and samples from a regional laboratory in the southern part of Sweden. The reason for the differences is not known, but geographical origin, type of herds and indication for sampling may influence differences in resistance.

Two isolates from 2010, one from 2012 and one from 2013 had a MIC of ceftiofur above the ECOFF. The isolates from 2010 and 2013 were not available for further investigation but since the MIC was just above the cut-off value, the results are probably due to methodological errors or the isolates express chromosomal AmpC. The isolate from 2012 had an AmpC phenotype, but no gene was detected with PCR.

Escherichia coli from uterine samples

In a study from January 2012 to February 2013 uterine samples from dairy cows with acute clinical metritis were analysed. Fetid vaginal discharge, body temperature above 39.5°C and poor general condition within one week from parturition were inclusion criteria for cows in the study. *Escherichia coli* was isolated from a majority of the samples, often in combination with other bacterial species. Since a combination of different bacteria in the uterine flora is common close after calving, it is not always easy to conclude what bacterial species that are causing the clinical disease. Isolates were not tested for presence of genes coding for virulence factors. Resistance was uncommon in isolates of *E. coli* from acute clinical metritis and markedly lower than in *E. coli* from the gastro-intestinal tract of calves (Tables 5.6 and 5.7), but in accordance with *E. coli* from mastitis in dairy cows (Table 5.8).

Escherichia coli from milk samples

Isolates included are from clinical submissions of milk samples from dairy cows. It is probable that most sampled cows had clinical mastitis. According to new legislation in 2013, susceptibility testing is generally required before fluoroquinolones are allowed for use in animals. Since fluoroquinolones may be the clinically most effective group of antimicrobials for treatment of *E. coli* mastitis, the number of isolates of *E. coli* susceptibility tested has increased considerably during 2013 compared to previous years.

TABLE 5.6. Resistance (%) in *Escherichia coli* from cattle 1992-2002 and 2005-2013. Distribution of MICs for isolates from 2012-2013. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antimicrobial	Resistance (%)				Distribution (%) of MICs (mg/L)									
	1992-02 n=220	2005-06 n=63	2007-11 n=70	2012-13 n=88	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	24	32	33	55				2.3	35.2	6.8	1.1	54.5		
Ceftiofur[a]	0[g]	0	3	2		4.5	83.0	10.2	2.3					
Enrofloxacin[b]	10	13	10	14	86.4	3.4	1.1	1.1	8.0					
Florfenicol	0[g]	0	1	0						33.0	66.0	1.1		
Gentamicin[c]	5	0	1	1					83.0	15.9		1.1		
Neomycin	8	13	24	17						63.6	19.3	2.3	1.1	13.6
Streptomycin[d]	42	54	49	76						2.3	18.2	3.4	2.3	73.9
Tetracycline	31	49	64	76				6.8	13.6	3.4		76.1		
Trim/Sulph.[e,f]	11	21	17	22			78.4			1.1	20.5			

[a] Cut-off value >2 mg/L until 2006; [b] Cut-off value >0.25 mg/L until 2004; [c] Cut-off value >8 mg/L until 2001; [d] Cut-off value >32 mg/L until 2006; [e] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [f] Cut-off value >4 mg/L until 2006; [g] 16 isolates tested.

TABLE 5.7. Distribution of MICs and resistance (%) in *Escherichia coli* from dairy cows 2012-2013. Clinical isolates from uterine samples from cows with acute clinical metritis.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)																
	2012-2013 n=60	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	5							6.7	45.0	43.3		1.7				3.3			
Cefotaxime	0			70.0	30.0														
Chloramphenicol	0								6.7	51.7	41.7								
Ciprofloxacin	2	1.7		35.0	61.7	1.7													
Florfenicol	0									35.0	63.3	1.7							
Gentamicin	0					1.7	63.3	30.0	5.0										
Kanamycin	0										100								
Nalidixic acid	0							1.7	31.7	66.7									
Streptomycin	5								1.7	33.3	51.7	8.3			5.0				
Sulphonamide	5										3.3	48.3	35.0	8.3			1.7		3.3
Tetracycline	2							53.3	43.3	1.7			1.7						
Trimethoprim	3					48.3	41.7	6.7		1.7			1.7						

In the material from 2013, resistance was uncommon and 81% of the isolates were susceptible to all tested antimicrobials (Table 5.8). The results are in accordance with the results of susceptibility testing of isolates of *E. coli* from dairy cows with acute clinical mastits in a study in 2002-2003 (Bengtsson et al., 2009).

In resistant isolates from 2013, multiresistance was common and occurred in 13% of all isolates. Resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole were the most common traits and 8% of the isolates were resistant to all three of these antimicrobials. One isolate was resistant to six antimicrobials (ampicillin, ceftiofur, enrofloxacin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole). This isolate was confirmed as ESBL-producing. For further information on ESBL-producing Enterobacteriaceae, see section Antimicrobial resistance as notifiable diseases.

Klebsiella pneumoniae from milk samples

Isolates included are from clinical submissions of milk samples from dairy cows. Resistance was uncommon and 83% of isolates were susceptible to all tested antimicrobials, excluding ampicillin (Table 5.9). As for isolates of *E. coli*, resistance was in accordance with the results from susceptibility testing of isolates from 2002-2003 (Bengtsson et al., 2009). Resistance to tetracycline, streptomycin or trimethoprim-sulphamethoxazole was the most common resistance trait. Multiresistance occurred in two isolates.

TABLE 5.8. Distribution of MICs and resistance (%) in *Escherichia coli* from dairy cows 2013. Clinical isolates from milk.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	n=142	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	14				6.3	56.3	23.2		14.1		
Ceftiofur	1		9.2	71.8	18.3		0.7				
Enrofloxacin	5	95.1	0.7	2.8		1.4					
Florfenicol	0					1.4	45.1	50.7	2.8		
Gentamicin	0					93.0	7.0				
Neomycin	4						93.0	3.5	0.7	2.8	
Streptomycin	16						2.8	42.3	38.7	0.7	15.5
Tetracycline	9				12.7	53.5	22.5	2.1	9.2		
Trim-Sulph.[a]	11			89.4				10.6			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphametoxazole)

TABLE 5.9. Distribution of MICs and resistance (%) in *Klebsiella pneumoniae* from dairy cows 2013. Clinical isolates from milk.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	n=41	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	NR[b]					2.4			97.6		
Ceftiofur	0		14.6	75.6	9.8						
Enrofloxacin	0	97.6	2.4								
Florfenicol	2						48.8	46.3	2.4	2.4	
Gentamicin	0					100					
Neomycin	2						97.6			2.4	
Streptomycin	7						82.9	7.3	2.4	2.4	4.9
Tetracycline	15				4.9	61.0	14.6	4.9	14.6		
Trim-Sulph.[a]	5			92.7	2.4			4.9			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] Not relevant as the genus is inherently resistant to ampicillin.

TABLE 5.10. Distribution of MICs and resistance (%) in *Pasteurella* spp. from calves 2005-2013. Clinical isolates from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	n=254	≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Ampicillin	0					100					
Enrofloxacin	0[b]		96.1	3.9							
Florfenicol	0							100		–	
Penicillin	0		51.2	40.6	8.3						
Tetracycline	0					96.5	3.5				
Trim/Sulph.[a]	0				96.8	1.6	1.2	0.4			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] 229 isolates tested.

Pasteurella spp.

Isolates of *Pasteurella* spp. are from nasal swabs from calves with respiratory disease or from post mortem investigations of lungs. Antimicrobial resistance is rare among isolates of *Pasteurella* spp. (Table 5.10) and penicillin is considered the substance of choice for treatment of pneumonia in calves in Sweden. Isolates of beta-lactamase producing *Pasteurella* spp. have been confirmed in one herd in 2003 and beta-lactamase producing *Mannheimia haemolytica* in one herd in 2010.

Farmed fish

Isolates presented are from clinical submissions of farmed fish. In 2013, data for 10 isolates of *Aeromonas salmonicida* subsp. *achromogenes*, 5 of *Flavobacterium columnare* and 23 of *Flavobacterium psychrophilum* were available. Data for 2009-2013 are compiled and presented as distributions of MICs in Table 5.11. The majority of the isolates from the two former species is from brown trout whereas most isolates of *F. psychrophilum* are from rainbow trout.

At present there are only published interpretative criteria for MIC data of *A. salmonicida* from aquatic animals (CLSI, 2010). An epidemiological cutoff of >4 mg/L has been proposed by CLSI for florfenicol and a clinical breakpoint of >4 for oxytetracycline. Using those criteria, one isolate is interpreted as resistant to florfenicol and one to tetracycline. Deviating high MICs of some other antimicrobials indicate the presence of acquired resistance. For example, in *A. salmonicida* and *F. psychrophilum* MIC distributions for the quinolone nalidixic acid are bimodal. Likewise, among *F. psychrophilum* there are some isolates with deviating MICs for tetracycline. Acquired resistance to these antimicrobials is plausible since there is a limited therapeutic use of the quinolone oxolinic acid as well as of tetracycline in aquaculture in Sweden.

TABLE 5.11. Distribution of MICs for *Aeromonas salmonicida* subsp. *achromogenes* (n=60), *Flavobacterium columnare* (n=31) and *Flavobacterium psychrophilum* (n=126) from farmed fish 2009-2013.

Bacterial species	Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)								
			≤0.5	1	2	4	8	16	32	64	>64
Aeromonas salmonicida subsp. *achromogenes*	Florfenicol	2			96.7	1.7		1.7			
	Nalidixic acid		81.7	1.7					1.7	6.7	8.3
	Tetracycline	2	93.3	3.3		1.7		1.7			
Flavobacterium columnare	Florfenicol				100						
	Nalidixic acid		77.4	12.9	3.2	3.2				3.2	
	Tetracycline		96.8	3.2							
Flavobacterium psychrophilum	Florfenicol				99.2		0.8				
	Nalidixic acid				16.7	20.6	2.4	0.8	3.2	5.6	50.9
	Tetracycline		44.4	26.2	11.1	15.9	2.4				

SVARMpat

The SVARMpat programme (Swedish Veterinary Antimicrobial Resistance Monitoring – farm animal pathogens) is a project in co-operation between SVA and the Swedish Animal Health Service that started in 2005. It is financed by the Swedish Board of Agriculture.

The purpose of SVARMpat is to reduce emergence and spread of antimicrobial resistance in pathogenic bacteria from farm animals. The work is performed by monitoring and documenting antimicrobial resistance, by activities that increase knowledge of antimicrobial resistance and prudent use of antimicrobials, and by communication of knowledge generated within the programme to practitioners and farmers.

Selected studies within SVARMpat in 2013:

Milk samples in dairy cows

- Screening for MRSA in milk samples from dairy cows was started in 2010 and is still ongoing. Selected isolates of beta-lactamase producing *Staphylococcus aureus* from routine submissions to SVA are investigated for methicillin resistance. During 2010-2013, 570 isolates were tested and MRSA with *mecC* was confirmed in three isolates from 2010, one from 2011 and one from 2013, and MRSA with *mecA* was confirmed in one isolate from 2012. In addition, 513 isolates of *S. aureus* without beta-lactamase production were tested in 2013, but MRSA was not detected. See section Resistance as notifiable diseases.

- Continuous monitoring of bacterial findings in clinical mastitis in dairy cows was started in 2013. Randomly collected milk samples are cultured and isolated bacteria are susceptibility tested. Resistance in pathogens from clinical mastitis were uncommon in a study in 2002-2003 (Bengtsson et al., 2009), but since mastitis is an important disease in dairy cows it is desirable to continuously monitor the situation.

Respiratory tract samples in pigs, cattle and sheep

- During 2013, lungs from pigs with signs of respiratory disease were sampled at slaughter to increase the number of isolates of *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* available for susceptibility testing. For resistance results see section Resistance in clinical isolates from animals, Pigs.

- Species identification of isolates of *Pasteurella* spp. and *Mannheimia* spp. from the respiratory tract of pigs, cattle and sheep were improved by MALDI-TOF MS. Due to some uncertainties in species identification with phenotypic methods, MALDI-TOF MS was introduced in 2013. Isolates from pigs (n=20) and cattle (n=24) were identified as *P. multocida* with MALDI-TOF MS. Of the isolates from sheep (n=18), 9 were identified as *Bibersteinia trehalosi* (former *Pasteurella trehalosi*) and 9 as *Mannheimia haemolytica*.

Enteric samples from pigs

- Swine dysentery and spirochaetal diarrhoea in pigs are important diseases in many countries. The resistance situation in *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli* in Sweden is favourable compared to other countries. Within SVARMpat, isolates from all identified herds with these diseases in Sweden are susceptibility tested. For resistance results see section Resistance in clinical isolates from animals, Pigs.

Enteric and environmental samples from broilers

- The occurrence of ESBL-producing *E. coli* in broilers, laying hens and turkeys are monitored and the epidemiology of this resistance is studied in several projects. See section Resistance as notifiable diseases.

Horses

Escherichia coli

Isolates of *E. coli* are from clinical samples from the genital tract of mares. As in previous years, resistance to trimethoprim-sulphamethoxazole and streptomycin was most common in 2013 (Table 5.12), but the rates have gradually declined (Figure 5.2).

Multiresistance was detected in 4% (6/140) of the isolates, which is less than in isolates from 2011 (11%) and 2012 (6%). All multiresistant isolates were resistant to at least ampicillin, streptomycin and trimethoprim-sulphamethoxazole. Three of the multiresistant isolates were resistant to six substances; the already mentioned plus ceftiofur, gentamicin and neomycin (n=2) or gentamicin, neomycin, and tetracycline (n=1).

One isolate with MIC of ceftiofur >2 mg/L was verified as an ESBL-producer by PCR. Two isolates with MIC 2 mg/L of ceftiofur were, however, not tested with molecular methods. For further information on ESBL-producing Enterobacteriaceae from horses, see section Antimicrobial resistance as notifiable diseases.

FIGURE 5.2. Resistance (%) in clinical isolates of *Escherichia coli* from horses 2001-2013. Isolates are from clinical sampling of the genital tract of mares. The number of isolates each year varies (n=43-273).

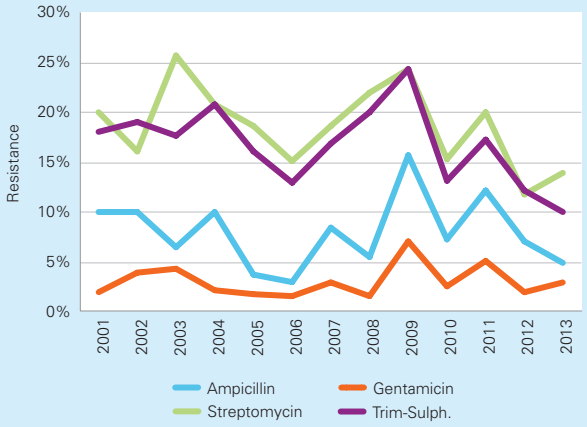


TABLE 5.12. Distribution of MICs and resistance (%) in *Escherichia coli* from horses in 2013. Clinical isolates from the genital tract of mares.

Antimicrobial	Resistance (%) 2013 n=140	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	5				4.3	54.3	36.4		5.0		
Ceftiofur	2		12.9	73.6	11.4	1.4	0.7				
Enrofloxacin	4	96.4	2.9	0.7							
Florfenicol	0					0.7	46.4	50.7	2.1		
Gentamicin	3					95.7	1.4	0.7		2.1	
Neomycin	3						95	2.1		0.7	2.1
Streptomycin	14						5.7	54.3	25.7	3.6	10.7
Tetracycline	3				12.9	75.7	8.6		2.9		
Trim-Sulph.[a]	10			89.3	0.7			10.0			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole)

TABLE 5.13. Distribution of MICs and resistance (%) in *Streptococcus zooepidemicus* from horses in 2013. Clinical isolates from the respiratory tract.

Antimicrobial	Resistance (%) 2013 n=123	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0				100						
Enrofloxacin	NR [b]			3.3	68.3	28.5					
Florfenicol	0					95.1	4.9				
Gentamicin	NR						0.8	43.9	51.1	4.1	
Penicillin	0	100									
Spiramycin	0						100				
Tetracycline	2				41.5	43.9	10.6	1.6	2.4		
Trim-Sulph.[a]	10			79.7	5.7	2.4	2.4	9.8			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole); [b] NR= Not relevant as the inherent susceptibility is above concentrations that can be obtained during therapy.

Streptococcus zooepidemicus

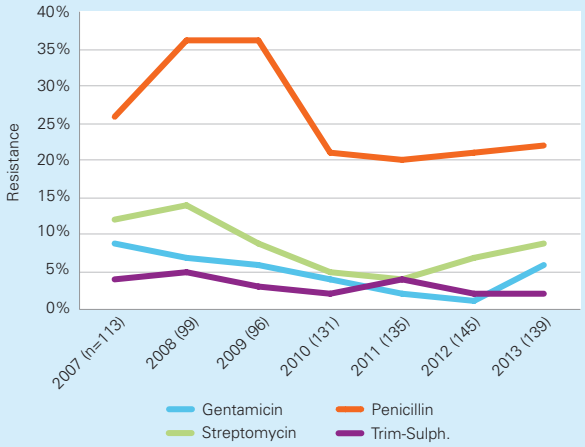
Isolates of *Streptococcus zooepidemicus* are from clinical samples from the respiratory tract. Resistance to antimicrobials was rare (Table 5.13). Over the years studied in SVARM, all isolates have been consistently susceptible to penicillin and ampicillin. Resistance to the other antimicrobials tested has also been rare. One exception is trimethoprim-sulphamethoxazole resistance which previously was common but which has gradually declined in the last years.

It is noteworthy that MICs of fluoroquinolones (enrofloxacin) and aminoglycosides (gentamicin) were high and above concentrations obtained during systemic therapy (Table 5.13). This emphasizes the low inherent susceptibility of *S. zooepidemicus* to these antimicrobials.

Staphylococcus aureus

Isolates of *Staphylococcus aureus* are from clinical sampling of skin, excluding wounds and abscesses. Resistance to penicillin due to beta-lactamase production dominated in 2013, while resistance to the other antimicrobials, with the exception of streptomycin, was uncommon (Table 5.14). Levels of resistance to gentamicin, streptomycin, and trimethoprim-sulphamethoxazole have remained stable over the last seven years (Figure 5.3). Resistance to penicillin has declined from a peak in 2008-2009 (36%) and has stabilised around 20% during the last four years.

FIGURE 5.3. Resistance (%) in clinical isolates of *Staphylococcus aureus* from skin of horses, 2007-2013. The number of isolates each year varies (n=96-145).



One multiresistant isolate, resistant to four substances; enrofloxacin, gentamicin, streptomycin and trimethoprim-sulphamethoxazole, was detected in the isolates from 2013. MRSA was not found in skin samples from 2013 . For more information on MRSA isolated from horses in Sweden, see section Antimicrobial resistance as notifiable diseases.

TABLE 5.14. Distribution of MICs and resistance (%) in *Staphylococcus aureus* isolated from horses in 2013. Clinical isolates from the skin.

Antimicrobial	Resistance (%) 2013 n=139	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ceftiofur	<1		0.7	10.1	82.7	5.8	0.7				
Enrofloxacin	<1	63.3	33.1	2.9	0.7						
Florfenicol	0					2.2	77.7	20.1			
Gentamicin	6					94.2	2.9		0.7	2.2	
Oxacillin	0			99.3	0.7						
Penicillin[a]	22										
Spiramycin	0						10.8	82.0	7.2		
Streptomycin	9						37.4	46.0	7.2	0.7	8.6
Tetracycline	4				96.4	2.2	1.4				
Trim-Sulph.[b]	2			97.8	0.7	0.7		0.7			

[a] Denotes beta-lactamase production; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Dogs

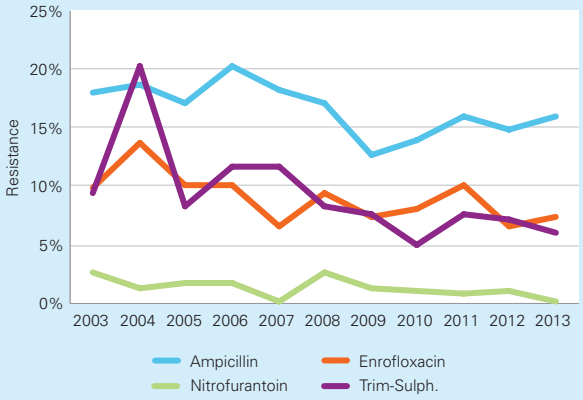
Escherichia coli

Isolates of *E. coli* are from clinical samples from urine, submitted either as urine or cultures from dip-slides or other agar plates. As in previous years, resistance to ampicillin was the most common trait in 2013 (Table 5.15). Levels of resistance to ampicillin, gentamicin, streptomycin and trimethoprim-sulphamethoxazole have been stable or slightly declining, except for a rise in trimethoprim-sulphametoxazole resistance in 2004 (Figure 5.4).

Multiresistance was detected in 3% (24/840) of the isolates which is almost halved compared to 2011-2012. Five isolates were resistant to four substances, most commonly to ampicillin, enrofloxacin, tetracycline, and trimethoprim-sulphamethoxazole (n=4). Furthermore, four isolates were resistant to five substances. Three of those were resistant to the already mentioned antimicrobials and cefotaxime.

Five of six isolates resistant to cefotaxime were further analysed for genotype by PCR. Genes conferring ESBL or pAmpC resistance were detected in four and one isolate, respectively. For more information on ESBL-producing Enterobacteriaceae from dogs, see section Antimicrobial resistance as notifiable diseases.

FIGURE 5.4. Resistance (%) in clinical isolates of *Escherichia coli* from dog urine, 2003-2013. The number of isolates each year varies (n=234-840).



Staphylococcus pseudintermedius

Isolates of *Staphylococcus pseudintermedius* are from clinical sampling of skin, excluding wounds and abscesses. Penicillin resistance due to beta-lactamase production is constantly high, 78% in 2013, and has during the 14 years studied been between 75 and 90% (Table 5.16. and Figure 5.5). Resistance to clindamycin, erythromycin, fusidic acid, and/or tetracycline has remained at approximately the same levels (Figure 5.5).

Multiresistance is common in *S. pseudintermedius* emanating from skin. Between 2009 and 2011 the figures have varied from 26 to 36% and were 30% (172/566) in 2013. Of the multiresistant isolates 2013, 16% (27/172) were resistant to five or more antimicrobials. This was 5% of all the isolates. The most common phenotype among the multiresistant isolates was resistance to penicillin, clindamycin and erythromycin, occurring in 77% (134/172) of the isolates. Thirty-six percent with that phenotype was also resistant to fusidic acid and 32% to tetracycline.

TABLE 5.15. Distribution of MICs and resistance (%) in *Escherichia coli* from dogs 2013. Clinical isolates from urine.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2013 n=840	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	16				3.2	57.6	23.0	0.5	15.7		
Cefotaxime	1			98.9	0.4	0.7					
Enrofloxacin	8	92.5	2.6	3.0	0.2	0.1		1.5			
Gentamicin	<1					94.8	5.0	0.1		0.1	
Nitrofurantoin	<1								99.2	0.7	0.1
Tetracycline	6				14.2	74.2	6.1	0.1	5.5		
Trim-Sulph.[a]	6			93.2	0.8	0.2		5.7			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Pseudomonas aeruginosa

Isolates of *Pseudomonas aeruginosa* are from clinical samples from the external ear canal.

Pseudomonas aeruginosa is considered clinically resistant to trimethoprim-sulphonamides, tetracyclines, and aminopenicillins including combinations with clavulanic acid. Fluoroquinolones, gentamicin and polymyxin B have indications for treatment of *P. aeruginosa* infections in dogs and data for these antimicrobials for 2013 are presented in Table 5.17.

Over the years studied in SVARM, tested isolates have been uniformly susceptible to polymyxin B but resistance to enrofloxacin or gentamicin has been found. Resistance to the latter antimicrobials has declined within the period 2009-2013. In 2009, 25% of the isolates were resistant to enrofloxacin and 5% to gentamicin.

FIGURE 5.5. Resistance (%) in clinical isolates of *Staphylococcus pseudintermedius* from skin of dogs, 2000-2013. The number of isolates each year varies (n=89-566).

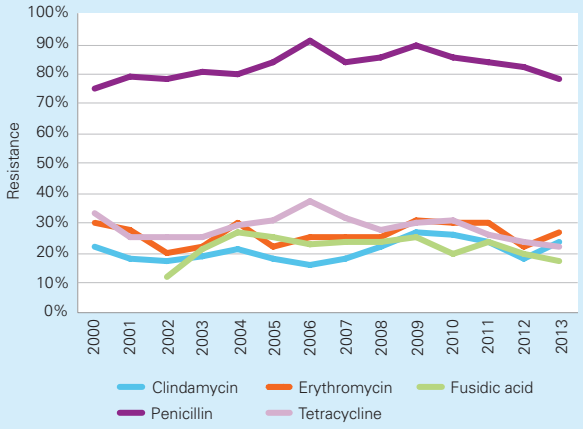


TABLE 5.16. Distribution of MICs and resistance (%) in *Staphylococcus pseudintermedius* from dogs 2013. Clinical isolates from skin.

Antimicrobial	Resistance (%) 2013 n=566	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Cephalothin	1					98.8	0.4	0.9			
Clindamycin	24				74.8		0.9	24.4			
Enrofloxacin	4	59.2	35.2	1.9	1.8	0.4		1.6			
Erythromycin	27			72.8	0.5			26.7			
Fusidic acid	17					78.0	4.9	17.1			
Gentamicin	2					96.6	1.8	0.2	0.7	0.7	
Nitrofurantoin	<1								99.3	0.5	0.2
Oxacillin	<1			99.1		0.9					
Penicillin[a]	78										
Tetracycline	22				77.2	0.5		0.2	22.1		
Trim-Sulph.[b]	3			66.1	29.5	1.2	0.2	3.0			

[a] Denotes beta-lactamase production; [b] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole

TABLE 5.17. Distribution of MICs and resistance (%) in *Pseudomonas aeruginosa* in dogs 2013. Clinical isolates from the external ear canal.

Antimicrobial	Resistance (%) 2013 n=309	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Enrofloxacin	14		1.0	11.3	47.6	26.5	8.1	5.5			
Gentamicin	1					84.5	11.7	2.6	1.0	0.3	
Polymyxin B	0					88.3	11.7				

Cats

Escherichia coli

Isolates of *E. coli* are from clinical samples from urine, submitted either as urine or cultures from dip-slides or other agar plates. Although declining, resistance to ampicillin was still the most common trait in 2013 (Table 5.18 and Figure 5.6). From 2006 and onwards, a decline in resistance was noticed also for the other substances shown in Figure 5.6.

Multiresistance was found in 2% (7/404) of the isolates from 2013. This is the same as in 2012, but slightly less compared to isolates from 2010-2011 (3%). Four of six isolates resistant to three substances were resistant to ampicillin, tetracycline and trimethoprim-sulphamethoxazole. One isolate was resistant to five substances; the already mentioned plus cefotaxime and tetracycline. This isolate had an AmpC phenotype, but no transferrable gene was detected with PCR. The other isolate with MIC of cefotaxime above the ECOFF was not available for further testing. For more information on ESBL-producing Enterobacteriaceae from cats, see section Antimicrobial resistance as notifiable diseases.

FIGURE 5.6. Resistance (%) in clinical isolates of *Escherichia coli* from urine of cats, 2003-2013. The number of isolates each year varies (n=52-404).

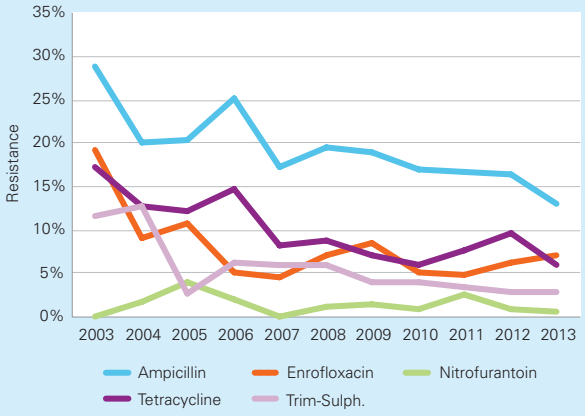


TABLE 5.18. Distribution of MICs and resistance (%) in *Escherichia coli* isolated from cats 2013. Clinical isolates from urine.

Antimicrobial	Resistance (%) 2013 n=404	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	13				5.0	66.8	15.3	0.2	12.6		
Cefotaxime	<1			99.5	0.2	0.2					
Enrofloxacin	7	93.3	3.2	2.5	0.2			0.7			
Gentamicin	0					97.2	2.7				
Nitrofurantoin	<1								98.5	1.0	0.5
Tetracycline	6				21.5	67.3	4.2	0.5	6.4		
Trim-Sulph.[a]	3			95.5	1.2	0.5	0.5	2.3			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphamethoxazole).

Dichelobacter nodosus

Reports on antimicrobial susceptibility in *Dichelobacter nodosus* are scarce because of the fastidious nature of this anaerobic bacterium and the difficulties in isolation. Susceptibility tests have been performed with variants of agar dilution (Gradin & Schmitz 1983; Jimenez et al., 2004) but no approved standardized method is available.

TABLE 5.19. Distribution (%) of MICs of four antimicrobial agents for 43 isolates of *Dichelobacter nodosus*.

Antimicrobial	Distribution (%) of MICs (mg/L)										
	≤0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4
Enrofloxacin			4.7	44.2	32.6	16.3	2.3				
Erythromycin			14.0	11.6	23.3	30.2	18.6			2.3	
Penicillin		2.3	34.9	14.0	20.9	2.3	25.6				
Tetracycline						14.0	30.2	39.5	14.0		2.3

In this study agar dilution was used to test the antimicrobial susceptibility for a set of field isolates. The *D. nodosus* isolates tested were mainly from clinical submissions from sheep in herds with clinical signs of footrot (n=39) but isolates from sheep in herds without footrot (n=4) were also included.

The tests were performed on fastidious anaerobe agar with 10% horse blood (FAA). Enrofloxacin, erythromycin, penicillin and tetracycline were added to the agar in twofold serial dilutions. As control strains *Staphylococcus aureus* ATCC 29213 and *Bacteroides fragilis* ATCC 25285 were used. Direct colony suspensions from FAA plates (*D. nodosus* three day´s old cultures and *B. fragilis* over night) and blood agar plates (*S. aureus* over night) were used as inoculum. For *D. nodosus* and *B. fragilis* an inoculum of 2 µl of a suspension with the density 0.5 McFarland (approximately 10^5 CFU per spot) was used and for *S. aureus* a tenfold dilution lower (approximately 10^4 CFU per spot). The agar dilution tests were incubated for four days in anaerobic jars at 37°C. The MIC was read as the first concentration with a marked reduction in appearance of growth as compared to that of growth on the control plate.

The tests were made in duplicate and read by the same person. The *D. nodosus* type strain, CCUG 27824, was included in nine test rounds. Of 172 read MICs, 155 were within 2 twofold dilution steps when the first and the second tests were compared. The majority of the varying results were MICs of erythromycin and penicillin but for the *D. nodosus* type strain most variation was seen for enrofloxacin and penicillin. The MICs for the field isolates are presented in Table 5.19.

In Sweden the main treatment of ovine footrot is through footbaths with zinc sulfate and relocation of the animals to uncontaminated surfaces, aggressive footrot is however treated with antibiotics parenterally. The drug most often used is tetracycline both for systemic and local treatment. One purpose of this study was to investigate if penicillin, which would be better from an antimicrobial resistance point of view, could be a choice for treatment of footrot. However, besides the low MICs obtained in this study, clinical trials are needed to show if penicillin is effective against footrot.

Despite the difficulties in interpreting the results for erythromycin and penicillin for some of the isolates the majority of the MICs were within the method error when the test was repeated. Elevated MICs of erythromycin and tetracycline was only found for one isolate. In conclusion, the MICs of the tested antimicrobial agents were low for the majority of the *D. nodosus* isolates.

Acknowledgments

The study was supported by the Swedish Farmers´ Foundation for Agricultural Research.

Indicator bacteria from animals

In programmes monitoring antimicrobial resistance in the veterinary field, *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus faecium* from the enteric flora of healthy animals or from the flora contaminating food serve as indicators for presence of acquired resistance. The prevalence of resistance in these so called indicator bacteria signifies the magnitude of the selective pressure from antimicrobial use in an animal population.

Although these bacteria are unlikely to cause disease they can be reservoirs for resistance genes that can spread to bacteria that cause infections in animals or humans. Hence, resistance in indicator bacteria contaminating meat signifies the potential human exposure to such reservoirs among farm animals.

In 2013, calves 6-11 months old and turkeys were studied. Intestinal content was collected at slaughter and cultured for indicator *E. coli*. Samples from calves were also cultured for enterococci. All samples from calves and turkeys were also screened for *E. coli* resistant to extended spectrum cephalosporins (ESC) by selective culture on media supplemented with cefotaxime. In addition samples of intestinal content from broilers and samples of broiler meat were screened for ESC resistant *E. coli*. For details on methodology see Material and methods, resistance in bacteria from animals.

Escherichia coli

Calves

Escherichia coli was isolated from 197 (98%) of 202 samples cultured. The vast majority of isolates (92%) were susceptible to all antimicrobials tested and only 9 isolates (8%) were resistant to one substance or more (Table 6.1). Three isolates (2%) were multiresistant. One of these was resistant to ampicillin, streptomycin, sulphonamide and trimethoprim and the other two to streptomycin, sulphonamide and tetracycline.

Low levels of resistance in *E. coli* from healthy cattle are in agreement with the three previous studies of cattle in SVARM where more than 90% of the isolates have been susceptible to all antimicrobials studied tested and resistance to any single substance has never exceeded 5% (SVARM 2009). This indicates a low selection pressure from use of antimicrobials in the categories of cattle studied, *i.e.* calves older than six months and dairy cows. The findings are in stark contrast to the high levels of resistance in clinical isolates of *E. coli*, see Resistance in clinical isolates from animals. The difference is probably due to the fact that the clinical isolates mostly are from younger calves and most likely from diseased animals.

Using selective culture, ESC resistant *E. coli* was isolated from 3 (1.5%) of the 202 samples of intestinal content from calves. Of these, one isolate carried resistance genes of the CTX-M-1 group but in the other two isolates genes conferring transmissible ESBL or AmpC resistance were not found. For details and comments see section Resistance as notifiable disease.

Turkeys

Escherichia coli was isolated from all 55 samples cultured. The majority of isolates (58%) was susceptible to all antimicrobials tested but 23 isolates (42%) were resistant to at least one substance (Table 6.1). Resistance to ampicillin or to tetracycline were the most common traits but sulphonamide or streptomycin resistance also occurred in about 10% of the isolates. Four isolates (7%) were multiresistant and of these, three isolates were resistant to both ampicillin and tetracycline in addition to other antimicrobials.

Turkeys have not been studied previously in SVARM and trends in resistance can therefore not be evaluated. Also the number of isolates tested is small and further studies are needed for confident evaluation of the situation. It is however noteworthy that resistance is about as prevalent as among broilers and involves the same antimicrobials (Table 6.1). Quinolone resistance however seems less common in *E. coli* from broilers than from turkeys and that the opposite applies for tetracycline resistance. Use of antimicrobials in poultry is however uncommon in Sweden and it is unlikely that the observed resistance is caused by a direct selection pressure from use of antimicrobials.

On selective culture, ESC resistant *E. coli* was isolated from 16 (29%) of the 55 samples from turkeys. However, genes conferring transmissible ESBL or AmpC resistance were not found. For details and comments see section Resistance as notifiable diseases.

Broilers and Broiler meat

In 45 (45%) of 100 samples of intestinal content from broilers cultured selectively ESC resistant *E. coli* was found. Genes conferring transmissible ESBL or AmpC resistance were found in isolates from 40 samples (40%).

Likewise, in 31 (52%) of 59 samples of fresh broiler meat cultured selectively ESC resistant *E. coli* was found in 30 samples (51%). For details and comments see section Resistance as notifiable diseases.

TABLE 6.1. Resistance (%) and multiresistance (%) in indicator *Escherichia coli* from calves and turkeys, 2013. Data from previous SVARM-reports are given for comparison.

Antimicrobial	ECOFF (mg/L)	Resistance (%)									
		Calves 2013 n=197	Turkeys 2013 n=55	Broilers 2012 n=194	Broiler meat 2012 n=92	Laying hens 2012 n=61	Pigs 2011 n=167	Pig meat 2011 n=20	Sheep 2006-09 n=115	Horses 2010-11 n=274	Dogs 2012 n=74
Ampicillin	>8	1	22	14	18	3	13	30	2	2	9
Cefotaxime	>0.25	0	0	0	0	2	<1	0	0	0	1
Ceftazidime	>0.5	0	0	-	-	-	-	-	-	-	-
Chloramphenicol	>16	0	2	<1	0	0	4	0	0	<1	0
Ciprofloxacin	>0.06	1	4	14	4	5	2	10	<1	<1	3
Colistin	>2	0	0	0	1	0	0	0	-	<1	0
Florfenicol	>16	0	0	0	0	0	0	0	0	0	0
Gentamicin	>2	0	4	<1	3	2	1	0	3	<1	0
Nalidixic acid	>16	<1	2	12	4	5	2	0	0	<1	0
Streptomycin	>16	2	9	9	7	5	16	10	3	13	4
Sulphonamide	>64	2	13	10	16	8	17	10	7	15	4
Tetracycline	>8	3	20	11	14	13	8	0	<1	2	8
Trimethoprim	>2	1	4	8	7	5	11	10	2	16	1
Multiresistance[a]											
Susceptible to all above		95	58	64	64	80	72	70	87	81	84
Resistant to 1		3	18	21	20	5	9	10	10	2	9
Resistant to 2		1	16	6	8	8	5	10	2	5	1
Resistant to 3		1	6	5	1	5	3		1	9	4
Resistant to >3		1	2	5	7	2	10	10		3	1

[a] Ciprofloxacin and nalidixic acid counted as one antimicrobial.

TABLE 6.2. Distribution of MICs and resistance (%) in *Escherichia coli* from intestinal content from calves (n=197) and turkeys (n=55), 2013.

Antimicrobial	Source	Resistance %	Distribution (%) of MICs (mg/L)																		
			≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	Calves	1								12.7	68.0	17.3	1.0					1.0			
	Turkeys	22								3.6	58.2	16.4						21.8			
Cefotaxime	Calves	0			1.5	64.5	33.5	0.5													
	Turkeys	0				47.3	49.1	3.6													
Ceftazidime	Calves	0						91.4	8.6												
	Turkeys	2						78.2	20.0	1.8											
Chloramphenicol	Calves	0									16.8	71.6	11.7								
	Turkeys	2									16.4	72.7	9.1				1.8				
Ciprofloxacin	Calves	1		1.0	61.9	36.0	0.5	0.5													
	Turkeys	4		5.5	54.5	36.4	1.8			1.8											
Colistin	Calves	0							35.5	46.2	18.3										
	Turkeys	0							45.5	45.5	9.1										
Florfenicol	Calves	0										74.6	25.4								
	Turkeys	0										89.1	10.9								
Gentamicin	Calves	0							59.4	37.6	3.0										
	Turkeys	4							43.6	43.6	9.1				3.6						
Nalidixic acid	Calves	<1								2.5	52.3	44.2	0.5				0.5				
	Turkeys	2								5.5	56.4	32.7	1.8	1.8			1.8				
Streptomycin	Calves	2										22.8	69.0	6.6		1.0		0.5			
	Turkeys	9									1.8	10.9	70.9	7.3	1.8	3.6	1.8		1.8		
Sulphonamide	Calves	2											26.4	42.6	26.9	2.5					1.5
	Turkeys	13											29.1	36.4	14.5	7.3	1.8				10.9
Tetracycline	Calves	3								92.9	4.6				1.5		1.0				
	Turkeys	20								76.4	3.6				10.9	7.3	1.8				
Trimethoprim	Calves	1					6.6	38.1	45.7	7.6	1.0				1.0						
	Turkeys	4					7.3	45.5	41.8	1.8					3.6						
			≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024

Enterococcus

Calves

A total of 11 isolates of *Enterococcus faecalis* and 42 isolates of *Enterococcus faecium* were obtained from 202 samples cultured. All isolates of *E. faecalis* were susceptible to all antimicrobials tested (Table 6.3). Resistance was rare also among *E. faecium* but four isolates (10 %) were resistant to erythromycin and occasional isolates also to bacitracin, aminoglycosides or tetracycline (Table 6.4). No isolate was resistant to more than two antimicrobials.

The number of isolates tested is small and conclusions on occurrence of resistance must be made with caution. The findings are however in full agreement with those of the three previous studies of enterococci from cattle in SVARM (SVARM 2009). The studies on enterococci in SVARM have been performed in cattle older than six months and the occurrence of resistance might be different in enterococci from younger calves in analogy to the situation in *E. coli*.

TABLE 6.3. Resistance (%) and multiresistance (%) in *Enterococcus faecalis* from calves, 2013. Data from previous SVARM-reports are given for comparison.

		Resistance (%)								
Antimicrobial	**ECOFF (mg/L)**	**Calves**	**Broilers**	**Broiler meat**	**Laying hens**	**Pigs**	**Pig meat**	**Horses**	**Sheep**	**Dogs**
		2013 n=11	**2012** n=44	**2012** n=78	**2012** n=20	**2011** n=22	**2011** n=29	**2010-11** n=34	**2006-09** n=24	**2006** n=135
Ampicillin	>4	0	0	0	0	0	0	0	0	<1
Bacitracin[a]	>32[a]	0	7	23	10	0	0	0	0	1
Chloramphenicol	>32	0	0	5	0	0	0	18	0	7
Erythromycin	>4	0	34	13	10	43	0	21	0	14
Gentamicin	>32	0	0	1	0	4	0	21	0	<1
Kanamycin	>1024	0	0	0	0	4	0	21	0	4
Linezolid	>4	0	0	1	0	0	0	0	0	0
Narasin	>2	0	23	37	0	0	0	0	0	1
Streptomycin	>512	0	2	5	0	17	3	9	4	9
Tetracycline	>4	0	20	36	45	74	7	44	8	32
Vancomycin	>4	0	0	0	0	0	0	0	0	0
Virginiamycin	>32	0	0	0	0	0	0	0	0	0
Multiresistance (%)										
Susceptible to all above		100	43	27	45	17	90	56	92	25
Resistant to 1			32	37	45	35	10	24	4	38
Resistant to 2			20	29	10	43			4	27
Resistant to 3			5	1						2
Resistant to >3				5		4		21		7

[a] MIC in U/ml

TABLE 6.4. Resistance (%) and multiresistance (%) in *Enterococcus faecium* from calves, 2013. Data from previous SVARM-reports are given for comparison.

Antimicrobial	ECOFF (mg/L)	Resistance (%)								
		Calves	Broilers	Broiler meat	Laying hens	Pigs	Pig meat	Horses	Sheep	Dogs
		2013 n=42	2012 n=136	2012 n=10	2012 n=36	2011 n=22	2011 n=1	2010-11 n=27	2006-09 n=15	2006 n=29
Ampicillin	>4	0	<1	0	0	0	0	15	0	0
Bacitracin	>32[a]	5	13	40	3	9	0	0	0	3
Chloramphenicol	>32	0	0	0	0	0	0	0	0	0
Erythromycin	>4	10	4	0	6	9	0	0	0	28
Gentamicin	>32	2	0	0	0	0	0	0	0	0
Kanamycin	>1024	2	0	0	0	9	0	0	0	0
Linezolid	>4	0	0	0	0	0	0	0	0	0
Narasin	>2	0	79	80	0	0	0	0	0	7
Streptomycin	>128	0	0	0	0	13	0	7	7	0
Tetracycline	>4	2	10	30	11	13	0	4	7	17
Vancomycin	>4	0	0	0	0	0	0	0	0	0
Virginiamycin	>4	0	1	10	8	4	100	4	0	0
Multiresistance (%)										
Susceptible to all above		83	15	50	78	74		74	87	62
Resistant to 1		12	63	40	17	13	100	22	13	30
Resistant to 2		5	21	10	6	4		4		6
Resistant to 3			1							
Resistant to >3						9				2

[a] MIC in U/ml

TABLE 6.5. Distribution of MICs and resistance (%) in *Enterococcus faecalis* (n=11) and *E. faecium* (n=42) from calves, 2013

Antimicrobial	Bacterial species	Resistance %	Distribution (%) of MICs (mg/L)															
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048
Ampicillin	*E. faecalis*	0			36.4	63.6												
	E. faecium	0		9.5	7.1	64.3	19.0											
Bacitracin[a]	*E. faecalis*	0					9.1	9.1	54.5	27.3								
	E. faecium	5					2.4		14.3	66.7	11.9	2.4		2.4				
Chloramphenicol	*E. faecalis*	0						45.5	54.5									
	E. faecium	0						50.0	47.6	2.4								
Erythromycin	*E. faecalis*	0			72.7	18.2	9.1											
	E. faecium	10			33.3	4.8	28.6	23.8	4.8	2.4	2.4							
Gentamicin	*E. faecalis*	0						9.1	36.4	54.5								
	E. faecium	2						31.0	52.4	14.3					2.4			
Kanamycin	*E. faecalis*	0								18.2	18.2	54.5	9.1					
	E. faecium	2										21.4	47.6	26.2	2.4		2.4	
Linezolid	*E. faecalis*	0			9.1	18.2	63.6	9.1										
	E. faecium	0				2.4	95.2	2.4										
Narasin	*E. faecalis*	0	18.2	54.5	27.3													
	E. faecium	0		11.9	78.6	9.5												
Streptomycin	*E. faecalis*	0									9.1	45.5	45.5					
	E. faecium	0								2.4	35.7	61.9						
Tetracycline	*E. faecalis*	0			45.5	54.5												
	E. faecium	2			33.3	64.3						2.4						
Vancomycin	*E. faecalis*	0				72.7	27.3											
	E. faecium	0				95.2	4.8											
Virginiamycin	*E. faecalis*	0			9.1		9.1	27.3	9.1	45.5								
	E. faecium	0			31.0	31.0	33.3	4.8										
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048

[a] MIC in U/ml

Background data, material, metods and references

Demographics and denominator data

Human beings

TABLE 7.1. Population by county and age group, December 31st 2013.

	0-6 years	7-19 years	20-64 years	65-79 years	80 years-	All ages
Stockholm	200031	197676	1289760	242173	85110	2127006
Uppsala	28827	32138	203885	44370	15222	341977
Södermanland	21976	26377	152569	43616	15258	274723
Östergötland	34919	41097	250165	61559	23796	433784
Jönköping	28028	33291	191153	48059	20039	339116
Kronoberg	14973	17556	105298	26921	11348	185887
Kalmar	16545	21015	129591	39735	15113	233548
Gotland	4015	5121	32367	9624	3348	57241
Blekinge	11412	13737	84692	25368	9409	152315
Skåne	108690	114706	735957	172869	66429	1263088
Halland	25187	30001	169870	45380	16917	304116
Västra Götaland	133920	147330	938496	215214	83225	1600447
Värmland	19594	24514	153703	44145	17546	273080
Örebro	22915	26315	160724	42322	15863	283113
Västmanland	20024	23977	145198	39208	14495	256224
Dalarna	20433	25393	153975	45474	17306	276555
Gävleborg	20230	25107	155003	45686	16747	276637
Västernorrland	18036	22063	134437	40246	14839	241981
Jämtland	9589	11571	70977	19966	7969	126201
Västerbotten	20420	23949	151487	37454	14073	260217
Norrbotten	17282	22223	141817	40746	14096	248637
Sweden	**797046**	**885157**	**5551124**	**1330135**	**498148**	**9555893**

TABLE 7.2. Population in Sweden 2000-2013. Numbers represent the population by December 31st 2013.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Population	8861426	8882792	8909128	8940788	8975670	9011392	9047752	9113257	9182927	9256347	9340682	9415570	9482855	9555893

TABLE 7.3. Number of admissions and patient-days in somatic medical care in Sweden, 2009-2012.

Year	Admissions	Patient-days
2009	1 463 273	7 136 591
2010	1 473 835	6 958 834
2011	1 496 324	6 979 857
2012	1 514 608	6 859 956

TABLE 7.4. Number of admissions and patient-days in somatic medical care 2012. Data represent production by acute care hospitals in the counties.

County	Admissions	Patient-days
Blekinge	23 307	114 249
Dalarna	45 964	201 051
Gotland	9 788	42 864
Gävleborg	42 770	188 551
Halland	44 641	189 788
Jämtland	18 820	87 580
Jönköping	56 119	242 513
Kalmar	42 589	162 293
Kronoberg	26 843	128 507
Norrbotten	40 019	186 484
Skåne	201 139	910 124
Stockholm	279 074	1 112 011
Södermanland	38 618	179 614
Uppsala	61 196	312 946
Värmland	41 535	189 486
Västerbotten	50 539	248 443
Västernorrland	39 035	172 292
Västmanland	38 934	182 814
Västra Götaland	249 534	1 149 633
Örebro	47 269	219 315
Östergötland	68 022	278 284
Sweden	**1 465 755**	**6 498 842**

TABLE 7.5. Denominator data from the microbiological laboratories 2013.

	Number of analyses 2013									Number of positive samples 2013	Number of positive cultures 2013				
Laboratory	**Blood (pair of bottles)**	**Cerebro-spinal fluid (CFS)**	**Nasopharynx**	**Throat**	**General culture**	**Screen MRB**	**Urine**	**Faeces SSYC**	**Faeces Clostridium difficile (toxin)**	**Blood (pair of bottles)**	**Staphylococcus aureus**	**Streptococcus pneumoniae**	**Streptococcus pyo-genes**	**Escherichia coli**	**Clostridium difficile (toxinpositive)**
Aleris Medilab	865	0	10470	3498	10290	24637	42772	7360	1405	113	4830	997	1004	10162	302
Borås	19161	464	4718	2055	6686	2470	24229	5294	1913	2153	4615	465	640	6993	165
Eskilstuna (Unilabs)	13416	207	5894	3798	7547	5019	28976	4698	1798	1997	4758	776	627	8304	353
Falun **	15921	416	3808	1477	11242	3688	27677	3419	1731	1705	4704	579	541	7498	294
Gävle	12927	242	2584	993	12680	10282	23267	3148	1913	1665	5154	430	468	8114	416
Göteborg	40380	1482	2230	3037	20000	44253	67611	11381	4445	4997	10785	666	1099	16368	773
Halmstad	13451	157	2245	2210	7750	9866	25604	6009	2034	1878	4376	532	753	8212	366
Jönköping	21059	207	5693	3012	16578	25659	36925	7176	2802	2660	7230	616	631	11470	522
Kalmar	11743	124	3798	1711	7291	3987	20635	2918	1518	1671	4657	655	623	8607	259
Karlskrona/ Växjö	19512	188	6156	2259	11029	6062	34086	5939	3439	2277	4873	700	853	9926	608
Karlstad	18027	168	3325	2565	12532	9337	35618	4492	1931	3609*	6021	460	777	9792	333
Karolinska Stockholm	83222	2774	30210	9032	77949	246588	149480	20765	11217	10254	28765	3007	3387	39339	1317
Linköping	22265	1029	7097	3392	19927	9636	44787	6389	3866	2150	7813	749	829	12462	668
Lund/Malmö	70198	1712	16884	12416	34288	49059	161580	25860	10900	8902	22837	2484	3747	45341	1229
Skövde (Unilabs)	15810	25	3595	2547	13800	17203	51789	8316	2520	NA	6401	480	868	12590	322
S:t Göran (Unilabs)	11697	103	6875	2627	11665	47933	45869	7924	1592	1530	6143	784	994	11235	392
Sunderby Luleå	12075	113	1973	2603	7577	5033	26991	3446	1357	NA	NA	NA	NA	NA	NA
Sundsvall	12621	155	1950	1268	6750	5754	26483	3812	1878	1839	3672	313	394	7872	230
NÄL Trollhättan	19939	329	1777	1574	8958	17144	32302	3796	1698	2513	5042	325	552	9221	170
Umeå	14784	502	3401	1813	13213	4828	30406	4114	1768	1460	4654	551	635	8605	558
Uppsala	20602	836	6000	2411	14956	6388	34527	5428	3285	2328	5428	671	832	8864	785
Visby	4069	25	2166	453	2761	NP	6918	954	528	55	1424	322	211	2138	30
Västerås	13213	240	2345	1751	9712	3753	27740	4163	2017	1980	3942	390	580	8906	337
Örebro	16687	236	9768	1652	14324	5255	32067	5266	2683	1586	5913	1233	755	7892	407
Östersund	7600	90	3216	1288	6449	4329	17211	2758	1050	800	3657	506	402	5988	204
Total	**511244**	**11821**	**148178**	**71442**	**365954**	**568163**	**1055550**	**164825**	**71288**	**60122**	**167694**	**18582**	**22000**	**287013**	**10576**

*not pair; ** data from 2012; NP, not performed; NA, data not available

Animals

Agricultural statistics are provided by Statistics Sweden in collaboration with the Board of Agriculture. The statistics are published annually as a Yearbook of Agricultural Statistics and continuously as Statistical Messages (SM) available on the websites for Statistics Sweden (www.scb.se) or the Board of Agriculture (www.jordbruksverket.se). Annual figures on number of animals and holdings are given in Table 7.6 & 7.7 and on numbers and volumes of animals slaughtered in Table 7.8. & 7.9. In brief, the number of dairy cows, pigs and laying hens has decreased notably over the last three decades while during the same time, herd size has increased. In the same period, the number of beef cows, sheep and chickens reared for slaughter has increased.

Data on the number of dogs and cats are also available from the Board of Agriculture. In a study 2012 the numbers of dogs and cats in Sweden were estimated to 784 000 and 1 159 000, respectively. The number of households with dogs was estimated to 572 000 and the number of households with cats to 745 000. This represents an increase by 8% in the number of dogs and a decrease by 8% in the number of cats since the most recent study carried out in 2006.

TABLE 7.6. Number of livestock and horses (in thousands) 1980-2013 (Yearbook of Agricultural Statistics for selected years and Statistical Message JO 20 SM 1401 & JO 24 SM 1101).

Animal Species	1980[a]	1985[a]	1990	1995	2000	2005	2010	2011	2012	2013
Cattle										
Dairy cows	656	646	576	482	428	393	348	346	348	344
Beef cows	71	59	75	157	167	177	197	196	193	189
Other cattle >1 year	614	570	544	596	589	527	513	495	479	497
Calves <1 year	595	563	524	542	500	509	479	475	481	467
Total, cattle	1 935	1 837	1 718	1 777	1 684	1 605	1 537	1 512	1 500	1 497
Sheep										
Ewes and rams	161	173	162	195	198	222	273	297	297	286
Lambs	231	252	244	266	234	249	292	326	314	291
Total, sheep	392	425	406	462	432	471	565	623	611	577
Pigs										
Boars & sows	290	260	230	245	206	188	156	153	142	150
Fattening pigs >20 kg[b]	1 254	1 127	1 025	1 300	1 146	1 085	937	901	851	847
Piglets <20kg[c]	1 170	1 113	1 009	769	566	539	427	429	370	401
Total, pigs	2 714	2 500	2 264	2 313	1 918	1 811	1 520	1 483	1 363	1 398
Laying hens										
Hens	5 937	6 548	6 392	6 100	5 670	5 065	6 061	6 376	6 735	6 874
Chickens reared for laying	2 636	2 159	2 176	1 812	1 654	1 697	1 647	1 828	1 551	1 708
Total, hens	8 573	8 708	8 568	7 912	7 324	6 762	7 707	8 204	8 286	8 582
Turkeys										
Total, turkeys						122	130			80
Horses										
Total, horses						283[d]	363			

[a] For 1980 and 1985 only cattle and sheep at premises with more than 2 ha counted; [b] Before 1995, the figure denotes pigs above 3 months of age; [c] Before 1995, the figure denotes pigs below 3 months of age; [d] Data from 2004.

TABLE 7.7. Number of holdings with animals of different types, 1980-2013 (Yearbook of Agricultural Statistics for selected years and Statistical Message JO 20 SM 1401.

Animal Species	1980	1985	1990	1995	2000	2005	2010	2011	2012	2013
Cattle										
Dairy cows	44 143	35 063	25 921	17 743	12 676	8 548	5 619	5 260	4 968	4 668
Beef cows	12 436	10 310	10 883	17 069	13 861	12 821	12 190	11 809	11 375	11 092
Other cattle >1 year	63 179	52 652	42 696	39 160	30 457	24 808	20 295	19 107	18 182	17 824
Calves <1 year	62 314	52 001	41 986	36 542	27 733	22 888	18 494	17 721	17 001	16 306
Total holdings with cattle	70 503	58 872	47 292	41 990	32 063	26 179	21 586	20 503	19 561	18 962
Sheep	10 238	10 595	9 749	10 037	8 089	7 653	8 657	9 449	9 263	4 469
Pigs	26 122	19 937	14 301	10 753	4 809	2 794	1 695	1 515	1 318	1 281
Laying hens	23 603	17 531	12 900	9 593	5 678	4 916	3 703	3 827	3 876	4 149
Chickens reared for laying	5 093	2 714	1 875	1 405	715	634	487	733	673	629
Broilers						234	181	202	217	242
Turkeys						383	102			126

TABLE 7.8. Number of animals slaughtered (in thousands) at slaughterhouses, 1980-2013. (Yearbook of Agricultural Statistics for selected years and Statistical Message JO 48 SM 1402).

Animal Species	1980	1985	1990	1995	2000	2005	2010	2011	2012	2013
Cattle										
Cattle >1 year	574	584	523	502	490	433	425	429	392	391
Calves < 1 year	130	152	70	30	39	33	27	27	29	27
Total, cattle	704	736	593	532	529	466	453	456	421	418
Sheep	302	328	280	189	202	206	255	262	260	281
Pigs	4 153	4 283	3 653	3 743	3 251	3 160	2 936	2 845	2 592	2 556
Broilers	40 466[a]	36 410[a]	38 577[a]	61 313	68 617	73 458	78 507	78 182	76 840	83 265
Turkeys							495	574	466	452

[a] Data supplied by the National Food Administration.

TABLE 7.9. Quantity of livestock slaughtered (in 1000 tonnes) at slaughterhouses, 1990-2013 (Yearbook of Agricultural Statistics for selected years and Statistical Message JO 48 SM 1402).

Animal Species	1990	1995	2000	2005	2010	2011	2012	2013
Cattle								
Cattle >1 year	139.5	140.1	145.4	131.4	133.5	133.5	121.0	121.9
Calves < 1 year	6.8	3.2	4.4	4.5	4.3	4.4	4.5	4.2
Total, cattle	146.3	143.3	149.8	135.9	137.8	138.2	125.5	126.1
Sheep	5.0	3.5	3.9	4.1	5.0	5.1	5.0	3.9
Pigs	293.1	308.8	277.0	275.1	263.5	256.1	233.7	234.6
Broilers	44.0[a]	73.6[a]	89.9	96.2	112.0	111.5	109.7	116.8
Turkeys					3.2	3.7	3.0	2.9

[a] Data supplied by the National Food Administration.

Materials and methods, use of antimicrobials

Legal framework and distribution of medicines

Marketing of drugs in Sweden is regulated by the Medicinal products act, which applies both to human and veterinary medicinal products. According to this Act, a medicinal product may not be sold until it has been granted marketing authorisation by the Medical Products Agency (MPA). In case there are no authorised medicinal products for a certain condition, the MPA can permit special licence prescription for a medical product for a specified pharmacy, prescriber or clinic.

Medicinal products have to be dispensed through pharmacies, which are supplied by drug wholesalers or manufacturers. In outpatient care, antimicrobial drugs (including medicated feed in veterinary use) may only be sold on prescriptions, ApoDos or requisitions. Prescribers (veterinarians or doctors) are not permitted to own a pharmacy or to otherwise sell medicinal products for profit. Veterinarians may deliver products to the animal care-taker in relation to examination of a case, however, for self cost (no profit). In hospital care, both for human and animal, antimicrobial drugs are bought on requisitions.

All pharmacies in Sweden are required to provide statistics on sales of all products on a daily basis to governmental agency called the Swedish eHealth Agency. This agency maintains a national database with sale statistics for all drugs and provides statistics to the competent national and regional authorities and to others on a commercial basis.

Feed mills may only mix antimicrobials in feed if they are controlled and authorised by the Swedish Board of Agriculture (SBA). The feed mills normally acquire the antimicrobial products from a pharmacy. All quantities of antimicrobial products used by feed mills are reported yearly to the Swedish board of agriculture (SBA) as part of the feed control. Mixing of antimicrobials in feed may also take place on farms; provided that the SBA has inspected and authorised the establishment for the purpose. In such cases, the premix is sold by a pharmacy following prescriptions from a veterinarian.

The ATC classification system and defined daily doses (DDD)

Since 1988, the Anatomical Therapeutic Chemical (ATC) and ATCvet classification system recommended by the WHO is used in Sweden for national drug statistics. For drugs sold for use in humans, 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 Swedish eHealth Agency are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway. The DDDs used in this report are shown in Table 7.10. The sales of drugs are presented as number of DDDs per 1000 inhabitants and day (DDD/1000 and day), which give an estimate of the proportion of the population daily exposed to a particular drug. This figure is a rough estimate and should be interpreted with caution.

Antimicrobial consumption in humans

Swedish national statistics on drug utilization

Since 1975, the National Corporation of Swedish Pharmacies regularly produces sales statistics on drugs, for the country as a whole and for individual counties. The sales are registered as number of DDDs, cash value and number of packages. Out-patient care data includes information on the sales of drugs dispensed on prescription by all Swedish pharmacies by the prescription survey, running since 1974. The statistical material was until 1995 built of samples of dispensed prescriptions. From 1996 all prescriptions dispensed by pharmacies are included. From 1999, ApoDos (individually packed doses of drugs often dispensed to elderly) is also included in the survey. Recorded data are trade name, quantity, patient fee, total cost, sex and year of birth of the patient. Data can be expressed as DDD/1000 and day or number of prescriptions/1000 inhabitants.

Hospital care data includes drugs delivered by all hospital pharmacies to the hospital departments (se bellow chapter Completeness of data). The system also produces sales statistics for each hospital department and on national and county sales to hospitals. The sales are expressed as cash value, number of packages and number of defined daily doses.

Following the re-regulation of the pharmacy market in Sweden in July 2009, the responsibility for collection of medicines statistics was transferred to the core infrastructure supplier for all pharmacies, Apotekens Service. In January 2014, the activity in the state-owned company Apotekens Service were transferred to the Swedish eHealth Agency.

The Swedish eHealth Agency (eHälsomyndigheten) aims to contribute to improved health care, care and the nation's health by pursuing development of a national e-health infrastructure. They are responsible for Sweden's national drug statistics.

Completeness of data

Concerns have been raised that after the reregulation, the statistics on sales of medical products to hospitals in Sweden is less complete than before. In Sweden, pharmacies are required by law to report sale statistics to the Swedish eHealth Authority. However, after the re-regulation of the pharmacy market, counties can choose to manage drug supplies to hospital by them self. If so, the counties are not required to

Definitions of DDD 2013

TABLE 7.10. DDD for all substances sold in Sweden in 2013. Substances are sorted according to ATC-code.

	DDD (g)		DDD (g)
J01AA02 – doxycycline	0.1	J01EA01 - trimethoprim	0.4
J01AA04 – lymecycline	0.6	J01EC02 - sulfadiazin	0.6
J01AA06 - oxitetracycline	1	J01EE01 - sulfamethoxazol and trimethoprim	0.4
J01AA07 - tetracycline	1	J01FA - erythromycin	1
J01AA12 - tigecycline	0.1	J01FA - erythromycin erythylsuccinat tablets	2
J01BA01 - chloramphenicol	3	J01FA06 - roxithromycin	0.3
J01CA01 - ampicillin	2	J01FA09 - clarithromycin - oral	0.5
J01CA04 - amoxicillin	1	J01FA10 - azithromycin - parenteral	0.5
J01CA08 - pivmecillinam	0.6	J01FA10 - azithromycin - oral	0.3
J01CE01 - benzylpenicillin	3.6	J01FA15 - telithromycin	0.8
J01CE02 - fenoximethylpenicillin	2	J01FF01 - clindamycin - parenteral	1.8
J01CF02 - cloxacillin	2	J01FF01 - clindamycin - oral	1.2
J01CF05 - flucloxacillin	2	J01GB01 - tobramycin - parenteral	0.24
J01CR02 - amoxicillin and enzyme inhibitor-oral	1	J01GB01 - tobramycin - oral inhalation solution	0.3
J01CR05 - piperacillin and enzyme inhibitor	14	J01GB01 - tobramycin - oral inhalation powder	0.112
J01DB01 - cefalexin	2	J01GB03 - gentamicin	0.24
J01DB03 - cefalotin	4	J01GB06 - amikacin	1
J01DB05 - cefadroxil	2	J01GB07 - netilmicin	0.35
J01DC02 - cefuroxime- parenteral	3	J01MA01 - ofloxacin	0.4
J01DC02 - cefuroxime - oral	0.5	J01MA02 - ciprofloxacin - parenteral	0.5
J01DC08 - loracarbef	0.6	J01MA02 - ciprofloxacin - oral	1
J01DD01 - cefotaxime	4	J01MA06 - norfloxacin	0.8
J01DD02 - ceftazidime	4	J01MA12 - levofloxacin	0.5
J01DD04 - ceftriaxon	2	J01MA14 - moxifloxacin	0.4
J01DD08 - cefixime	0.4	J01XA01 - vancomycin	2
J01DD14 - ceftibuten	0.4	J01XA02 - teicoplanin	0.4
J01DE01 - cefepime	2	J01XB01 - colistin	3 MU
J01DF01 - aztreonam - parenteral	4	J01XC01 - fusidic acid	1.5
J01DF01 - aztreonam - inhalation	0.225	J01XD01 - metronidazole	1.5
J01DH02 - meropenem	2	J01XE01 - nitrofurantoin	0.2
J01DH03 - ertapenem	1	J01XX04 - spectinomycin	3
J01DH51 - imipenem and enzyme inhibitor	2		

report data to the national database. Since October 2013, one county has chosen to organize their own drug supplies organization for hospitals.

Therefore, no national database with complete sale statistic is available at this time. Efforts have been made to complement the data from the Swedish eHealth Agency with data from counties.

Data sources and inclusion criteria

Data on sales of antimicrobials in outpatient care is obtained from the Swedish eHealth Agency. For the overall statistics, the data include all antimicrobial products marketed in Sweden in the ATC classes J01 and J02. The data includes all sales of these products, even if the antimicrobial (J01 and J02) is prescribed by a veterinarian. Measures used are defined daily doses per 1000 inhabitants and day (DDD/1000 and day) and prescriptions per 1000 inhabitants. Every purchase of a medicine prescribed in outpatient care is also recorded in the Prescribed Drug Register, held by the Swedish National Board of Health and Welfare. This register provides the opportunity to link each prescription to an individual, which makes it possible to investigate the actual number of individuals or the fraction of the population treated with a specific medicine.

Antimicrobial use in hospital care is measured as DDD/1000 inhabitants and day and DDD/100 patient-days

or admissions. The number of DDDs is obtained from the Swedish eHealth Agency and from local medicines statistics systems in the counties. The National Board of Health and Welfare has provided data on patient-days and admissions to hospitals. Admission is calculated as number of discharges (one patient can be discharged and admitted multiple times if transferred between wards during one hospital stay). Patient-day is calculated as each additional day during one hospital stay.

When this report is compiled, data on patient-days and admissions in 2013 is not available. Therefore, data from 2012 is used. The number of patient-days and admissions represent production of somatic medical care by each county (to be distinguished from consumption of the county's inhabitants). This gives a more accurate comparison of antibiotic use in hospitals, since the amount of medicines used is related to the quantity of medical care produced.

The Swedish Prescribed Drug Register

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

Number of admissions and patient-days

Each of the 21 county councils in Sweden deliver once a year data to the National Patient Register kept by The National Board on Health and Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Since data for 2013 is not available until August 2014, denominator data from 2012 are used in some figures in this report. The number of admissions and patient-days in Swedish somatic medical care (produced by acute care hospitals) 2012 is shown Demographic and denominator data. Table 7.3. The National Board of Health and Welfare keeps a searchable database at the web, http://www.socialstyrelsen.se/statistik.

Antimicrobial consumption in animals

Data sources, inclusion criteria and analysis

Raw data on sales is obtained from the Swedish eHealth Agency and represent the sales of antimicrobial products sold by pharmacies. When products are dispensed for animals, the animal species as given on the prescription is recorded and reported to the Swedish eHealth Agency jointly with the sales, unless the product is sold for use in veterinary practice (on requisition). For the overall statistics, the data include all antimicrobial products marketed in Sweden and sold for use in terrestrial animals in the ATCvet classes QA07, QG04, QJ01 and QJ51. Medicinal products authorised for human use but prescribed for use in animals is not included in the overall statistics. However, to follow prescriptions for dogs, information on number of packages sold per product-presentation belonging to QA07, QJ01 and drugs authorised for use in humans and prescribed for dogs belonging to J01 were retrieved. That data-set closely corresponds to out-patient use.

Data are retrieved as number of packages sold per product presentation and per animal species, if recorded. Calculation to kg active substance is done based on product information obtained from the national product register of the MPA.

In rare cases, premixes mixed in medicated feed may be delivered from feed mills without the sales being recorded by a pharmacy. Examination of the reports by all feed mills to the SBA shows that this happened only once during 2005-2009 (a total quantity of 40 kg active substance). The ionophoric antibiotics are presently regulated as feed additives and not sold through pharmacies. However, the SBA collects figures on sales of ionophores from the feed mills as a part of the feed control system. As the source differs, data on ionophores are given only in the table on sales of products for mixing in feed or water in Table 1.9.

Completeness of data

Concerns have been raised that after the reregulation, the statistics on sales of veterinary medical products with a general marketing authorisation in Sweden is less complete than before 2010, in particular for drugs authorised for animals. The competent authority will investigate these claims. SVA has attempted to estimate the magnitude of the potential problem. Overall, by comparing sales of injectable products to and from pharmacies, in 2013 there is a lack of completeness of about 5-10% in the sales from parmacies. For further information see Use of antimicrobials for animals, completeness of data.

Products sold with special licence

Previously, most antimicrobial products sold with special licence (products prescribed and sold on exemption from general Swedish market authorization) were also included. However, in 2011 it was noticed that the information on sales of products with special licence was less complete than in previous years. The information in the database of the Swedish eHealth Agency on sales of such products is still incomplete. Efforts have been made to identify companies who might have statistics on sales of products sold with special licence to the Swedish market. Products formulated for administration via feed or water were prioritized, as were those with fluoroquinolones and other products where the number of granted licences was above 30. No effort was made to get additional data on sales of products for intramammary use, as the amounts sold have historically been very low. Whenever the information on number of packages sold per product-packtype from the Swedish eHealth Agency was lower than that obtained from pharmaceutical companies, the figure was adjusted. This means that for some products, the figures may represent a slight overestimate of sales from pharmacies as they may include products kept in stock.

Materials and methods, resistance in bacteria from humans

Antibiotic Susceptibility testing

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

The disk diffusion method has been successfully standardized by the Swedish clinical microbiology laboratories in collaboration with the former SRGA-M, which since 2011 is replaced by NordicAST, a Nordic AST Committee with representatives from Denmark, Norway and Sweden. Until 2009 all laboratories used the methodology based on ISA medium and a semi-confluent bacterial inoculum as recommended by SRGA-M. From 2011 all laboratories have adopted the new European method as described by EUCAST, based on Mueller Hinton agar and an almost confluent inoculum (equivalent to a 0.5 McFarland turbidity standard). The disk diffusion method is still the most commonly used routine method for susceptibility testing. It can also be used as a screening method which in some cases needs to be followed up by methods for gene detection (e.g. MRSA, VRE) and in other instances by MIC-determination (e.g. beta-lactam resistance in pneumococci, chromosomally mediated beta-lactam resistance in *Haemophilus influenzae*), and still in others by methods for enzyme detection (e.g. beta-lactamase detection in *Haemophilus influenzae* and *Neisseria gonorrhoeae*).

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

National surveillance of antibiotic resistance

Surveillance regulated in the Communicable Disease Act

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

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

Infections (or colonisation) with different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with bensylpenicillin MIC ≥ 0.5 mg/L (PNSP) have been notifiable since 1996 (MIC > 1 mg/L from 2012). 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. The definition of an ESBL was extended in 2009 to include not only ESBLs inhibited by clavulanic acid (now referred to as $ESBL_A$) but also plasmid-mediated AmpC enzymes ($ESBL_M$) and carbapenemase enzymes ($ESBL_{CARBA}$).

All notifications are entered into the national computerized surveillance system, SmiNet2. At the Public Health Agency of Sweden, the clinical and laboratory notification for each case are merged and checked for errors. If data are missing, contact persons in the counties are asked to supplement the information. As an important complement to the notifications, the MRSA, VRE and PNSP isolates are sent for epidemiological typing. For MRSA *spa* typing is the primary typing method, for VRE it is pulsed-field gel electrophoresis (PFGE), and for PNSP serotyping. Depending on needs also other molecular biology methods are used, e.g. MLST.

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

The feedback of notification data is done monthly on the webpage (http://www.folkhalsomyndigheten.se) and yearly in this and other reports. Data on drug-resistant TB is also annually published in "the Swedish Tuberculosis Index".

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

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

In 1994 a model for the concomitant surveillance of antimicrobial resistance and quality assurance of antimicrobial susceptibility testing was devised. In Sweden there are at present 28 clinical microbiology laboratories, each covering a county (or part of county) of Sweden. The demographics of the laboratories, their geographic areas and their corresponding populations are well characterized. The antimicrobial susceptibility testing methods of the laboratories have been standardized through the combined work of the former SRGA-M (since 2011 replaced by NordicAST) and the microbiological laboratories.

Each year the laboratories are asked to collect quantitative data (zone diameters) for defined antibiotics in 100-200 consecutive clinical isolates of a defined set of bacterial species. Since 1994, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* have been part of this yearly program. Since 2001 *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* have been part of these surveys. The number of antibiotics tested for each pathogen has varied between 4 and 6.

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

EARS-Net

The European network of national surveillance systems of antimicrobial resistance (EARSS) performed on-going surveillance of invasive infections of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis/faecium*, and monitors variations in antimicrobial resistance over time and place. From 2005 invasive isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are also part of the scheme.

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

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

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

Surveillance of invasive isolates additional to EARS-Net data

Data on invasive isolates on all positive blood cultures were obtained from ten laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is at present 5 millions, thus representing more than 55% of the Swedish population. From these laboratories data for the pathogens specified by the EARS-net network are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In the SWEDRES reports from 2007 to2011 data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* are presented.

Sentinel surveillance

A national surveillance programme for *Clostridium difficile* was initiated by SMI in 2009. The programme included both a voluntary laboratory reporting system of all new cases of *C. difficile* infection (CDI) through SmiNet2 and a determination of resistance and epidemiological typing of isolates from the clinical microbiology laboratories. All *C. difficile* strains isolated during weeks number 11 and 39 were sent to SMI for typing by PCR ribotyping and antibiotic susceptibility testing.

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

Materials and methods, resistance in bacteria from animals

Sampling strategy

Antimicrobial resistance as notifiable diseases

ESBL

$ESBL_A$ and $ESBL_M$-producing *Escherichia coli* were isolated from the same samples as the indicator bacteria, *i.e.* from colon content from calves and caecal content from turkeys, see below. Furthermore, caecal content from 100 broilers sampled at slaughter during May and September and 59 samples of fresh broiler meat from retail were also investigated. Clinical isolates from dogs, cats, horses and cattle were submitted to the Dept. of Animal Health and Antimicrobial Strategies, SVA as bacterial strains.

MRSA and MRSP

Findings of MRSA and MRSP in animals are notifiable in Sweden and hitherto the majority of isolates from notified incidents has been confirmed using molecular methods at SVA.

Monitoring of MRSA in dairy cattle was performed by screening isolates of beta-lactamase producing *Staphylococcus aureus* from routine submissions of milk samples sent to SVA. From each submission where beta-lactamase producing *S. aureus* was found, one isolate, selected by convenience, was tested. In addition, from July to December 2013 monitoring of isolates of *S. aureus* without beta-lactamase production was performed. From each submission where *S. aureus* without beta-lactamase production was found, one isolate, selected by convenience, was tested.

Zoonotic pathogens

Salmonella

Salmonellosis in animals is a notifiable disease in Sweden and isolates from each notified incident must be confirmed at SVA. Data presented in SVARM are from susceptibility testing of these isolates. The summary for each year includes one isolate of each serovar from each warm-blooded animal species in notified incidents. An exception is isolates from cats and wild birds from which a subset of isolates are selected by convenience. In addition, isolates from incidents previously notified and still under restrictions are included in the yearly statistics. Also included are isolates obtained in the salmonella surveillance programme from samples collected at slaughter (carcass swabs, neck skins and lymph nodes).

Campylobacter

Campylobacter spp. were isolated from colon content from healthy calves 6-11 months old sampled at slaughter. Seven abattoirs participated in collection of samples under the supervision of the National Food Agency (SLV). The number of samples from each abattoir was roughly proportional to the annual slaughter volume of the abattoir. Samples were collected during April-June and September-October. From 109 of the samples *Campylobacter jejuni* was isolated and subsequently susceptibility tested.

Campylobacter spp. were isolated from fresh broiler meat collected by convenience at retail 2013 or from neck skins collected by convenience at slaughter, 2011-2013. From 111 of these samples *C. jejuni* was isolated and subsequently susceptibility tested.

Clinical isolates from animals

Clinical isolates included are from routine bacteriological examinations of clinical submissions or post-mortem examinations. Isolates of *Actinobacillus pleuropneumoniae* from pigs and part of the isolates of *Pasteurella* spp. from calves are, however, isolated from samples collected in surveys initiated within the SVARMpat programme.

In pigs, isolates of *E. coli* are from the gastro-intestinal tract and isolates of *Brachyspira* spp. from faecal samples. Isolates of *Pasteurella* spp. from pigs are isolated from nasal swabs collected within a control programme for atrophic rhinitis in nucleus and multiplying herds or from tissue samples from lungs taken post mortem. Isolates of *A. pleuropneumoniae* in pigs emanate from tissue samples from lungs sampled post mortem.

In cattle, isolates of *E. coli* are from samples from the gastro-intestinal tract, from uterine samples or from milk samples. Isolates of *Pasteurella* spp. are from the respiratory tract.

In horses, isolates of *E. coli* are from the genital tract of mares, *Streptococcus zooepidemicus* from the respiratory tract and *S. aureus* from skin samples.

In dogs, isolates of *E. coli* are from urine samples, *Staphylococcus pseudintermedius* from skin samples and *Pseudomonas aeruginosa* from the external ear. In cats, isolates of *E. coli* are from urine samples.

In farmed fish, isolates of *Aeromonas salmonicida* subsp. *achromogenes*, *Flavobacterium columnare* and *Flavobacterium psychrophilum* are from post mortem examinations.

Indicator bacteria

Cattle

Indicator bacteria, *E. coli* and *Enterococcus* spp., were isolated from colon content from healthy calves about 6-11 months old sampled at slaughter. Seven abattoirs participated in collection of 200 samples under the supervision of National Food Agency. The number of samples from each abattoir was roughly proportional to the annual slaughter volume of the abattoir. Samples were collected during April-June and September-October.

Turkeys

Indicator *E. coli* was isolated from caecal content of healthy turkeys sampled at slaughter. Sampling was performed at two abattoirs in Sweden, from June to November. Each sample is from a unique flock but not always from a unique production site.

Isolation and identification of bacteria

Antimicrobial resistance as notifiable diseases

ESBL

$ESBL_A$ and $ESBL_M$-producing *E. coli* were isolated by culture on MacConkey agar with cefotaxime (1 mg/L) after incubation overnight at 37°C. For additional information, see section about indicator bacteria below, Broiler meat.

MRSA

In the screening for MRSA among isolates of beta-lactamase producing *S. aureus* from dairy cows, isolates were susceptibility tested using microdilution (see below). Isolates with MICs of oxacillin >1 mg/L and/or cefoxitin >4 mg/L were tested for presence of *mecA* and *mecC* with PCR (see below).

Zoonotic pathogens

Salmonella

Salmonella was isolated and identified at the Dept. of Bacteriology, SVA or at regional laboratories in accordance with standard procedures. All samples within official control programmes are cultured according to the procedures detailed by the MSRV (ISO-EN 6579:2002/ Amd 1:2007). Confirmatory identification and serotyping was performed according to the procedures of Kaufmann and White.

Isolates of *Salmonella* Enteritidis were phage-typed by the Swedish Institute for Infectious Disease Control (SMI), Stockholm using the Colindale scheme. As from 2013 other serovars are not phagetyped.

Campylobacter

Thermophilic *Campylobacter* spp. from calves were isolated and identified at SVA. Briefly, samples were enriched in Preston broth at 42°C for 24 h and subsequently cultured on Preston selective agar at 42°C for 48 h. Identification was based on colony morphology, microscopic appearance including motility and the production of oxidase and catalase. Additionally, all isolates of *C. jejuni* were identified by MALDI-TOF MS. Mass spectra were compared against the MALDI Biotyper database using the MALDI Biotyper 3.0 Realtime Classification (RTC) software (Bruker Daltonik GmbH, Bremen, Germany).

Thermophilic *Campylobacter* spp. from broiler meat were isolated and identified at the Dept. of Bacteriology, SVA according to ISO 10272-1:2006. A sample of 10 g of broiler meat was enriched in 90 ml Bolton broth for 48 h in 42°C, then 20 µl were cultured on CCDA (Charcoal Cephoperazone Desoxycholate Agar) plates and incubated 48h in 42°C. Identification was based on colony morphology, microscopic appearance including motility, hippurate hydrolysis and production of oxidase and catalase. With these tests, isolates of hippurate-positive *C. jejuni* were identified.

Clinical isolates from animals

Most clinical isolates were isolated and identified with accredited methodology, following standard procedures at SVA. Part of the isolates of *Pasteurella* spp. from pigs and cattle and part of the isolates of *E. coli* from cattle were isolated and identified following standard procedures at a regional laboratory.

Indicator bacteria

Escherichia coli

Approximately 0.5 g of colon content from calves was diluted in 4.5 mL saline. After thorough mixing, 0.1 mL of this suspension was spread on MacConkey agar and MacConkey agar with cefotaxime (1 mg/L) and incubated overnight at 37°C.

For selective culture for *E. coli* resistant to ESCs in broiler meat, twenty-five g of broiler meat was homogenized thoroughly in 2 min with 225 ml buffered pepton water (BPW). From the homogenized BPW, 100 ml with addition of cefotaxime (1 mg/L) was incubated at 37°C overnight. From the pre-enrichment 100 µL was spread on MacConkey agar with cefotaxime (1 mg/L) and incubated overnight at 37°C.

One lactose positive colony with morphology typical for *E. coli* was sub-cultured onto horse-blood agar (5% v/v), after which the isolate was tested for production of tryptophanase (indole). Only lactose and indole positive isolates with typical morphology were selected for susceptibility tests. Colonies growing on MacConkey agar with cefotaxime were sub-cultured on horse-blood agar (5% v/v) and further tested for ESBL detection.

Enterococci

Colon content from calves was diluted as described for *E. coli* and 0.1 mL was spread on Slanetz-Bartley (SlaBa) agar and incubated at 37°C for 48 h.

Four colonies, randomly chosen, were sub-cultured on bile-esculin agar and blood agar (37°C, 24 h). Colonies with morphology consistent with enterococci, and with a positive reaction on bile-esculin agar were identified to species level by MALDI-TOF MS. Mass spectra were compared against the MALDI Biotyper database using the MALDI Biotyper 3.0 Realtime Classification (RTC) software (Bruker Daltonik GmbH, Bremen, Germany). If available, one isolate of *E. faecium* and one isolate of *E. faecalis* from each sample were tested for antimicrobial susceptibility.

Susceptibility testing

Microdilution

At SVA, bacteria from terrestrial animals are tested for antimicrobial susceptibility with accredited methodology using dilution methods in cation adjusted Mueller-Hinton broth (CAMHB) (Difco). Tests are performed following the standards for microdilution of the Clinical and Laboratory Standards Institute (CLSI, 2013a). The microdilution panels used, VetMIC, are produced at the Dept. of Vaccines and Laboratory products, SVA. Different panels are used depending on the bacterial species tested and the purpose of the investigation (monitoring or clinical diagnostics). Minimum inhibitory concentration (MIC) is recorded as the lowest concentration of an antimicrobial that inhibits bacterial growth.

Some adaptations from the CLSI standard are employed. For *Pasteurella* spp. three different protocols are used at SVA. Either by dilution in CAMHB supplemented with 5-10% horse serum followed by incubation in aerobic atmosphere, 37°C for 16-18 hours, or by dilution in Haemophilus test medium (HTM) followed by incubation in CO_2, 37°C for 16-18 hours. Also dilution in CAMHB supplemented with 5-10% horse serum and incubation in CO_2, 37°C for 16-18 hours was used. For testing of *A. pleuropneumoniae* dilution in HTM broth is used followed by incubation in CO_2 at 37°C for 16-18 hours. Also, *S. zooepidemicus* is tested using CAMHB supplemented with 5-10% horse serum followed by incubation at 37°C for 16-18 hours.

Susceptibility of *Campylobacter* spp. is tested according to the CLSI standard M45-A2 for fastidious bacteria (CLSI, 2010).

Susceptibility of *Brachyspira hyodysenteriae* and *B. pilosicoli*, is tested by a broth dilution method described by Karlsson et al. (2003). The antimicrobials are dried in serial two-fold dilutions in tissue culture trays with 48 wells per plate. The wells were filled with 0.5 mL of a suspension of bacteria in brain heart infusion broth (BHI) with 10% foetal calf serum ($1x10^6$-$5x10^6$ CFU/ml). The trays were incubated in an anaerobic atmosphere at 37°C for four days on a shaker.

Bacteria from fish are tested for antimicrobial susceptibility by the same methodology as described above but adapted for aquatic bacteria according to CLSI (2006).

Phenotypic confirmatory test for production of extended spectrum beta-lactamases (ESBLs) in *E. coli* was performed by the double disc diffusion test according to CLSI (CLSI, 2013b).

Genotyping

Suspected isolates of MRSA were confirmed by detection of the *nuc*, *mecA* and *mecC* genes by PCR as described by Stegger et al. (2012) or real-time PCR as described by Pichon et al. (2012). *Spa*-typing, a single locus sequence typing method using the polymorphic region X of the protein A gene, was performed on all isolates confirmed as MRSA. It was performed according to the method described by Harmsen et al. (2003) and the specific *spa*-type was determined using BioNumerics® (Applied Maths). For MRSP *spa*-typing was performed according to Moodley et al. (2009) and MLST according to Solyman et al. (2013).

PCR was performed for identification of plasmid-mediated AmpC (Perez-Perez and Hanson 2002), CTX-M mediated ESBL (Woodford et al., 2006) and OXA-1 group, TEM and SHV genes (Fang et al., 2006).

The specific gene variants were determined by sequencing using in-house primers and Big-Dye™ v1.1. or submitted to Macrogene Inc. (South Korea) for sequencing.

Quality assurance system

Laboratories performing antimicrobial susceptibility testing at SVA are accredited according to SS-EN ISO/IEC 17025 by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC) to perform antimicrobial susceptibility tests with microdilution methods. In addition, Dept. of Bacteriology is accredited for isolation and identification of animal pathogens and of *Salmonella* and *Campylobacter* according to the same standard.

For susceptibility tests of zoonotic, pathogen and indicator bacteria, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* CCUG15915 (analogue to ATCC 29213) and *Campylobacter jejuni* CCUG 11284 (analogue to *Campylobacter jejuni* ATCC 33560) were included as quality controls. Relevant control strains were also included and evaluated at least once weekly for animal pathogens. For testing of *Brachyspira*, the *B. hyodysenteriae* type strain B78T ATCC 27164T was used for quality control.

Dept. of Animal Health and Antimicrobial Strategies participates in several proficiency tests for antimicrobial susceptibility testing. These are arranged either by the European Union Reference Laboratory - Antimicrobial resistance or as national studies. Likewise, Dept. of Bacteriology participates in proficiency tests concerning isolation and identification of *Salmonella* spp. and general clinical veterinary bacteriology and susceptibility tests.

Data handling

Records on *Salmonella* and animal pathogens such as source of cultured sample, identification results, antimicrobial susceptibility etc. were registered in a database at SVA. Data for indicator bacteria data was recorded in an Access database.

Cut-off values for resistance

For interpretation of MICs from susceptibility testing of zoonotic bacteria (*Salmonella* and *Campylobacter*) and indicator bacteria (*Escherichia coli* and enterococci) epidemiological cut-off values (ECOFF) issued by EUCAST (www.eucast.org) are used. When no ECOFF is issued, a value based on MIC distributions obtained in the SVARM programme is used. This approach was used also for interpretation of narasin MICs for *E. faecium* because the recommended cut-off value (>4 mg/L) cuts through MIC distributions for *E. faecium* from some animal categories studied in SVARM (*e.g.* broilers) in a manner not in agreement with the concept of wild-type distributions.

ECOFFs are used when available also for clinical isolates from animals. When ECOFFs are not available, or the range of concentrations tested precludes use of a recommended value, values based on MIC distributions obtained in the SVARM programme are used but clinical breakpoints issued by CLSI (CLSI, 2013b) are also taken into consideration.

ECOFFs classify isolates with acquired reduced susceptibility as non-wild type. In SVARM, non-wild type isolates are called resistant. This classification is relevant for monitoring purposes, but it should be understood that resistance defined in this manner not always implies clinical resistance.

TABLE 7.11. Cut-off values (mg/L) for resistance. Values in red are current (March 2014) EUCAST epidemiological cut-off values (ECOFFs), blue underlined values deviate from ECOFFs and for values in black, ECOFFs are not defined.

Antimicrobial	*Actinobacillus pleuropneumoniae*	*Aeromonas salmonicida*	*Brachyspira hyodysenteriae*	*Campylobacter jejuni*	*Campylobacter coli*	*Enterococcus faecalis*	*Enterococcus faecium*	*Escherichia coli* (indicator)	*Escherichia coli* (pathogen)	*Klebsiella pneumoniae*	*Pasteurella* spp.	*Pseudomonas aeruginosa*	*Salmonella enterica*	*Staphylococcus pseudintermedius*	*Staphylococcus aureus*	*Streptococcus zooepidemicus*
Ampicillin	>1			>8	>8	>4	>4	>8	>8		>1		>8			>8
Bacitracin[a]						>32	>32									
Cefotaxime	>0.06							>0.25	>0.5				>0.5			
Cefoxitin															>4	
Ceftiofur								>1	>1	>1			>2		>2	
Cephalothin														>2	>1	
Chloramphenicol	>2					>32	>32	>16	>16		>2		>16		>16	
Ciprofloxacin	>0.06			>0.5	>0.5			>0.06	>0.06		>0.06		>0.06		>1	
Clindamycin														>4	>0.25	
Colistin								>2								
Doxycycline			>0.5													
Enrofloxacin								>0.12	>0.12	>0.25	>0.25	>2	>0.25	>0.5	>0.5	
Erythromycin				>4	>8	>4	>4							>1	>1	
Florfenicol	>16	>4						>16	>16	>16	>4		>16		>8	>8
Fusidic acid														>4	>0.5	
Gentamicin	>8			>2	>2	>32	>32	>2	>4	>4	>8	>8	>2	>4	>2	
Kanamycin						>1024	>1024		>8				>16		>8	
Linezolid						>4	>4									
Nalidixic acid	>16			>16	>16			>16	>16		>16		>16			
Narasin						>2	>2									
Neomycin									>8	>8			>4			
Nitrofurantoin									>32					>32		
Oxacillin														>0.5	>1	
Penicillin	>1										>1			[c]	[c]	>1
Polymyxin B												>4				
Spiramycin															>16	>16
Streptomycin	>32			>4	>4	>512	>128	>16	>16	>16	>32		>16		>16	
Sulphamethoxazole								>64	>64				>256			
Tetracycline	>2	>4		>1	>2	>4	>4	>8	>8	>8	>2		>8	>8	>1	>8
Tiamulin			>0.25													
Trimethoprim	>4							>2	>2				>2		>2	
Trim & sulpha[b]									>1	>1	>4		>0.5	>2	>0.5	>4
Tylosin			>16													
Tylvalosin			>1													
Valnemulin			>0.12													
Vancomycin						>4	>4									
Virginiamycin						>32	>4									

[a] MIC in U/mL; [b] Concentration of trimethoprim given, tested with sulphamethoxazole in concentration ratio 1/20; [c] beta-lactamase production.

SVARM 2000-2013

The number of isolates of different matrices reported in SVARM since 2000 is presented below.

TABLE 7.12. *Salmonella enterica,* number of isolates 2000-2013.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Warm-blooded animals	67	52	49	101	68	105	101	112	122	117	82	71	71	86
Cold-blooded animals										17				

TABLE 7.13. *Campylobacter* spp., number of isolates 2000-2013.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Cattle		67					68							109
Pigs		98		105		100	46		97			83		
Broilers		50	100		100				38		100		100	
Broiler meat														111
Meat (different sources)		74												
Water		19												

TABLE 7.14. Indicator *Escherichia coli,* number of isolates 2000-2013.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Cattle	293						314			223				197
Pigs	260	308		303		390		342	349			167		
Pig meat									19			20		
Broilers	274	296	306		300			296			181		194	
Broiler meat											77		92	
Laying hens													61	
Turkeys														55
Horses											274			
Dogs							257						74	
Willow grouse						19								
Wild boars		87												
Sheep									115					

TABLE 7.15. Indicator *Enterococcus faecalis* and *E. faecium,* number of isolates 2000-2013 *(E. faecalis/E. faecium).*

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Cattle	22/71						13/98			10/24				11/42
Pigs	56/48	52/106		87/71		55/47			68/39			22/22		
Pig meat									17/3			29		
Broilers	24/151	49/204	57/189		48/163			28/197			35/136		44/136	
Broiler meat											81/17		78/10	
Laying hens													20/36	
Horses											34/27			
Dogs							135/29							
Wild boars		12/35												
Sheep									24/15					

TABLE 7.16. Clinical isolates from animals, number of isolates 2000-2013.

Animal species & bacterial species	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Cattle														
Escherichia coli (enteric)			220		87	39	24			40	15	15	58	30
Escherichia coli (uterine)														60
Escherichia coli (udder)				169										142
Klebsiella spp. (udder)				44			24							41
Pasteurella spp.	254			100				27	32	14	27	80	37	39
Staphylococcus aureus (udder)		100	100			96			87					
Streptococcus dysgalactiae (udder)			100											
Streptococcus uberis (udder)			100											
Fusobacterium necrophorum										41				
Pigs														
Actinobacillus pleuropneumoniae	18							84	39	24	39	57	33	36
Brachyspira hyodysenteriae	50	75	109	100		31	26	23	15	24	9	7	7	8
Brachyspira pilosicoli				93		57	72	44	31	24	13	16	17	12
Escherichia coli (enteric)	399	82	340	340	386	325	298	93	83	102	94	91	74	142
Pasteurella spp.		75						38	25	24	10	17	24	95
Staphylococcus hyicus					20									
Streptococcus equisimilis												82		
Poultry (laying hens)														
Escherichia coli (infection)								70						
Sheep														
Staphylococcus aureus (udder)								25						
Fusobacterium necrophorum										24				
Fish														
Aeromonas salmonicida subsp. *achrom.*								67	20	23	8	14	5	10
Flavobacterium columnare								30	16	10	5	8	3	5
Flavobacterium psychrophilum								42	27	24	21	27	31	23
Horses														
Actinobacillus spp.		40												
Escherichia coli (genital)	323	103	166	188	188	161	124	273	174	210	236	174	196	140
Rhodococcus equi	73	20			187									
Streptococcus zooepidemicus	301	174	163	150	185	175	174	180	159	152	43	311	140	123
Staphylococcus aureus										308	131	135	145	139
Dogs														
Escherichia coli (urinary)	185	183	204	234	247	304	366	425	503	599	803	666	407	840
Pasteurella multocida					231									
Pseudomonas aeruginosa				234						261	313	353	178	309
Staphylococcus pseudintermedius	145	156	133	102	159	126	89	220	258	381	444	388	229	566
Cats														
Escherichia coli (urinary)			46	52	55	74	95	131	170	245	236	274	310	404
Beta-hemolytic streptococci												184		

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SWEDRES|SVARM 2013

The 2013 Swedish report from the monitoring of antimicrobial resistance and antimicrobial usage in human and veterinary medicine, SWEDRES-SVARM, is an integrated report from the Public Health Agency of Sweden and the National Veterinary Institute, with data from humans, animals and food.

From an international perspective the situation in Sweden is still favorable regarding antimicrobial resistance in bacteria in the human and veterinary sectors. The strategy to promote rational antibiotic use and to contain the spread of resistant bacteria has been effective, but this year's report also shows unfavorable trends.

The report covers:
- Use of antimicrobials in humans and animals
- Occurrence of resistance in
  - Notifiable diseases
  - Zoonotic pathogens
  - Clinical isolates from humans and animals
  - Indicator bacteria from animals

The report also focuses on:
- Diagnos linked prescribing data from primary and hospital care
- Repeated courses for respiratory tract infections
- Outbreaks caused by resistent bacteria in Swedish healtcare
- Surveillance by Svebar
- All about ESBL-producing bacteria
- Penicillin resistance in *Bacillus anthracis*
- SVARMpat
- *Dichelobacter nodosus*

The Public Health Agency of Sweden has a national responsibility for public health issues and also a mission to monitor the epidemiology of communicable diseases among Swedish citizens and promote control and prevention of these diseases. The Public Health Agency of Sweden is responsible for national surveillance of antibiotic use and antibiotic resistance, and aims at providing expert analyses and advice to laboratories, infection control officers, Strama-groups and county medical officers.

The National Veterinary Institute (SVA) is a Government expert authority that strives for good animal and human health, a good environment and sustainable food production. SVA has expertise within the fields of risk assessment, prevention, diagnostics and the control of contagious and other serious infectious diseases including zoonotic agents and antimicrobial resistance. SVA is mandated to monitor antimicrobial resistance in animals and food and to promote rational use of antimicrobials in animals.