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Consumption of antibiotics and occurrence of antibiotic resistance in Sweden

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A report on Swedish Antibiotic Utilisation and Resistance in Human Medicine (Swedres) and Swedish Veterinary Antibiotic Resistance Monitoring (Svarm)

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Preface

The 2014 Swedish report from the monitoring of antibiotic resistance and antibiotic consumption in human and veterinary medicine, Swedres-Svarm, is an integrated report from the Public Health Agency of Sweden and the National Veterinary Institute that includes data from humans, animals and food. The report is a result of the successful collaboration between the relevant sectors in Sweden.

Through a 'One Health' approach, we stand a better chance to respond to the challenges of antibiotic resistance and the way we use, and sadly, misuse, antibiotics. Veterinary and human medicine must act and work in a synchronised manner, and this is the reason why a large number of Swedish governmental authorities have been working together to prepare a joint action plan against antibiotic resistance in 2014. In parallel with that work, a joint communication strategy has been adopted that will ensure greater impacts for whatever actions are taken. During the last year, several initiatives have been taken that cross traditional political and national boundaries and involve many of our experts. Of particular importance in a Swedish context was a high-level meeting focusing on a global programme for surveillance of antibiotic resistance that was co-hosted by the WHO, the Public Health Agency of Sweden and the Swedish Ministry of Health and Social Affairs.

This year's report shows that Sweden is still in a very favourable situation and that the levels of resistance continue to be low. In some areas of the veterinary sector, we have even seen some improvements relative to previous years. Thankfully, the screening of all breeding herds once again showed that MRSA has not spread among breeding pigs in Sweden.

We can conclude that in a global perspective Sweden is better off compared to most countries, but we are far from being spared the problems associated with antibiotic resistance. 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 in the country.

This December it will be 70 years since Sir Alexander Fleming held his now famous Nobel Laureate lecture in Stockholm. Even then he warned the audience about the perils of misusing antibiotics and what would happen if we chose not to use them wisely. His warnings still hold true, and hopefully there is still time to act upon them in truly global manner.

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Strama collaboration group of the Public Health Agency of Sweden formerly the Strama advisory board.

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.

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Content

Sammanfattning/Summary

Sammanfattning

När det gäller antibiotikaresistens hos bakterier från människor och djur har Sverige en gynnsam situation sett i ett internationellt perspektiv. Detta bekräftar att vi har effektiva strategier för att främja rationell antibiotikaanvändning och begränsa spridning av resistenta bakterier bland djur och människor. Ändå beskriver årets rapport även ogynnsamma trender, t.ex. sjukhusutbrott med VRE (vankomycinresistenta enterokocker) och humana fall av Enterobacteriaceae med $ESBL_{CARBA}$ (betalaktamas med utvidgad spektrum som även har aktivitet mot karbapenemer) som smittats inrikes och där smittkällorna är okända. Detta betonar än en gång att arbetet med att optimera antibiotikaanvändningen, förebygga infektioner och minska spridningen av resistenta bakterier måste fortgå och ständigt förbättras.

Förbrukning av antimikrobiella medel

Antibiotikaförbrukning inom humanmedicin

Den totala antibiotikaförsäljningen (öppenvård och slutenvård) minskade med 4 procent (från 13,4 till 12,8 DDD per 1 000 invånare och dag).

I öppenvården (inkluderar all antibiotika försålt på recept) minskade försäljningen med 4 procent, från 343 till 328 recept per 1 000 invånare och år. Minskningen sågs i alla åldersgrupper och den största förändringen gäller barn 5–14 år (8 procent).

Antibiotikaförsäljningen minskade i samtliga 21 län. Skillnaden mellan länen är dock fortfarande stor, och varierar från 359 recept per 1 000 invånare och år i Stockholm till 260 i Västerbotten. Minskningen omfattade de flesta antibiotikagrupper med undantag för pivmecillinam, nitrofurantoin, trimetoprim med sulfonamider, penicillin med klavulansyra samt makrolider. Pivmecillinam och nitrofurantoin är förstahandsmedel för nedre okomplicerad urinvägsinfektion och den ökade användningen bedöms bero på ökad följsamhet till nationella behandlingsrekommendationer. Den ökade försäljningen av makrolider kopplas till det leveransproblem av erytromycin som uppstod under våren 2013. Betalaktamaskänsliga penicilliner tillsammans med tetracykliner var de antibiotika som förskrevs mest på recept under 2014.

Antibiotika som ofta används mot luftvägsinfektioner (LVI) är den antibiotikagrupp som används mest, och det är även i denna grupp som försäljningen minskade mest under 2014 (7 procent). Denna minskning är främst relaterad till en nedgång i användningen av betalaktamaskänsliga penicilliner (8 procent) och tetracykliner (10 procent).

Behandlingen av nedre urinvägsinfektioner (UVI) hos kvinnor ser ut att följa nationella behandlingsrekommendationer. Under 2014 minskade den totala försäljningen av UVI-antibiotika till kvinnor 18–79 år något (1 procent) jämfört med 2013. Under året fortsatte den positiva trend som setts under de senaste åren med en ökad försäljning av förstahandspreparaten pivmecillinam och nitrofurantoin, i stället för de breda och mer resistensdrivande preparaten trimetoprim och fluorokinoloner. Försäljningen av trimetoprim minskade med 13 procent under 2014 och fluorokinoloner med 2 procent.

Den totala försäljningen av antibiotika mot nedre UVI hos män i åldersgruppen 65 år och äldre minskade något (1 procent) under 2014 jämfört med 2013. Fluorokinoloner är fortfarande det preparat som används mest bland UVI-antibiotika till män i denna åldersgrupp, och under 2014 fortsatte denna försäljning att minska med 2 procent. Däremot ökade försäljningen av pivmecillinam och nitrofurantoin även till män, med 20 respektive 12 procent mätt som recept per 1 000 invånare och år.

Försäljningen av antibiotika förskrivet av tandläkare minskade med 9 procent under 2014 jämfört med 2013, från 26,0 till 23,6 recept per 1 000 invånare och år (J01 inklusive metronidazol P01AB01). Störst minskning sågs för amoxicillin (13 procent) och klindamycin (14 procent).

Under 2014 ökade den totala antibiotikaförbrukningen på sjukhus något jämfört med 2013 (mätt som DDD per 100 vårddagar och DDD per 100 vårdtillfällen). Användningen av betalaktamaskänsliga penicilliner, cefalosporiner och aminoglykosider låg kvar på samma nivå medan försäljningen av betalaktamas-resistenta penicilliner, fluorokinoloner, karbapenemer och penicilliner med betalaktamashämmare fortsatte att öka likt föregående år. Användningen av penicilliner med betalaktamashämmare har ökat kraftigt på svenska sjukhus under de senaste åren, och 2014 var ökningen 7,3 procent. Användningen av karbapenemer har ökat marginellt. Karbapenemer och piperacillin med tazobaktam används oftare, och det finns en möjlig koppling till ett ökande antal infektioner orsakade av bakterier med ESBL (Extended-Spectrum Betalaktamases). I länen varierar andelen bredspektrumantibiotika (fluorokinoloner, cefalosporiner, karbapenemer och piperacillin med tazobaktam) av den totala antibiotikaförbrukningen på svenska sjukhus, från 28,6 procent i Värmland till 37,6 procent i Östergötland. Sett över en längre tid har försäljningen av antibiotika på slutenvårdsrekvisition (alla sjukhus inklusive viss förbrukning inom äldreboenden och andra vårdenheter) gått från en hög användning av breda preparat till smala antibiotikapreparat. Sedan 2008 är betalaktamasresistenta penicilliner (J01CF) och betalaktamaskänsliga penicilliner (J01CE) de antibiotikagrupper som försäljs mest på slutenvårdsrekvisition.

Försäljning av antimykotika

Under 2014 var den totala användningen av antimykotika på svenska sjukhus densamma som 2013, det vill säga 61 DDD per miljon invånare och dag. Liksom tidigare är flukonazol det mest använda preparatet och utgör två tredjedelar av all sjukhusanvändning (39,5 DDD per miljon invånare och

dag). När det gäller preparat med bredare antifungal täckning ökade amfotericin B med 28 procent och står nu för 16 procent av den totala förbrukningen.

Under de senaste sex åren har försäljningen av echinokandinerna ökat och denna grupp utgör 12 procent av den totala förbrukningen. Tidigare var caspofungin det absolut dominerande preparatet i gruppen, men det har förlorat en stor del av sin dominans och utgör nu cirka 44 procent av den totala användningen. Anidulafungin och det nyare preparatet mikafungin står nu för 38 respektive 18 procent. Den totala förbrukningen av bredspektrumazoler är relativt oförändrad, men vorikonazol fortsätter att minska till förmån för posakonazol. Många landsting med universitetssjukhus har ökat förbrukningen av både andiulafungin och mikafungin och minskat sin användning av caspofungin.

Antibiotikaförbrukning inom veterinärmedicin

Efter omregleringen av apoteksmarknaden 2009 finns indikationer på ett bortfall i statistiken när det gäller försäljning av antibiotika för djur. Bortfallet berör troligen främst läkemedel för injektion, men eftersom dessa utgör minst 70 procent av den totala förbrukningen är det svårt att bedöma trender sedan 2010. Den totala förbrukningen av antibiotika har dock minskat sedan mitten av 1990-talet, och det är troligt att det finns en sann minskning även sedan 2010.

Databortfallen har troligen ingen större betydelse för statistik över läkemedel för medicinering av enskilda djur via munnen och för medicinering av grupper av djur via foder och vatten. Mellan 2010 och 2014 ses en påtaglig minskning av dessa två typer av antibiotikaprodukter (32 respektive 55 procent).

Jämförelse av förbrukning inom human- och veterinärmedicin

Under 2014 förbrukades 60,5 och 10,2 ton antibiotika inom human- respektive veterinärmedicin. Mätt som milligram aktiv substans per skattad kilogram biomassa var förbrukningen 96,4 respektive 12,7 milligram per kilogram. Förbrukning inom humanmedicin dominerade alla antibiotikaklasser utom trimetoprim-sulfa och aminoglykosider.

Anmälningspliktig resistens

ESBL-producerande Enterobacteriaceae

År 2014 rapporterades totalt 8 902 fall av Enterobacteriaceae med betalaktamaser med utvidgat spektrum (ESBL) hos människa, vilket var en ökning med 9 procent jämfört med året innan. Ökningen skedde i 15 län, och liksom tidigare år var *Escherichia coli* den helt dominerande arten och förekom i 89 procent av fallen. *Klebsiella pneumoniae* var näst vanligast med 7 procent. Bakteriefynden gjordes framför allt i urinprov. Invasiva infektioner med ESBL-producerande bakterier ökade under 2014 till 520 anmälningar, från 402 året innan.

En viss typ av ESBL, $ESBL_{CARBA}$, har en bredare resistensmekanism, och bakterier med denna resistens blev under 2012 anmälningspliktiga både av den behandlande läkaren och av laboratoriet som gjorde fyndet. Totalt 46 nya fall upptäcktes 2014, och de två vanligaste enzymtyperna var OXA-48 och NDM. Under året inträffade två inhemska smittspridningar med fyra personer inblandade, varav den ena spridningen skedde på sjukhus och den andra inom vård och omsorg utanför sjukhus. Dessa extremt resistenta bakterier är hittills ovanliga i Sverige men en ökad vaksamhet är 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.

Hos djur förekommer Enterobacteriaceae med ESBL-produktion både som tarmkolonisation och som kliniska isolat, då främst från sår eller urogenitalia. Förekomsten är relativt låg, undantaget slaktkyckling där en stor andel av djuren bär på ESBL-producerande *E. coli*. Det har dock skett en signifikant minskning av förekomsten hos slaktkyckling och andelen positiva prov är nu jämförbar med situationen 2010 då problemet först uppmärksammades.

MRSA

Totalt anmäldes 2 921 nya fall hos människa av meticillinresistenta *Staphylococcus aureus* (MRSA) 2014, vilket är en ökning med 19 procent. Andelen smitta utomlands och i Sverige var lika stora. Samhällsförvärvad smitta var vanligare bland de inhemskt smittade fallen (76 procent) än bland de utomlands smittade (50 procent), medan sjukhusförvärvad smitta var vanligare bland importerade fall (28 procent) än bland inhemska (8 procent). Invasiva infektioner med MRSA rapporterades hos 39 personer under 2014. Epidemiologisk *spa*-typning visade att de fem vanligaste *spa*-typerna var t223, t008, t044, t002 och t127. Andelen PVL-positiva MRSA hade minskat något till 35 procent jämfört med året innan.

Förekomsten av MRSA hos djur är fortfarande låg i Sverige, vilket begränsar risken för spridning till människa. Under 2014 provtogs samtliga livdjursproducerande grisbesättningar och MRSA hittades inte. Däremot isolerades MRSA sporadiskt från häst, hund, katt, nötkreatur och igelkott. Hos hundar och katter dominerar samma typer av MRSA som hos människor, vilket tyder på att människor är smittkällan. Hos hästar är lantbruksdjurstypen MRSA CC398 vanligast.

MRSP

Under 2014 anmäldes 39 fall av meticillinresistent *Staphylococcus pseudintermedius* hos hund (36 fall), katt (2 fall) och häst (1 fall). De anmälda fallen har minskat sedan 2009 då 130 fall anmäldes. Under 2014 rapporterades inget fall av MRSP hos människor 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 per liter, vilket har medfört en kraftig minskning av antalet anmälda fall. Totalt anmäldes 70 fall av PNSP

under 2014. För att kunna följa effekten av vaccination mot pneumokocker samlar Folkhälsomyndigheten regelbundet in PNSP-isolat med MIC ≥ 0,5 mg per liter för serotypning. De vanligast förekommande serotyperna 2014 var 19F, NT, 35B, 19A, 23F, 14, 11A, 6B och 9V.

VRE

År 2014 anmäldes 402 nya fall av vankomycinresistenta enterokocker (VRE) hos människa, vilket var en ökning med 77 procent jämfört med 2013. Merparten av isolaten var *Enterococcus faecium*, och liksom 2013 är nu *vanB* (281 fall) vanligare än *vanA* (110 fall). Tretton sjukvårdsrelaterade utbrott rapporterades under året i sex län, varav alla med *E. faecium*. Sju var med *vanA* och sex med *vanB*. Det största utbrottet inträffade i Gävleborgs län. Det började i september 2013 och avslutades under vintern 2014, och omfattade 314 fall.

Resistens hos zoonotiska smittämnen

Salmonella är ovanligt hos djur i Sverige och isolerade stammar är oftast känsliga för antibiotika. Någon överförbar resistens mot tredje generationens cefalosporiner har aldrig påvisats och resistens mot antibiotikagruppen fluorokinoloner är mycket ovanligt. Svenska djur är en osannolik källa till *Salmonella* som orsakar invasiva infektioner hos människor eftersom sådana stammar vanligen tillhör andra typer än de som finns hos djur och dessutom ofta är resistenta mot kinoloner.

Campylobacter-stammar från djur i Sverige är oftast känsliga för relevanta antibiotika och exempelvis är resistens mot erytromycin mycket ovanligt. *Campylobacter* som isoleras från människor är däremot ofta resistenta och det är därför osannolikt att de stammarna kommer från svenska djur.

Vanligtvis behandlas inte infektioner orsakade av *Salmonella* eller *Campylobacter* med antibiotika, varken hos människor eller hos djur. Det innebär att det när det gäller infektioner hos människor framför allt finns data angående antibiotikaresistens för ett litet antal invasiva infektioner.

Resistens hos kliniska isolat från människor

I det europeiska nätverket för resistensövervakning, EARS-Net, ingår åtta olika bakteriearter. Endast isolat från blododlingar omfattas. År 2014 var det 16 svenska laboratorier som medverkade i EARS-Net. Totalt 15 laboratorier rapporterade till publiceringen av Swedres, det täcker cirka 80 procent av befolkningen. Sju laboratorier har även rapporterat övriga blodisolat under året och följande fynd gjordes 2014: *Escherichia coli* förekom i 26,4 procent av de positiva blododlingarna och *S. aureus* i 13,4 procent. De övriga sex bakteriearterna som ingår i övervakningen är viktiga men utgjorde en avsevärt mindre andel av fynden. Hos *E. coli* och *K. pneumoniae* har andelen cefalosporinresistenta (till största delen orsakad av ESBL-produktion) isolat ökat varje år och uppgick till 5,4 respektive 4,0 procent 2014. Andelen MRSA av drygt 3 500 rapporterade *S. aureus* var 0,9 procent, vilket ur ett europeiskt perspektiv är lågt. VRE utgjorde 0,7 procent av *E. faecium* (3 fall), och för *E. faecalis* är läget oförändrat med inga rapporterade fall. Andelen PNSP av de knappt 800 *S. pneumoniae* var 6,3 procent.

Den andra delen av den nationella resistensövervakningen är tillgänglig i applikationen ResNet, och i den undersöks samma bakteriearter som i EARS-Net. Alla kliniska laboratorier ombeds testa isolat från urinvägs-, sår- eller luftvägsinfektioner, med syftet att bättre kunna spegla situationen i öppenvården. Andelen resistenta bakterieisolat i de båda övervakningssystemen ligger på likartade nivåer.

För vissa bakteriearter finns speciella övervakningsprogram och/eller speciallaboratorier som kan utföra analyserna. Det gäller dels tarmbakterien *Clostridium difficile* som kan orsaka svåra diarrétillstånd, dels bakteriearterna *Neisseria gonorrhoeae* (gonokocker), *N. meningitidis* (meningokocker) och *Mycobacterium tuberculosis* (tuberkulosbakterien). Andelen *C. difficile*-isolat som är resistenta mot erytromycin och klindamycin ökade något under 2014, medan den var densamma som 2013 för moxifloxacin. Ribotyp 027 ökade under 2014 till följd av utbrottet i Kronoberg (separat rapport). År 2014 var resistensen hos gonokocker mot cefixim 2 procent, vilket innebar en fortsatt minskning, och resistensen mot ceftriaxon var 0,3 procent. Detta är ytterst lovande eftersom ceftriaxon är ett viktigt medel för empirisk behandling av gonorré. Resistens hos *M. tuberculosis* är en ständigt aktuell frågeställning. Tuberkulos övervakas noggrant och situationen i Sverige är god.

Resistens hos kliniska isolat från djur

Bakterier som orsakar sjukdom hos djur är fortfarande oftast känsliga för de antibiotika som vanligen används. Till exempel är bakterier som orsakar luftvägsinfektioner hos lantbrukets djur och hästar generellt känsliga för bensylpenicillin. Penicillinresistens är däremot vanligt hos *S. pseudintermedius* från hundar och förekommer hos *S. aureus* från hästar och *Staphylococcus felis* från katter. Resistens hos *E. coli* från olika djurslag förekommer också men är vanligast i isolat från träckprover från unga kalvar. Resistensundersökning är motiverat för att välja lämpligt antibiotikum vid behandling, särskilt för stafylokocker och *E. coli*.

Indikatorbakterier från friska djur

Resistens hos *E. coli*, *E. faecalis* och *E. faecium* från tarmfloran hos friska djur kan användas som indikator för utbredningen av antibiotikaresistens hos bakteriefloran i en djurpopulation. Indirekt kan den även visa på omfattningen av antibiotikaanvändning till djuren. I Sverige är förekomsten av resistens hos dessa indikatorbakterier låg hos de flesta undersökta djurslag och situationen är gynnsam i ett internationellt perspektiv.

Summary

The situation in Sweden regarding antibiotic resistance in bacteria from humans and animals is favourable when seen in an international perspective. This confirms that the Swedish strategies to promote rational use and to contain antibiotic resistance in bacteria from animals and humans have been effective. Still, this year's report also reports some unfavourable trends, for example, a large hospital in Sweden has been hit with VRE (vancomycin resistant enterococci) and there have been domestic human cases of Enterobacteriaceae with $ESBL_{CARBA}$ (extended spectrum beta-lactamase with activity against carbapenems) where the sources of infection are unknown. This highlights once again that efforts to optimize antibiotic use, prevent infections, and minimize dissemination of antibiotic resistance must be ongoing and continually improved activities.

Consumption of antimicrobials

Antibiotic consumption in humans

The total consumption (including outpatient care and hospital care) of antibiotics decreased by 4 percent in 2014 compared to 2013 (from 13.4 DDD to 12.8 DDD per 1 000 inhabitants and day).

In outpatient care (including sales on prescriptions), antibiotic sales decreased by 4 percent from 343 prescriptions per 1 000 inhabitants and year in 2013 to 328 in 2014. This decrease was seen in all age groups and was most evident in the age group 5–14 years (an 8 percent reduction). In total, a decreased number of antibiotic prescriptions was seen in all 21 Swedish counties in 2014.

There are still significant regional differences between parts of Sweden, and the number of prescriptions per 1 000 inhabitants ranges from 359 in Stockholm County to 260 in Västerbotten County.

The decrease encompasses most antibiotic groups with the exception of nitrofurantoin, pivmecillinam, trimethoprim with sulphonamides, and penicillins with enzyme inhibitor and macrolides. The increase of pivmecillinam and nitrofurantoin is in accordance with national treatment recommendations since they are recommended as first line antibiotics for urinary tract infections (UTIs). A shortage of erythromycin during the spring of 2013 affected the statistics and explains the increased sales of macrolides in 2014. Beta-lactamase–sensitive penicillins together with tetracyclines were the most commonly used antibiotics in outpatient care.

Antibiotics commonly used to treat respiratory tract infections were the most frequently prescribed antibiotics. Among these substances, we also found the greatest decrease in sales (7 percent) in 2014 compared to 2013. The decrease is mainly related to a significant reduction in sales of beta-lactamase–sensitive penicillins (8 percent) and tetracyclines (10 percent).

Treatment of lower UTIs in women appears to be following national recommendations. In 2014, the total sales of antibiotics commonly used to treat UTIs in women aged 18–79 years decreased slightly (1 percent) compared to 2013. The same positive trend as previously described with increased use of the first-line drugs pivmecillinam and nitrofurantoin and reduced sales of trimethoprim (13 percent) and fluoroquinolones (2 percent) was seen.

The total sales of antibiotics commonly used to treat UTIs in men 65 years and older increased slightly (1 percent) in 2014 compared to 2013. Fluoroquinolones are still the most common antibiotics for treating UTIs in this population, but sales of fluoroquinolones decreased by 2 percent in 2014 compared to 2013. In 2014, the sales of pivmecillinam and nitrofurantoin increased by 20 percent and 12 percent, respectively, as measured by prescriptions per 1 000 men and year, compared to 2013.

The sales of antibiotics prescribed by dentists decreased by 9 percent in 2014 compared to 2013, from 26.0 to 23.6 prescriptions per 1 000 inhabitants and year for J01 and metronidazole (P01AB01). The greatest decrease in 2014 was seen for amoxicillin (13 percent) and clindamycin (14 percent).

In 2014, the total consumption of antibiotics in Swedish acute care hospitals increased slightly compared to 2013. The consumption of beta-lactamase–sensitive penicillins, cephalosporins, and aminoglycosides did not change during the last year, and the consumption is at almost the same level as in 2013. The use of beta-lactamase–resistant penicillins, fluoroquinolones, penicillins with enzyme inhibitor and carbapenems continues to increase as in previous years.

Penicillins with enzyme inhibitor have increased significantly in recent years, and carbapenems have increased marginally, these agents have replaced the cephalosporins in many situations. In 2014, penicillins with enzyme inhibitor increased by 7.3 percent when measured as DDD per 100 patient-days compared to 2013. The increase is probably a result of an increased number of infections with ESBL (Extended spectrum beta-lactamase). The percentage of broad-spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam, and carbapenems) out of all antibiotics in Swedish acute care hospitals varied from 28.6 percent in Värmland County to 37.6 percent in Östergötland County. When analyzing the total antibiotic consumption in hospitals (including all hospitals and parts of nursing homes and other care units) from 2000–2014, a clear shift from high use of broad-spectrum antibiotics to narrow-spectrum antibiotics can be seen.

Sales of antifungals

Compared to 2013, the total consumption of antifungal drugs for systemic use has remained unchanged with a national average of 61 DDD per million inhabitants and day. Every year since 2000, except for 2011 and 2014, there has been a small but steady increase in the total consumption of antifungals. Since the year 2000 when the total consumption was 40 DDD per million inhabitants and day, the increase has been 50 percent.

Fluconazole still constitutes the absolute majority of the antifungals used at 65 percent or 39.5 DDD per million inhabitants and day. Amphotericin B is the second most used compound. The sales of amphotericin B increased by 28 percent compared to 2013 and now accounts for 16 percent of the total consumption.

Since 2005, there has been a small but steady increase in the consumption of the echinocandins. In 2014, consumption increased by 11 percent bringing the total amount to 7.3 DDD per million inhabitants and day, and the group now constitutes 12 percent of all systemic antifungal consumption in hospital care. The consumption of caspofungin, which has been available in Sweden since 2002, has decreased every year. It now constitutes 44 percent of the echinocandins down from 60 percent in 2013. Anidulafungin increased its share from 30 percent to 38 percent last year. The third member of the group, micafungin, that appeared for the first time in the statistics in 2012 now constitutes 18 percent of the total echinocandin consumption. Many of the counties with tertiary care hospitals have largely increased their use of both anidulafungin and micafungin at the expense of caspofungin.

Consumption of antibiotics in animals

There are indications that the data on sales from Swedish pharmacies are less complete than before the reregulation of the Swedish pharmacy market in 2009. This problem probably mainly affects the sales of antibiotics for parenteral use, but because such drugs make up at least 70 percent of the overall consumption the magnitude of overall trends from 2010 cannot be assessed with certainty. The overall consumption of antimicrobials has decreased gradually since the mid-1990s, and there has also most likely been a true decrease since 2010.

Products for oral medication of individual animals and oral medication of groups of animals via feed or water are less likely to be affected by the lack of completeness in the data. Major downward trends are noted from 2010 to 2014 for both of these categories (by 32 percent and 55 percent, respectively).

Comparing sales for humans and animals

In 2014, a total of 60.5 tons and 10.2 tons of antibiotics were consumed in human and veterinary medicine, respectively. When measured as mg active substance per kg estimated biomass, the corresponding figures were 96.4 mg per kg and 12.7 mg per kg. Consumption in human medicine by far outweighs consumption in veterinary medicine for most classes except for trimethoprim-sulphonamides and aminoglycosides.

Notifiable resistance

ESBL-producing Enterobacteiaceae

A total of 8 902 human cases of extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae were reported in 2014, and this corresponds to an incidence of 91 cases per 100 000 inhabitants. This is an increase of 9 percent compared to 2013, and increases occurred in 15 counties. The most commonly reported species was *Escherichia coli* with 89 percent of all cases followed by *Klebsiella pneumoniae* with 7 percent. Most ESBL-producing bacteria were found in urine samples (59 percent). Invasive infections with ESBL-producing bacteria increased from 402 cases in 2013 to 520 cases in 2014.

A special type of ESBLs, so-called $ESBL_{CARBA}$, constitute a broader mechanism. Bacteria with this extended resistance mechanism became notifiable from both clinicians and laboratories in 2012. Forty-six new cases were detected in 2014, and the two most common types of enzymes were OXA-48 and NDM. Two domestic transmissions involving four persons were reported in 2014, one occurred in a hospital and the other in care outside a hospital. Because the treatment alternatives for these infections are few if any, it is necessary to have an active surveillance of these new and extremely resistant bacteria in order to detect them at an early stage and thereby hinder their spread within the health care system.

In animals, ESBL-producing Enterobacteriaceae occurs both as gut colonization and as clinical isolates, mainly from wounds or from the urogenital tract. The occurrence is relatively low, with the exception of broilers were ESBL-producing *E. coli* is isolated from a large proportion of the caecal samples. However, there has been a significant decrease in the occurrence in broilers and the proportion of positive samples is now comparable to the situation in 2010 when the problem was first discovered.

MRSA

The total number of human cases of methicillin-resistant *Staphylococcus aureus* (MRSA) was 2 921 in 2014, an increase of 19 percent compared to 2013. According to the systematically reviewed notification reports, infections were as often acquired in Sweden as abroad. Community-acquired infections dominated among domestic cases (76 percent) but were less frequent among imported cases (50 percent). Hospital-acquired infections were comparatively more common in imported cases (28 percent) than among domestic cases (8 percent), indicating continued good compliance to basic hygiene principles among healthcare staff in Sweden. Thirty-nine invasive isolates of MRSA were reported in 2014. Epidemiological typing of isolates by *spa*-typing showed that the five most commonly encountered *spa*-types in 2014 were t223, t008, t044, t002, and t127. The prevalence of MRSA with PVL toxin had decreased to 35 percent.

The occurrence of MRSA in animals in Sweden is still low, and this limits the spread from animals to humans. In 2014, MRSA was not detected in a screening of nucleus and multiplying pig herds. MRSA was found sporadically in horses, dogs, cats, cattle, and hedgehogs in 2014. 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 is most common.

MRSP

In 2014, 39 cases of methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) were reported in dogs (36 cases), cats (2 cases), and horses (1 case). The number of cases reported yearly has declined since 2009 when 130 cases were reported. No human cases were reported in 2014, but MRSP in humans is not generally notifiable to the authorities.

PNSP

In 2012, the definition for *Streptococcus pneumoniae* with reduced susceptibility to penicillin (PNSP) was changed to include only isolates with an MIC (minimal inhibitor concentration) of

penicillin > 1 mg/L, and this resulted in a dramatic decrease in reported cases. A total of 70 new cases of PNSP were reported in 2014. In order to follow and evaluate the effect of vaccination against pneumococcal disease, The Public Health Agency of Sweden 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 in 2014 were 19F, NT, 35B, 19A, 23F, 14, 11A, 6B, and 9V.

VRE

In 2014, a total of 402 new cases of vancomycin-resistant enterococci (VRE) were reported, which was an increase of 77 percent compared to 2013. The majority of isolates were *Enterococcus faecium*, and in contrast to 2013 isolates with the resistance gene *vanB* outnumbered those with the *vanA* gene. Thirteen healthcare-related outbreaks were reported from six counties, all with *E. faecium*, and seven carried the *vanA* gene and six carried the *vanB* gene. The largest outbreak, in Gävleborg County, started in September 2013 and ended at the end of 2014 and comprised approximately 314 cases.

Zoonotic pathogens

Salmonella is rare in animals in Sweden, and few incidents involve antibiotic-resistant strains. Strains with ESBL-resistance have never been found, and resistance to fluoroquinolones is rare. Invasive infections in humans are mainly caused by other *Salmonella* serovars than those found in animals and isolates are often quinolone resistant. Animals in Sweden is therefore an unlikely source of *Salmonella* causing these infections.

Campylobacter from animals in Sweden are mostly susceptible, and for example resistance to erythromycin is most uncommon. Animals in Sweden are, therefore, an unlikely source for the highly resistant *Campylobacter* seen in isolates from humans.

Infections caused by *Salmonella* or *Campylobacter* are usually not treated with antibiotics, neither in humans nor in animals. In humans, this means that data on antibiotic resistance is mainly available from a small number of invasive infections.

Human clinical isolates

EARS-Net surveillance

Invasive isolates of eight bacterial species have been reported to EARSS/EARS-Net. In 2014, seven laboratories reported data on all positive blood cultures. *Escherichia coli* was the most frequently found pathogen in blood cultures at 26.4 percent followed by *S. aureus* at 13.4 percent. The six 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 5.4 and 4.0 percent, respectively. MRSA isolates accounted for 0.9 percent of all invasive *S. aureus*, which is low from a European perspective. The rates of non-susceptibility to penicillins in *S. pneumoniae* (referred to as PNSP) was higher than in previous years at 6.4 percent in 2014. There were still no VRE reported for *E. faecalis* in 2014, and the level was at 0.7 percent among invasive isolates of *E. faecium* (3 cases), but high-level resistance to aminoglycosides (HLAR) was common at 15.6 percent and 22.5 percent in *E. faecalis* and *E. faecium*, respectively.

National surveillance and quality assurance programme, ResNet

The same bacterial species as in EARS-Net are part of the ResNet programme, but samples from UTIs (*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 also included in the ResNet programme. 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. These species include *Clostridium difficile* and *Mycobacterium tuberculosis* (The Public Health Agency of Sweden) and *Neisseria gonorrhoeae* and *N. meningitidis* (National Reference Laboratory in Örebro).

The proportion of *C. difficile* isolates resistant to the indicator antibiotics erythromycin and clindamycin increased slightly in 2014, while that of moxifloxacin was the same as in 2013. Ribotype type 027 increased in 2014 due to the outbreak in Kronoberg (separate report).

In 2014, the resistance in gonococci to cefixime (2 percent) continued to decrease, and the resistance to ceftriaxone (0.3 percent) remained low. This is promising because ceftriaxone is the last remaining option for empirical antimicrobial monotherapy of gonorrhoea. Rates of resistance to antituberculosis drugs in *M. tuberculosis* are carefully monitored, and the situation is good.

Animal clinical isolates

Bacteria causing clinical disease in animals are mostly susceptible to antibiotics relevant for treatment. Respiratory pathogens from farm animals and horses are generally susceptible to bensylpenicillin, but penicillin resistance is common in *S. pseudintermedius* from dogs and it occurs in *S. aureus* from horses and *Staphylococcus felis* from cats. Resistance in *E. coli* occurs in all animals but is most prominent in enteric isolates from young calves. Susceptibility testing for guidance in antibiotic therapy is warranted, especially for staphylococci and *E. coli*.

Indicator bacteria from healthy animals

Antibiotic resistance in *E. coli*, *E. faecalis*, and *E. faecium* from the intestinal flora of healthy animals serves as an indicator for the presence of resistance in an animal population. Also, the prevalence of acquired resistance in such commensal bacteria indirectly indicates the magnitude of the selective pressure from the use of antibiotics in an animal population. Prevalence of resistance in indicator bacteria from animals in Sweden 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 with the aim to present data relating to both humans and animals on the use of antibiotics and on antibiotic resistance in a joint report.

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 programs 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 program in the veterinary field Svarm. This program is specifically designed to monitor resistance in bacteria from animals and food and is organized and run at the National Veterinary Institute. Data in the veterinary field also emanate from other sources, such as the Svarmpat project and specific research projects. For details on data sources see Background material and references.

Antibiotic resistance

Swedres

Most of the data on resistance in Swedres is derived from routine diagnostic samples sent for testing at clinical laboratories. The results are mostly presented as proportion resistance in tables or graphs. The methods used for antibiotic 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

The vast majority of 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 from EUCAST (www.eucast.org) 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. 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 *E. faecium* serve as indicators for presence of antibiotic 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 antibiotics 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 in Svarm 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 antibiotic and vertical bold lines indicate cut-off values used to define resistance.

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

Example of a table with MIC distributions

Antibiotic	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 antibiotic 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	Ceftazidim	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-sulfonamide
Cli	Clindamycin	Mec	Mecillinam	Tob	Tobramycin
Col	Colistin	Mer	Meropenem	Van	Vancomycin
Ctx	Cefotaxim	Nal	Nalidixic acid	Vir	Virginiamycin
Enr	Enrofloxacin	Nar	Narasin		

first shaded field to the right of the tested range. For MICs equal to or lower than the lowest concentration tested for an antibiotic (≤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 antibiotic classes. This implies, for example, that resistance to ciprofloxacin, enrofloxacin and nalidixic acid represents resistance to one class of antibiotics.

Antibiotic consumption

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. In this report the term antibiotic is used. However the report also includes a chapter regarding sales of antifungals (J02).

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

Wherever sales of antibiotics to a certain group of people is displayed (children 0-6 years, women 18-79 years, inhabitants in a county), the denominator is 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, parts of nursing homes and other care units). Since national data on antibiotic consumption in hospitals in Sweden are 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

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
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)
MDR	Multidrug resistance, i.e. phenotypic resistance to three or more antibiotic classes
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
PVL	Panton-Valentine leukocidin
ResNet	Webb application for Resistance surveillance and quality control programme
RTI	Respiratory tract infection
spa	Staphylococcal protein A
SSTI	Skin and soft tissue infection
ST	Sequence type
Strama	Swedish strategic programme against antibiotic resistance
Svarm	Swedish antibiotic resistance monitoring program
TB	Tuberculosis
UTI	Urinary tract infection
VRE	Vancomycin resistant enterococci
XDR	Extreme drug resistance (used for *Mycobacterium tuberculosis*)

Consumption of antimicrobials

Total consumption of antibiotics in humans

In 2014, the total consumption of antibiotics (J01 excl. methenamine) in Sweden (outpatient care and hospital care) decreased by 4% compared with 2013 (13.4 to 12.8 DDD per 1 000 inhabitants and day). The overall consumption has decreased by 11% since 2000, from 14.5 to 12.8 DDD per 1 000 inhabitants and day, Table 1.1.

Eighty-seven percent of all antibiotic sales in Sweden 2014 were sold on prescriptions in outpatient care as indicated in Figure 1.1. This proportion vary within the country, from 90% in Halland County to 83% in Kronoberg County.

Even though the majority of all antibiotics is prescribed in outpatient care, data from the Swedish Association of Local Authorities and Regions point prevalence survey in the spring of 2014, indicated that 35.3% of all inpatients were treated with an antibiotic on a specific day, this figure exclude patients in psychiatric care (the Swedish Association of Local Authorities and Regions, 2014).

Beta-lactamase sensitive penicillins and tetracyclines were the two most used antibiotic classes in Sweden during 2014, Figure 1.2.

TABLE 1.1. Consumption of antibiotics in outpatient care (sales on prescriptions) and in hospital care (sales on requisition including hospitals and parts of nursing homes) in Sweden, 2000-2014, DDD/1 000 inhabitants and day.

		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
J01 exclusive J01XX05	Total	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	12.8
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	11.2
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	1.60
J01XX05	Total	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	1.22
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	1.20
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	0.02
J01	Total	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	14.1
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	12.4
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	1.62

FIGURE 1.1. Consumption of antibiotics (J01 excl. methenamine) in outpatient care (sales on prescriptions) and in hospital care (sales on requisition including hospitals and parts of nursing homes) per county, 2014, DDD/1 000 inhabitants and day.

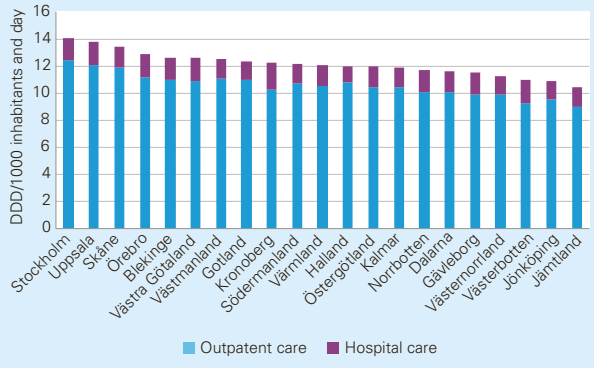
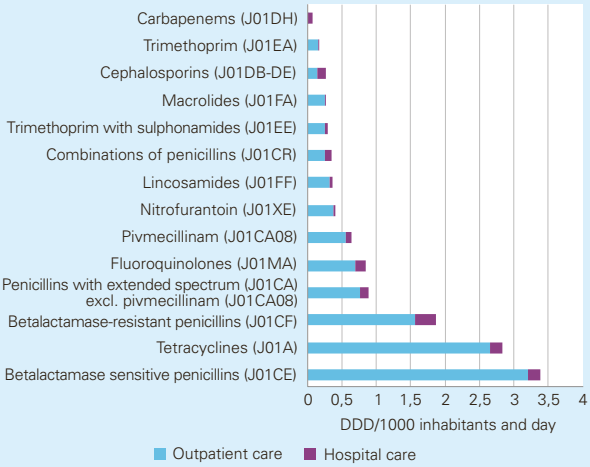


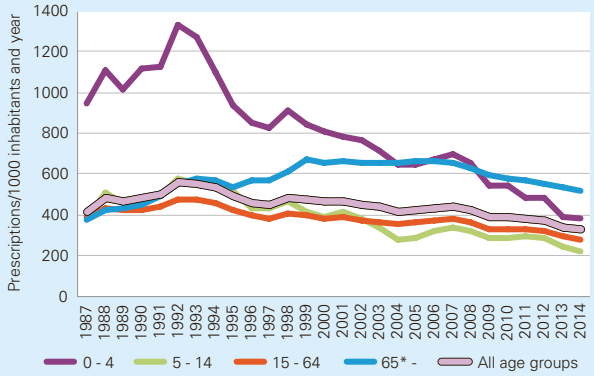
FIGURE 1.2. Antibiotics (ATC-5) in outpatient care (sales on prescriptions) and hospital care (sales on requisition including hospitals and parts of nursing homes) in 2014, DDD/1 000 inhabitants and day.



Antibiotics in outpatient care

Note that the statistics for outpatient care reported in Swedres-Svarm includes all sales of antibiotics on prescriptions, both from healthcare centers as well as prescriptions from hospital care.

FIGURE 1.3. The sales of antibiotics for systemic use in out-patient care (sales on prescriptions) 1987- 2014, prescriptions/1 000 inhabitants and year, both sexes, different age groups. The sales in 2014 decreased in all age groups.



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

Sales of antibiotics in outpatient care has continued to decrease (4%) during 2014, from 343 in 2013 to 328 prescriptions per 1 000 inhabitants and year. The decrease in 2014 was seen in all age groups and is most evident in the age group 5-14 years (8%), Figure 1.3.

Since 1992, the total sales of antibiotics on prescriptions has decreased by 41%. The greatest decrease during these years has been in the 0-4 years age group, where sales decreased by 71%, from 1328 in 1992 to 328 prescriptions per 1 000 inhabitants and year in 2014.

The age group 65 years and older had the highest use of antibiotics in Sweden, as measured by prescriptions per 1 000 inhabitants and year, Figure 1.3. As mentioned in the chapter "Guidance for readers", some of the antibiotic use among elderly people is not included in the statistics for outpatient care and possible underestimate in the age group 65 years and older cannot be ruled out.

The decrease in antibiotics sales in outpatient care during 2014 encompasses all but nitrofurantoin (J01XE), penicillins with enzyme inhibitor (J01CR), trimethoprim with sulphonamides (J01EE), macrolides (J01FA) and pivmecillinam (J01CA08), Figure 1.4.

Beta-lactamase sensitive penicillins (J01CE) and tetracyclines (J01AA) were the most commonly sold antibiotics in 2014, Figure 1.4 and Table 1.2. In 2014, the sales of beta-lactamase sensitive penicillins decreased by 8% and tetracyclines by 10% compared with 2013. Doxycycline (J01AA02) is the most frequently sold tetracycline and represents 72% of the sales in this group as measured by prescriptions per 1 000 inhabitants and year.

Trimethoprim (J01EA) is the antibiotic group with the proportionally greatest decrease during 2014 compared with 2013 (13%), Figure 1.4. Trimethoprim is mostly used to treat lower urinary tract infections. The decrease in sales of trimethoprim is seen in both sexes in the same amount (13% in both sexes).

In summary, a great decrease in the sales are seen in most of the antibiotic groups during 2014, Figure 1.4 and Table 1.2. Possible explanations for the change in the sales during 2014 will be discussed in following chapters.

FIGURE 1.4. Sales of antibiotics in outpatient care (includes sales on prescriptions) 2000-2014, prescriptions/1 000 inhabitants and year, both sexes, all ages. The data are sorted according to ATC codes.

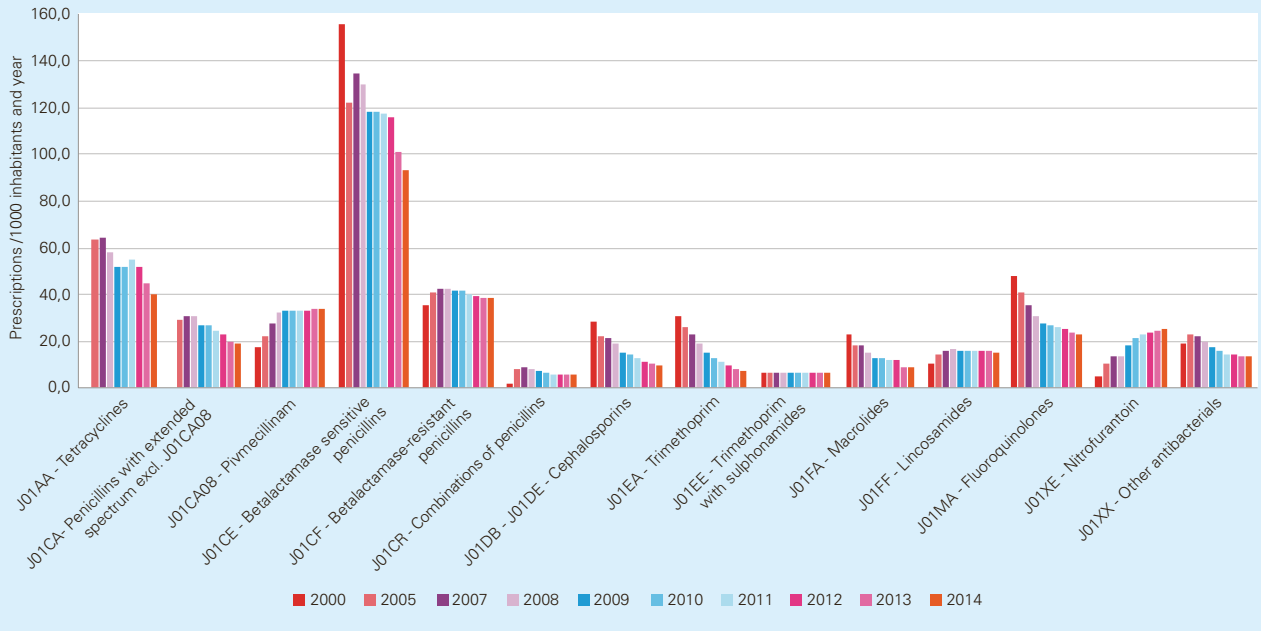
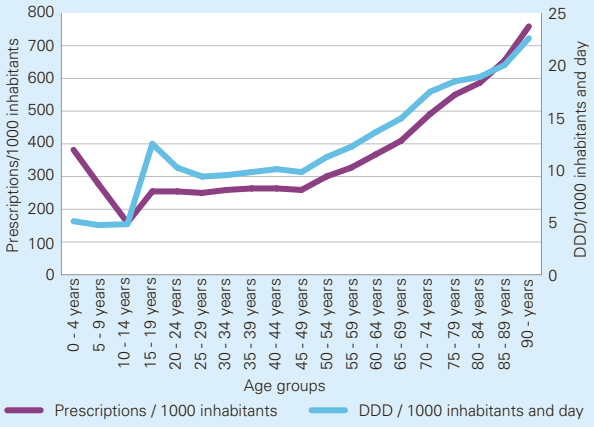


FIGURE 1.5. Sales of antibiotics (J01 excl. methenamine) in outpatient care (sales on prescriptions) in different age groups. Measured by both prescriptions/1 000 inhabitants and year and as DDD/1 000 inhabitants and day, in 2014.



Gender differences

Out of all antibiotic prescribed in Sweden during 2014, 60% were prescribed to females and 40% to males. This proportion has almost been constant over time and the decrease in antibiotic sales during the last years has been seen in both sexes equally. During 2014, the antibiotic sales decreased by 4% in men and 3% in women. The greatest differences between genders occurred in the age group 20-39 years were 65-70% of the total antibiotic sales were to women. In this age group the main differences is among antibiotics commonly used to treat urinary tract infections (UTI) which are predominant sold to women. Read more about gender differences in antibiotic sales in SWEDRES 2011 (Swedres-Svarm 2011).

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

In different age groups

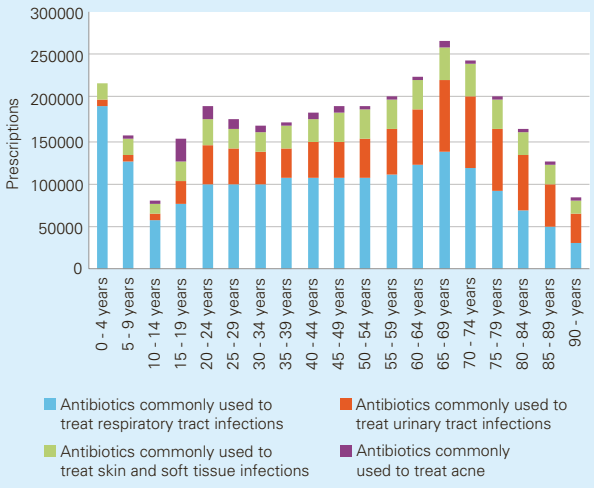
The antibiotic use is greatest in the age groups 65 years and older, both as measured by prescriptions/1 000 inhabitants and years and by DDD/1 000 inhabitants and day, Figure 1.5. However, even though the antibiotic use is high among children and elderly, other age groups represent a significant share of the total antibiotic sales, Figure 1.6.

Figures 1.6 and 1.7 illustrate the sales of different antibiotics in different age groups. In children, antibiotics commonly used to treat respiratory tract infections (RTI) are the most frequently prescribed antibiotics and represents 90% of the total antibiotic sales. In the older age groups antibiotic commonly used to treat UTI are as common as antibiotics commonly used to treat RTI. 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 1 000 inhabitants and day.

Antibiotics commonly used to treat treat respiratory tract infections

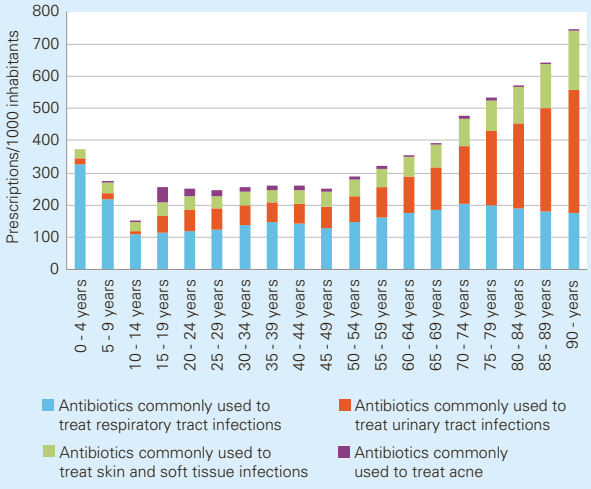
Antibiotics commonly used to treat respiratory tract infections (RTI) are overall the most frequently prescribed antibiotics in Sweden. Among these substances we also find the greatest decrease in sales during 2014 (7%), as well as over time in terms of number of prescriptions per 1 000 inhabitants and year, from 294 in 2000 to 166 in 2014.

FIGURE 1.6. 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 2014.



*Excluding packages containing more than 50 tablets.
** Including packages containing more than 50 tablets.

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/1 000 inhabitants in 2014.



*Excluding packages containing more than 50 tablets.
** Including 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	2014	2007	2008	2009	2010	2011	2012	2013	2014	2007	2008	2009	2010	2011	2012	2013	2014
Tetracyclines (J01AA)																								
0-6	0.00	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	0.0	0.1	0.0	0.0	0.0
7-19	3.23	3.25	3.31	3.40	3.48	3.29	3.06	2.82	33.9	32.0	31.6	32.5	35.1	31.2	27.6	25.1	21.3	19.5	19.2	20.1	22.9	19.6	16.8	15.5
20-64	3.77	3.56	3.30	3.35	3.54	3.43	3.10	2.92	71.9	64.5	56.2	56.3	60.2	56.5	47.7	43.1	56.3	50.3	43.6	43.8	47.2	43.8	36.4	32.9
65-79	4.21	3.99	3.64	3.60	3.78	3.75	3.36	3.06	98.8	90.6	79.9	78.0	81.1	80.0	68.9	60.4	75.4	68.8	61.2	60.1	62.1	61.3	52.5	46.2
80-	2.93	2.77	2.43	2.32	2.35	2.41	2.15	1.97	77.8	71.7	62.2	58.6	58.8	59.8	52.5	45.7	62.1	57.1	49.7	46.8	47.2	47.7	41.9	36.3
All age groups	3.44	3.28	3.08	3.11	3.25	3.15	2.85	2.66	64.3	58.3	51.7	51.6	54.7	52.0	44.4	39.8	49.0	44.1	38.8	38.9	41.7	39.2	33.1	29.8
Penicillins with extended spectrum (J01CA) excl. Pivmecillinam (J01CA08)																								
0-6	1.74	1.70	1.52	1.62	1.35	1.32	1.07	1.08	95.2	90.8	72.7	73.3	59.1	54.9	43.8	43.7	72.5	69.0	56.5	57.4	45.3	42.1	33.6	33.5
7-19	0.46	0.43	0.39	0.43	0.43	0.37	0.32	0.31	14.5	13.6	11.8	12.4	12.0	10.1	8.5	8.2	12.7	11.7	10.1	10.6	10.1	8.3	6.9	6.7
20-64	0.84	0.82	0.72	0.73	0.69	0.64	0.59	0.56	21.2	20.6	18.2	18.0	16.9	15.4	13.9	13.2	18.1	17.4	15.4	15.3	14.1	12.6	11.2	10.5
65-79	1.74	1.75	1.67	1.62	1.59	1.55	1.50	1.44	45.6	45.0	41.7	40.2	38.7	37.0	34.3	32.4	36.5	35.8	32.8	31.9	30.6	29.2	26.8	25.2
80-	1.79	1.82	1.76	1.74	1.75	1.77	1.73	1.71	46.8	46.5	44.0	42.1	41.0	39.7	37.7	36.8	38.0	37.9	35.4	34.1	33.2	32.3	30.4	29.4
All age groups	1.02	1.01	0.93	0.94	0.89	0.85	0.79	0.76	31.0	30.5	26.9	26.9	24.4	22.7	20.1	19.3	24.7	23.9	21.1	21.1	19.3	17.7	15.6	15.0
Pivmecillinam (J01CA08)																								
0-6	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.5	0.7	0.8	1.1	1.0	1.0	1.0	1.0	0.5	0.6	0.8	1.0	1.0	0.9	0.9	1.0
7-19	0.19	0.24	0.24	0.24	0.22	0.21	0.20	0.20	12.4	15.5	16.1	15.9	15.7	14.4	13.8	13.4	10.9	13.5	13.9	13.9	13.5	12.5	12.0	11.7
20-64	0.38	0.45	0.45	0.46	0.45	0.44	0.46	0.48	23.0	27.8	28.2	28.6	29.2	28.7	29.5	29.8	19.6	23.2	23.6	24.0	24.3	23.8	24.3	24.6
65-79	0.87	0.98	0.98	0.97	0.95	0.93	0.98	1.00	50.6	57.7	57.9	57.5	58.7	57.3	59.3	59.5	39.4	44.1	43.7	43.3	44.0	42.8	44.0	44.2
80-	1.84	1.94	1.92	1.90	1.79	1.75	1.83	1.92	109.3	116.6	115.8	115.0	112.6	109.3	112.3	114.7	81.9	85.5	83.9	83.1	81.4	78.4	80.5	82.1
All age groups	0.46	0.53	0.54	0.53	0.52	0.51	0.53	0.55	27.6	32.2	32.8	33.0	33.5	32.8	33.7	34.0	22.5	25.8	26.0	26.2	26.4	25.7	26.3	26.5
Beta-lactamase sensitive penicillins (J01CE)																								
0-6	4.03	4.13	3.56	3.71	3.52	3.78	3.07	2.82	350.7	343.7	287.4	290.6	271.1	285.9	226.3	211.5	251.3	244.4	211.8	218.7	198.8	205.6	169.8	159.2
7-19	3.68	3.63	3.46	3.52	3.61	3.47	2.92	2.66	142.5	135.0	123.3	124.6	127.5	124.1	103.6	94.0	116.3	109.6	100.9	102.1	103.5	99.1	83.9	75.7
20-64	4.53	4.43	4.05	3.99	4.09	3.95	3.55	3.24	113.0	108.5	98.2	96.8	98.6	95.1	84.8	77.6	95.5	91.6	84.3	83.4	85.0	81.4	72.7	66.2
65-79	4.42	4.40	4.16	4.01	4.18	3.96	3.86	3.58	106.0	104.1	97.8	94.5	98.4	93.9	89.9	83.4	89.0	87.4	83.2	81.0	84.4	80.3	76.4	70.4
80-	3.36	3.50	3.38	3.29	3.33	3.34	3.24	3.07	84.2	85.7	81.7	79.5	80.4	81.0	78.3	73.9	72.3	72.7	69.9	68.3	69.5	69.6	67.4	63.3
All age groups	4.30	4.25	3.96	3.93	3.99	3.88	3.49	3.21	134.3	130.0	118.6	118.4	117.7	115.7	101.1	93.1	108.8	104.9	96.2	96.1	96.2	93.5	82.7	75.8
Beta-lactamase resistant penicillins (J01CF)																								
0-6	0.33	0.33	0.31	0.30	0.28	0.29	0.26	0.26	32.9	32.8	30.8	29.4	28.0	29.0	26.1	26.2	25.9	25.6	24.3	23.4	22.0	22.9	20.4	20.6
7-19	0.69	0.80	0.79	0.77	0.76	0.77	0.78	0.77	31.9	31.9	31.2	31.0	30.0	28.5	27.8	27.4	26.2	26.0	25.4	25.5	24.6	23.1	22.6	22.2
20-64	1.04	1.22	1.20	1.18	1.19	1.27	1.31	1.30	34.9	34.8	34.0	34.2	33.9	33.0	32.2	32.1	27.6	27.4	26.9	27.4	27.0	26.3	25.6	25.5
65-79	2.24	2.63	2.55	2.52	2.51	2.67	2.77	2.74	61.4	62.5	60.8	60.0	58.5	58.1	57.1	56.2	40.4	40.9	39.9	40.3	39.5	38.6	38.1	37.3
80-	4.40	4.99	4.92	4.92	4.69	4.85	5.11	5.18	122.6	122.1	119.4	113.2	106.2	103.2	103.2	102.6	68.0	67.1	65.5	66.8	64.8	63.2	63.4	62.8
All age groups	1.25	1.46	1.45	1.43	1.42	1.51	1.56	1.56	42.2	42.3	41.7	41.3	40.3	39.5	38.7	38.5	30.9	30.8	30.2	30.6	29.9	29.2	28.5	28.2
Combinations of penicillins (J01CR)																								
0-6	0.75	0.67	0.52	0.39	0.28	0.26	0.21	0.21	52.7	46.4	33.7	25.3	17.8	16.7	13.9	13.5	36.2	31.9	24.0	17.9	12.3	11.1	8.8	8.3
7-19	0.21	0.20	0.18	0.17	0.16	0.14	0.14	0.14	6.4	6.0	5.4	4.9	4.7	4.0	3.9	4.0	4.9	4.5	4.1	3.8	3.6	3.0	2.8	2.7
20-64	0.21	0.22	0.21	0.22	0.22	0.22	0.22	0.24	4.5	4.7	4.4	4.7	4.7	4.7	4.7	5.0	4.0	4.1	3.8	4.0	4.0	3.9	3.9	4.0
65-79	0.23	0.27	0.29	0.31	0.32	0.34	0.34	0.37	4.8	5.5	5.7	6.1	6.3	6.7	6.8	7.5	3.9	4.3	4.6	4.8	5.0	5.1	5.2	5.6
80-	0.17	0.20	0.22	0.24	0.27	0.29	0.32	0.35	3.4	4.1	4.3	4.8	5.2	5.8	6.2	6.7	2.7	3.2	3.4	3.9	4.1	4.3	4.6	5.0
All age groups	0.26	0.26	0.24	0.24	0.24	0.23	0.23	0.25	8.5	8.3	7.2	6.7	6.1	6.0	5.8	6.1	6.5	6.3	5.5	5.2	4.7	4.6	4.4	4.5
Cephalosporins (J01DB-DE)																								
0-6	0.52	0.46	0.36	0.34	0.32	0.32	0.27	0.27	49.7	43.6	34.1	33.2	31.6	29.2	25.7	26.9	39.0	34.9	28.2	27.7	25.6	24.1	21.2	22.2
7-19	0.29	0.26	0.21	0.20	0.18	0.16	0.15	0.13	20.2	18.4	14.9	13.8	12.8	11.6	10.4	9.3	17.1	15.6	12.7	11.6	10.7	9.6	8.5	7.6
20-64	0.29	0.26	0.20	0.18	0.15	0.14	0.12	0.11	16.4	14.6	11.5	10.3	9.2	8.2	7.3	6.7	13.8	12.3	9.7	8.7	7.7	6.8	6.0	5.5
65-79	0.43	0.39	0.31	0.29	0.23	0.20	0.19	0.17	21.7	19.1	14.9	13.9	12.6	11.0	10.4	9.4	17.0	14.8	11.5	10.6	9.5	8.2	7.8	7.0
80-	0.65	0.54	0.41	0.38	0.34	0.32	0.31	0.29	35.4	29.4	22.7	21.6	19.9	18.5	17.6	17.0	27.5	23.0	17.9	16.6	15.5	14.2	13.4	13.1
All age groups	0.35	0.31	0.25	0.23	0.20	0.18	0.16	0.14	21.5	19.0	15.2	14.1	12.8	11.5	10.4	9.8	17.4	15.4	12.3	11.4	10.3	9.2	8.3	7.8

Age groups (years)	DDD/1000 and day								Prescriptions/1000 and year								User/1000 and year							
	2007	2008	2009	2010	2011	2012	2013	2014	2007	2008	2009	2010	2011	2012	2013	2014	2007	2008	2009	2010	2011	2012	2013	2014
Trimethoprim (J01EA)																								
0-6	0.12	0.10	0.09	0.09	0.08	0.08	0.07	0.07	15.4	14.0	12.6	12.2	11.3	11.0	10.0	9.2	10.8	10.1	9.7	9.5	8.8	8.4	7.6	6.9
7-19	0.18	0.15	0.11	0.10	0.08	0.06	0.05	0.04	10.9	8.9	7.0	5.9	4.8	3.9	3.3	2.8	9.4	7.7	6.0	5.1	4.1	3.3	2.7	2.2
20-64	0.31	0.26	0.20	0.17	0.15	0.13	0.11	0.10	15.6	12.7	9.4	7.8	6.5	5.4	4.5	3.9	13.0	10.5	7.7	6.4	5.2	4.3	3.5	3.0
65-79	0.90	0.76	0.61	0.57	0.50	0.43	0.39	0.34	42.0	34.7	27.5	24.3	20.9	17.7	15.5	13.5	30.9	25.1	19.6	17.3	14.6	12.3	10.7	9.2
80-	1.91	1.58	1.30	1.23	1.08	0.94	0.83	0.71	104.5	84.7	69.6	63.6	56.4	49.1	41.5	35.5	61.7	49.3	38.6	34.5	29.4	24.6	21.4	18.8
All age groups	0.43	0.36	0.29	0.26	0.23	0.20	0.17	0.15	22.8	18.8	14.9	13.1	11.2	9.7	8.3	7.2	17.0	13.9	10.7	9.3	7.9	6.7	5.7	4.9
Trimethoprim with sulphonamides (J01EE)																								
0-6	0.16	0.14	0.13	0.12	0.10	0.10	0.09	0.09	18.8	16.7	14.8	13.7	11.8	11.8	10.2	9.6	13.9	12.4	10.7	10.0	8.2	7.6	6.2	5.7
7-19	0.10	0.10	0.11	0.10	0.10	0.10	0.10	0.10	4.1	4.2	4.3	4.0	4.1	3.9	3.8	3.8	2.6	2.6	2.6	2.4	2.5	2.2	2.1	2.0
20-64	0.16	0.17	0.18	0.19	0.19	0.19	0.20	0.20	3.5	3.6	3.8	4.0	4.2	4.3	4.6	4.8	2.3	2.4	2.5	2.6	2.7	2.6	2.6	2.7
65-79	0.42	0.48	0.52	0.52	0.54	0.54	0.56	0.57	10.2	11.3	11.7	12.1	12.2	12.2	12.4	13.0	7.1	7.9	8.2	8.5	8.5	8.3	8.4	8.6
80-	0.39	0.43	0.43	0.46	0.46	0.47	0.51	0.51	12.2	13.1	12.5	13.1	12.5	12.6	13.0	13.2	9.1	10.0	9.7	10.1	9.8	9.5	9.7	9.9
All age groups	0.20	0.21	0.22	0.23	0.24	0.24	0.25	0.25	6.4	6.5	6.6	6.8	6.7	6.6	6.7	6.8	4.2	4.3	4.3	4.3	4.2	4.1	4.0	4.0
Macrolides (J01FA)																								
0-6	0.85	0.68	0.51	0.53	0.51	0.39	0.26	0.26	38.1	29.9	22.4	23.1	22.2	18.1	12.1	12.4	31.2	24.0	18.1	18.7	18.3	14.8	9.5	9.7
7-19	0.51	0.38	0.31	0.33	0.40	0.32	0.24	0.22	21.7	15.4	12.7	13.8	15.4	13.2	8.3	8.6	17.0	11.7	9.7	10.7	12.1	10.0	5.8	6.1
20-64	0.36	0.33	0.28	0.28	0.28	0.30	0.27	0.24	16.5	14.3	12.0	11.9	10.4	11.4	8.7	9.1	13.1	11.3	9.5	9.5	8.3	8.8	6.4	6.8
65-79	0.35	0.34	0.32	0.30	0.32	0.32	0.33	0.30	13.9	12.4	11.1	10.3	9.3	10.4	8.7	9.0	10.6	9.3	8.2	7.6	6.7	7.4	5.6	5.9
80-	0.24	0.23	0.23	0.21	0.20	0.19	0.20	0.19	8.7	8.4	7.4	6.9	6.0	6.4	5.7	5.8	6.8	6.4	5.5	5.3	4.4	4.8	4.0	4.0
All age groups	0.42	0.36	0.31	0.31	0.32	0.31	0.27	0.25	18.4	15.3	12.8	12.8	11.9	11.9	8.9	9.2	14.5	11.9	9.9	10.0	9.3	9.1	6.3	6.7
Lincosamides (J01FF)																								
0-6	0.03	0.02	0.02	0.02	0.02	0.03	0.02	0.02	5.3	5.0	5.2	5.0	5.3	6.5	5.0	5.1	4.0	3.8	3.8	3.9	4.0	4.9	3.7	3.6
7-19	0.12	0.12	0.12	0.12	0.12	0.12	0.11	0.11	8.3	8.4	8.2	8.1	8.0	7.9	7.4	7.3	6.7	6.8	6.6	6.5	6.5	6.5	5.9	5.7
20-64	0.32	0.32	0.31	0.31	0.32	0.32	0.31	0.31	16.3	16.3	15.7	15.6	16.0	15.8	15.4	14.7	12.5	12.7	12.4	12.4	12.7	12.5	12.2	11.5
65-79	0.59	0.61	0.61	0.59	0.59	0.58	0.58	0.56	25.8	26.2	25.4	25.0	24.6	24.2	24.3	22.9	16.9	17.3	17.1	16.9	16.8	16.8	16.8	15.7
80-	0.74	0.76	0.72	0.73	0.71	0.70	0.71	0.73	32.8	33.2	31.0	31.7	30.8	30.2	29.9	29.9	18.7	19.3	18.8	19.2	19.0	18.7	18.9	18.9
All age groups	0.32	0.33	0.32	0.32	0.33	0.32	0.32	0.32	16.3	16.4	15.9	15.9	16.0	16.0	15.6	14.9	11.8	12.0	11.7	11.7	11.9	11.9	11.6	11.0
Fluoroquinolones (J01MA)																								
0-6	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.8	0.7	0.7	0.8	0.7	0.7	0.9	0.8	0.4	0.4	0.4	0.5	0.4	0.5	0.5	0.4
7-19	0.13	0.12	0.12	0.12	0.12	0.11	0.11	0.10	5.5	4.8	4.3	4.3	4.3	4.0	3.6	3.4	4.4	3.8	3.5	3.5	3.4	3.2	2.9	2.7
20-64	0.86	0.78	0.72	0.68	0.68	0.65	0.62	0.59	31.4	27.0	23.8	22.9	21.9	20.8	19.7	18.9	22.6	19.5	17.3	16.7	15.9	15.1	14.4	13.8
65-79	2.10	1.90	1.84	1.79	1.77	1.73	1.64	1.61	81.4	70.8	65.6	63.8	61.1	58.8	55.7	54.8	55.1	48.3	44.9	43.9	41.8	40.4	38.6	37.6
80-	2.74	2.41	2.25	2.26	2.18	2.08	2.00	1.95	119.7	98.5	88.2	87.3	82.0	77.6	73.7	72.5	81.6	68.4	61.4	60.9	57.8	54.9	52.6	51.4
All age groups	0.93	0.84	0.80	0.78	0.77	0.75	0.71	0.69	35.7	30.6	27.8	27.1	26.1	25.0	23.8	23.3	25.0	21.7	19.6	19.2	18.4	17.7	16.9	16.4
Nitrofurantoin (J01XE)																								
0-6	0.07	0.06	0.06	0.06	0.06	0.05	0.05	0.06	6.3	6.2	6.9	7.2	7.3	7.0	7.1	7.2	4.3	4.3	5.0	5.1	5.1	5.0	5.1	5.2
7-19	0.14	0.13	0.15	0.14	0.14	0.13	0.13	0.13	6.7	6.6	9.2	10.6	10.8	10.4	10.1	9.8	5.7	5.7	7.9	9.0	9.2	8.9	8.6	8.3
20-64	0.25	0.24	0.27	0.27	0.28	0.29	0.30	0.31	11.3	11.1	15.3	17.8	19.1	19.8	20.5	21.1	9.3	9.1	12.5	14.6	15.6	16.1	16.6	17.0
65-79	0.53	0.55	0.62	0.61	0.64	0.67	0.72	0.74	22.6	24.2	32.6	37.3	39.9	41.5	44.0	44.9	16.9	18.1	24.0	27.5	29.3	30.3	31.9	32.5
80-	0.97	0.95	1.05	1.06	1.12	1.15	1.23	1.30	46.7	47.7	61.7	70.6	76.0	77.4	80.6	84.0	30.4	31.3	40.3	45.6	47.8	49.0	51.6	53.8
All age groups	0.30	0.29	0.32	0.32	0.34	0.35	0.37	0.38	13.5	13.6	18.5	21.3	22.8	23.5	24.5	25.1	10.4	10.5	14.1	16.3	17.3	17.8	18.4	18.9
All agents (J01 excl. Methenamine)																								
0-6	8.61	8.32	7.11	7.21	6.55	6.66	5.43	5.15	666.8	630.8	522.4	515.0	467.6	471.9	382.4	367.2	358.6	342.4	299.5	300.7	273.3	274.4	232.0	222.7
7-19	9.95	9.83	9.52	9.65	9.83	9.27	8.33	7.75	319.8	301.4	280.8	282.5	286.1	268.0	232.7	217.8	206.5	194.6	182.5	183.8	185.5	173.2	152.1	141.8
20-64	13.34	13.09	12.14	12.03	12.25	11.98	11.19	10.62	380.4	361.7	331.8	329.9	331.7	320.0	294.4	280.8	234.9	224.7	209.1	207.8	208.9	200.7	184.9	175.8
65-79	19.13	19.16	18.23	17.78	18.00	17.76	17.28	16.55	587.3	566.6	535.0	525.3	524.7	510.7	489.2	468.7	306.9	297.5	282.9	278.6	278.9	270.6	258.1	246.5
80-	22.25	22.24	21.13	20.85	20.38	20.34	20.22	19.95	807.9	765.1	723.5	710.9	690.7	673.0	654.2	640.3	373.0	357.7	340.2	336.1	330.9	323.2	314.7	307.8
All age groups	13.70	13.53	12.76	12.68	12.76	12.51	11.74	11.20	443.8	423.1	391.9	390.3	385.3	373.9	342.7	328.0	255.9	245.1	228.3	227.5	226.3	218.7	201.0	191.7

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 1.8. The sales of penicillin V decreased in all age groups during 2014 compared to 2013, 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, Figure 1.8. The sales pattern differ between age groups. In the age group 65 years and older, broader antibiotic substances doxycycline and amoxicillin are used to a greater extent, Figure 1.9.

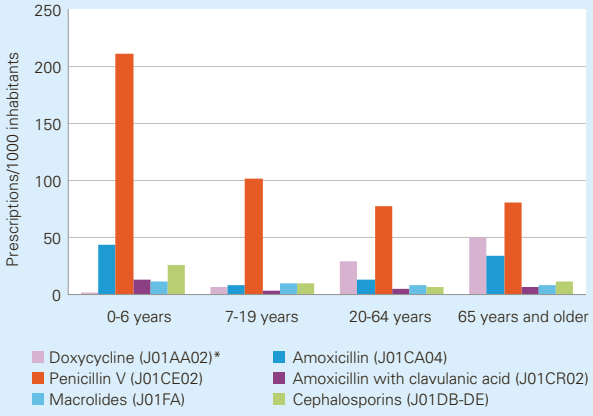
Even though the total sales of antibiotics commonly used to treat RTI decreased during 2014 the sales of macrolides and amoxicillin with clavulanic acid increased by 4 and 5% respectively, Figure 1.8. During spring 2013, the pharmacy ran out of macrolides in Sweden which may affect the statistics and partly explain the increase seen during 2014. The increased sales of amoxicillin with clavulanic acid might be a consequence of an increased number of urinary tract infections caused by ESBL producing bacteria, where amoxicillin with clavulanic acid could possibly be an oral treatment alternative (Public Health Agency of Sweden, 2014). In addition, amoxicillin with clavulanic acid has since 2013 been part of initial sensitivity testing against Enterobacteriaceae for patient with uncomplicated UTI. This might have affected the prescription rate of amoxicillin with clavulanic for this indication (RAF, 2013).

However, when analyzing the sales of antibiotics commonly used to treat RTI during 2014 compared with 2013 a noteworthy reduction exists throughout the year. The greatest decrease during 2014 was seen for doxycycline (packages smaller than 50 tablets) (10%) and penicillin V (8%). The decrease in sales of doxycycline seen during the last two years may indicate an improved compliance to national treatment recommendations (Medical Products Agency and Strama, 2008) where it is stated that acute bronchitis (including Mycoplasma pneuomoniae) should generally not be treated with antibiotics.

As cited in previous Swedres-Svarm, a new national recommendation for treatment of pharyngotonsillitis was published in 2012 (Medical Products Agency & Swedish Institute for Communicable Disease Control, 2012). Successful communication about treatment recommendations may be one contributed explanation for the decreased sales of antibiotics commonly used to treat RTI.

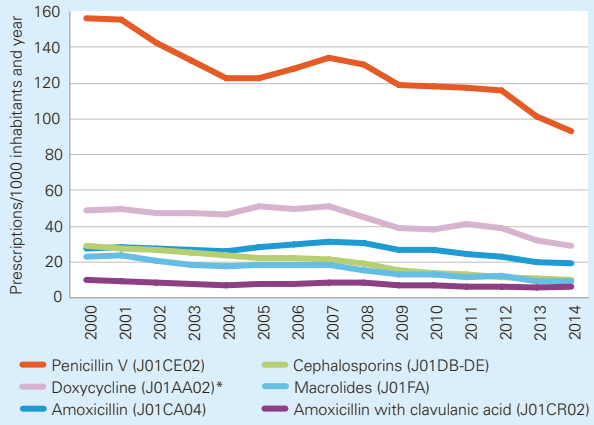
Furthermore, the ESAC-net quality indicator (ECDC; 2014) for seasonal variation shows less seasonal variation in the sales of antibiotics over the years in Sweden. This indicates a more rational antibiotic use and less misuse of antibiotics for cold or flu, Figure 1.10.

FIGURE 1.9. Sales of antibiotics commonly used to treat respiratory tract infections in outpatient care (sales on prescriptions), 2014, prescriptions/1 000 inhabitants and year, both sexes, different age groups.



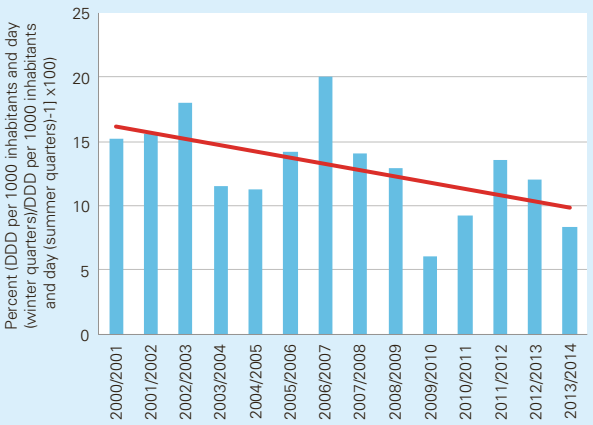
*Excludes packages containing more than 50 tablets

FIGURE 1.8. Sales of antibiotics commonly used to treat respiratory tract infections in outpatient care (sales on prescriptions), 2000-2014, prescriptions/1 000 inhabitants and year, both sexes, all ages.



*Excludes packages containing more than 50 tablets

FIGURE 1.10. ESAC quality indicator on seasonal variation of the total antibiotic consumption (J01 excl. methenamine) of a 12-month period starting in July and ending the following June, expressed as percentage. Total sales of antibiotic on prescription in Sweden 2000-2014.



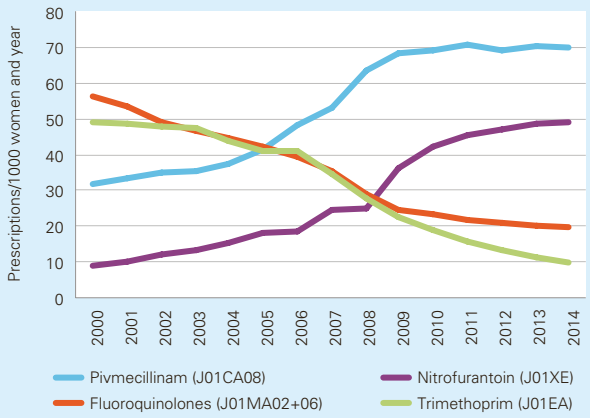
Antibiotics commonly used to treat urinary tract infections in women

National treatment recommendations for 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. In 2014, the total sales of antibiotics commonly used to treat UTI in women aged 18-79 years slightly decreased (1%) compared with 2013. However, the same positive trend as previously with increased use of the first-line drugs pivmecillinam and nitrofurantoin and reduced sales of trimethoprim (13%) and fluoroquinolones (2%) was also seen, Figure 1.11.

The total sales of these antibiotics have decreased slowly over the years; by 2% since 2000, as measured by prescriptions per 1 000 women and year. However, if measured by DDD per 1 000 women and day, the sales has decreased by 13% since 2000. This suggest shorter treatment duration for this condition with time, which is also according to recommendations.

Antibiotics commonly used to treat UTI is mostly prescribed to the age group 65 years and older, Figure 1.7. In this age group the total sales has decreased by 20% since 2000, as measured by prescriptions per 1 000 women and year. As mentioned in the chapter "Guidance for readers", some of the antibiotic use among elderly people is not included in the statistics and a possible under-estimation in the age group 65 years and older cannot be ruled out. Nevertheless, the great decrease in the age group 65 years and older indicates increased compliance to recommendations. Many elderly have asymptomatic bacteria in urine (ABU) and should not normally be treated with antibiotics (Medical Products Agency & STRAMA, 2007). Information and education at local and national level regarding treatment recommendation and ABU might be one explanation for the great decrease in sales over time in this age group. The same trend is seen in men, see below.

FIGURE 1.11. Sales of antibiotics commonly used to treat lower urinary tract infections in women (sales on prescriptions), 18-79 years, 2000-2014, prescriptions/1 000 women and year.



Antibiotics commonly used to treat urinary tract infections in men

The total sales of antibiotics commonly used to treat UTI in men 65 years and older has decreased by 27% since 2000. In 2014, however, the sales slightly increased (1%).

Because of increasing resistance in gram-negative bacteria, the use of fluoroquinolones has been questioned and nitrofurantoin and pivmecillinam may now be considered as first line antibiotics for treatment of symptomatic UTI without fever in men (Public Health Agency of Sweden, 2013).

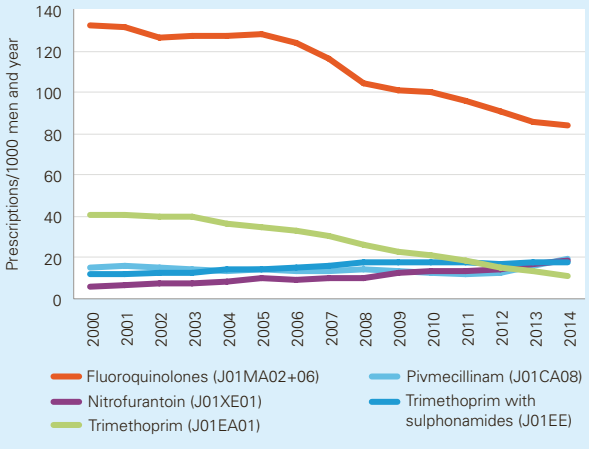
The sales of fluoroquinolones to men aged 65 years and older has decreased significantly since 2000 (37%), as measured by prescriptions per 1 000 men and year. The decrease continued in 2014 by 2% compared with 2013. During the last years, sales of pivmecillinam and nitrofurantoin have increased. In 2014, the sales of these two antibiotics increased by 20% and 12% respectively, as measured by prescriptions per 1 000 men and year, compared with 2013, Figure 1.12.

Antibiotic consumption in children

The total sales of antibiotics to children aged 0-6 years has decreased by 51% since 2000 (from 746 to 367 prescriptions per 1 000 children and year). Between 2013 to 2014, the sales decreased by 4%. A decrease was seen in 17 out of 21 counties. There are still great national variations in antibiotic sales to children 0-6 years, from 432 prescriptions per 1 000 children and year in Stockholm County to 200 in Jämtland County, Figure 1.13. The great variation between the counties may suggest antibiotic overuse in some counties. Even counties with the lowest antibiotic sales continued to decrease significantly during 2014, which also suggests antibiotic overuse in other counties.

The reduction in sales during 2014 includes the majority of the available antibiotic agents, Table 1.2. Measured by prescriptions, the greatest decrease 2014 was seen in the sales of penicillin V (15 prescriptions/1 000 children and year)

FIGURE 1.12. Sales of antibiotics commonly used to treat UTI in men 65 years and older 2000-2014, measured as prescriptions/1 000 men and year.



followed by trimethoprim (1 prescriptions/1 000 children and year), Figure 1.14.

Different kinds of penicillins are the most commonly prescribed antibiotics in this age group and penicillin V (J01CE02), amoxicillin (J01CA04) and flucloxacillin (J01CF05) represent 77% of the total sales in 2014, Table 1.2 and Figure 1.14.

The great decrease in antibiotic sales seen over time in children can be explained by a more appropriate antibiotic use in Sweden. 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 in young children.

In Sweden, the proportion of children (0-6 years) treated with at least one course of antibiotics was 22%, which is less than in 2013, Table 1.2. The proportion decreased in 18 out of 21 counties during 2014 and it ranges within the country, from 257 users per 1 000 children in Stockholm County to 130 users per 1 000 children in Jämtland County, Figure 1.15.

FIGURE 1.13. Sales of antibiotics (J01 excl. methenamine) on prescriptions to children 0-6 years, per county and in Sweden, prescriptions/1 000 children and year. The data are sorted according to the use in 2014. A decrease is seen in 17 out of 21 counties during 2014.

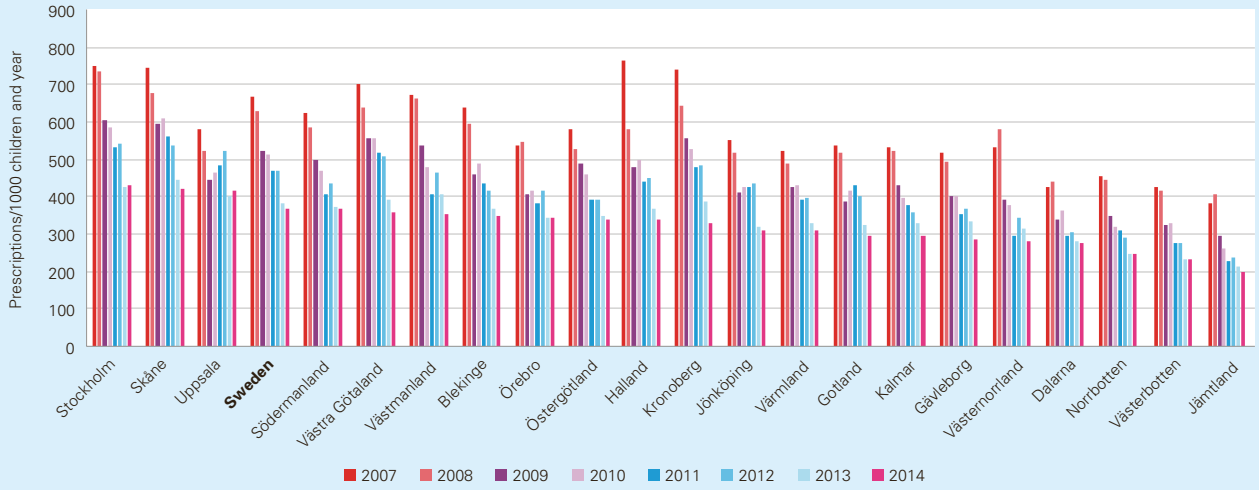


FIGURE 1.14. Sales of antibiotics in outpatient care to children 0-6 years, 2000-2014, prescriptions/1 000 inhabitants and year, both sexes. The data are sorted according to ATC codes.

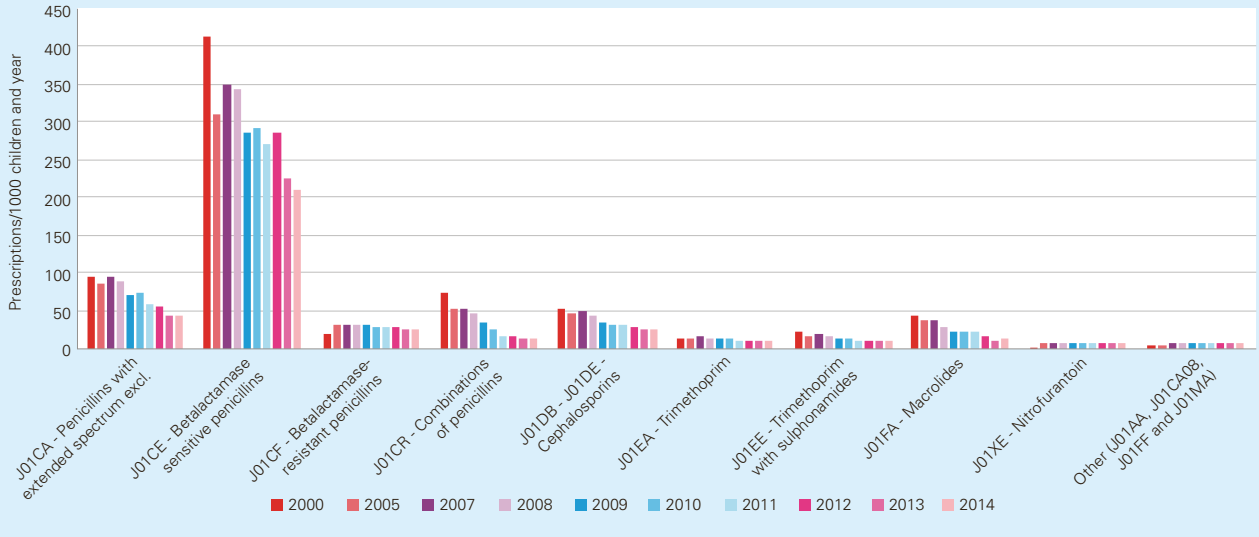


FIGURE 1.15. Proportion of children 0-6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2012-2014 (user/1 000 children and year).

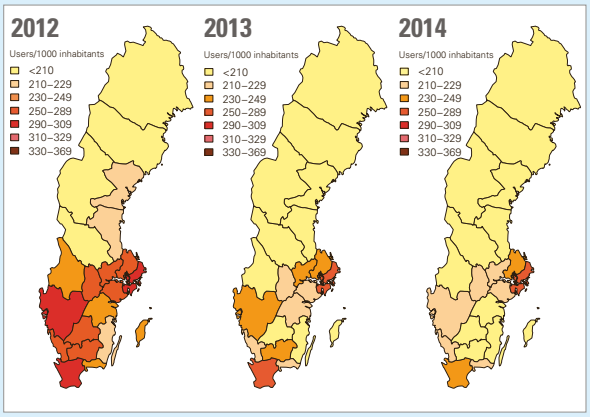
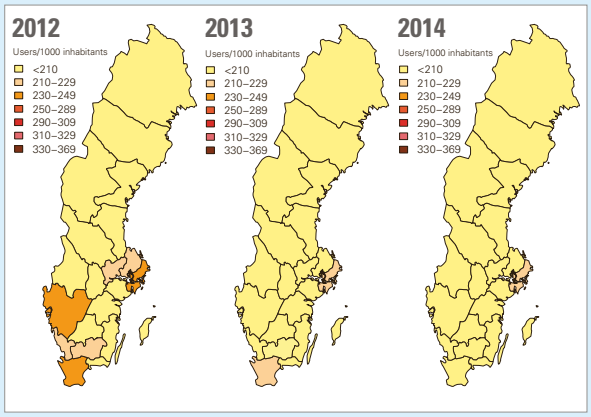


FIGURE 1.16. Proportion of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2012-2014 (user/1 000 inhabitants and year).



County data

In 2014, 19% of the Swedish population was treated with at least one course of antibiotics, which is marginally less than in 2013 where 20% was treated, Table 1.2. However, the proportion of people treated with antibiotics varies within Sweden, from 21% in Stockholm County to 15% 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 2014, Figure 1.16.

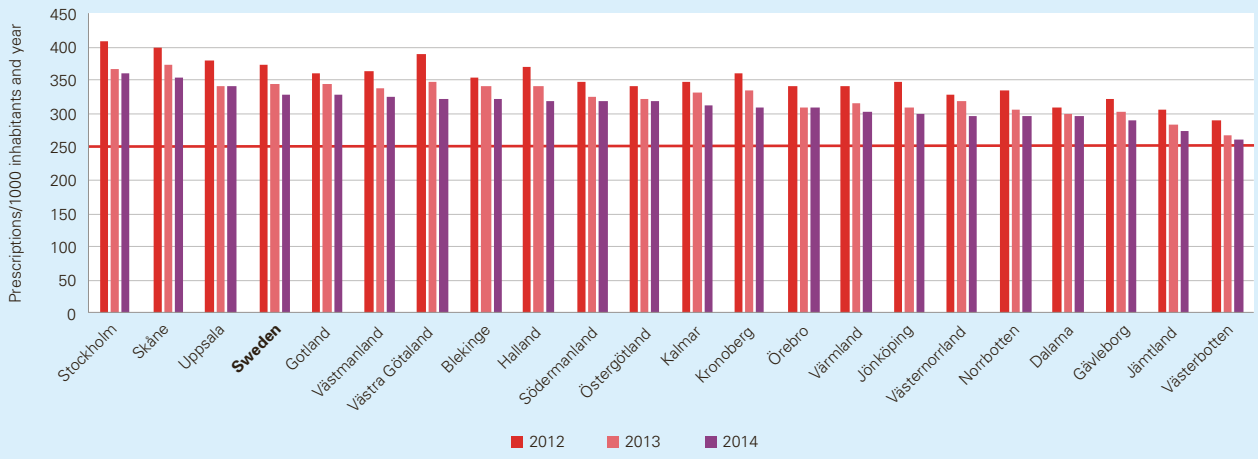
In 2014, the average sales of antibiotics in outpatient care measured as prescriptions per 1 000 inhabitants in Sweden was 328. To reach the Swedish long term target of 250 prescriptions per 1 000 inhabitants and year the antibiotic use in Sweden still must be reduced by 24%, Figure 1.17.

In 2014, a reduced number of prescriptions per 1 000 inhabitants was seen in all 21 counties, Figure 1.17. One reason for the great decrease in antibiotic sales in all counties in Sweden during the latest years might be the patient safety initiative, that started in 2011 and continued until the end of 2014. This is a governmental performance-based initiative partly focusing on optimizing the antibiotic use through financial incentives (Public Health Agency of Sweden, 2014). Reed more about the agreement and evaluation on antibiotic use in relation to the initiative in the chapter "National campaign for improved patient safety".

There are still great regional differences between different parts of Sweden and prescriptions per 1 000 inhabitants range from 359 in Stockholm County to 260 in Västerbotten County, Figure 1.17.

The great variation between counties is probably not explained by differences in morbidity (Hedin K, Andre M, et al. 2006), but more likely explained by overuse of antibiotics. Factors influencing antibiotic prescription at healthcare centers has been investigated in a recently published study, see results from the study in a report on the webpage of the

FIGURE 1.17. Sales of antibiotics in outpatient care 2012-2014, prescriptions/1 000 inhabitants and year. The red line indicates the Swedish long term target of 250 prescriptions/1 000 inhabitants and year. The data are sorted according to the sales in 2014.



Public Health Agency of Sweden (Public Helath Agency of Sweden, 2014). Factors that seems to positively affect antibiotic prescribing habits are for example; “time and forum for discussion about management and treatment of respiratory tract infections within and between professional groups”, “leadership and support to local opinion leaders” and “interprofessional collaboration”.

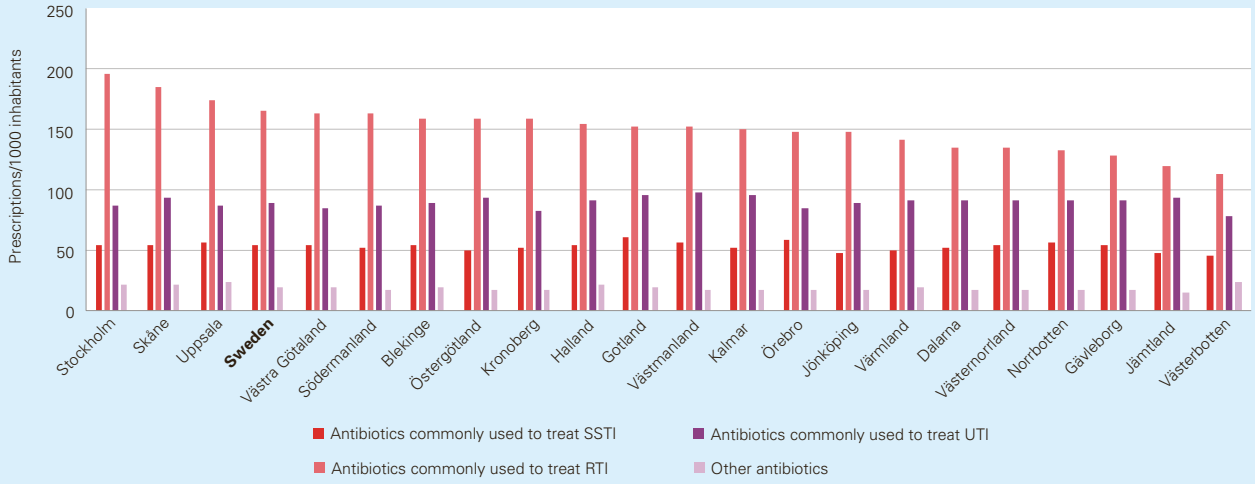
Earlier studies have shown overuse of antibiotics in RTI (Mölstad S, Andre M, et al. 2009, Neumark T et al. 2009). Notably, the greatest differences in the sales of antibiotics between counties relate to treatment of RTI, Figure 1.18. This supports the hypothesis of overuse.

When promoting appropriate use of antibiotics, it is of great importance to study and analyze the incidence of morbidity and complications, to ensure that these do not increase as a consequence of a more restricted use. The Public Health Agency of Sweden is regularly analyzing the incidence of known complications. Despite the great decrease in antibiotic sales to children over the last years, incidence of mastoiditis have not increased. Read more about this in Swedres-Svarm 2013 (Swedres-Svarm 2013).

As mentioned in earlier editions of Swedres-Svarm, Strama has proposed two qualitative targets for antibiotic prescribing in outpatient care:

1. At least 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).

FIGURE 1.18. Sales of antibiotics commonly used to treat RTI (J01AA02*, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), UTI (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), SSTI (J01FF01 and J01CF05) and other antibiotics in outpatient care 2014, per county, prescriptions/1 000 inhabitants. The data are sorted according to the county with the highest sales of antibiotics commonly used to treat RTI.



*Excluding packages containing more than 50 tablets.

FIGURE 1.19. Proportion penicillin V of antibiotics commonly used to treat respiratory tract infections in children 0-6 years, per county, 2013-2014. The red line indicates Strama´s goal at minimum 80% penicillin V.

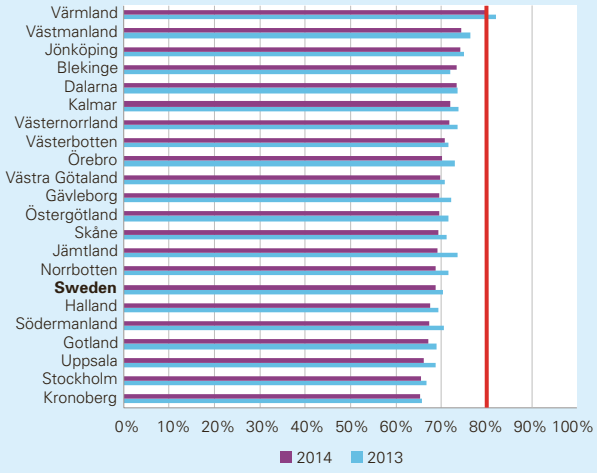
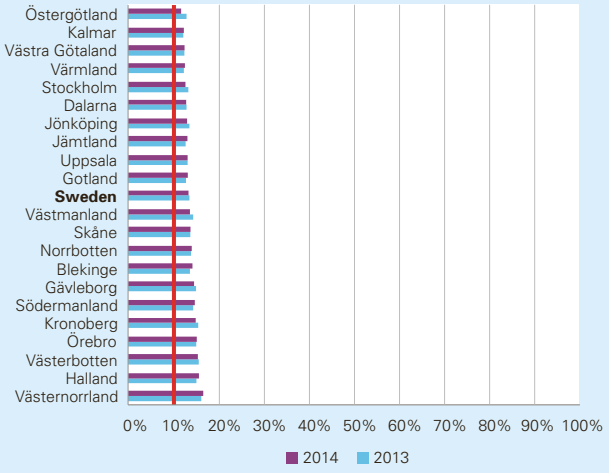


FIGURE 1.20. Proportion of fluoroquinolones of antibiotics commonly used to treat urinary tract infections in women 18-79 years, per county, 2013-2014. The red line indicates Strama´s goal of maximum 10% fluoroquinolones.



In 2014 the proportion of penicillin V was 69% on a national level, which is marginally less than in 2013. Värmland County had the greatest proportion, 80%, and Kronoberg County the lowest, 65%, Figure 1.19. In total, 20 out of 21 counties decreased this proportion in 2014 compared to 2013. The great decrease in use of penicillin V to children during the latest years, from 351 prescriptions/1 000 inhabitants and year in 2007 to 212 in 2014, needs to be considered when analyzing this indicator.

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 was 13% in 2014. Västernorrland had the highest proportion (16%), Figure 1.20.

When analyzing sales data excluding prescriptions from hospitals, the proportion of penicillin V to children was 75% in 2014 at a national level and the proportion of fluoroquinolones to women 18-79 years was 8%.

Antibiotics in dentistry

The sales of antibiotic prescribed by dentists decreased by 9% in 2014 compared with 2013, from 26.0 to 23.6 prescriptions per 1 000 inhabitants and year for J01 and metronidazole (P01AB01), see Figure 1.21. Penicillin V (J01CE02) is the most commonly prescribed antibiotic followed by amoxicillin (J01CA) and clindamycin (J01FFA01). These antibiotic substances represent 78%, 10% and 9% respectively of all antibiotics prescribed by dentists. However, the greatest decrease in 2014 was seen for amoxicillin (13%) and clindamycin (14%), measured as prescriptions per 1 000 inhabitants and year. Amoxicillin has decreased by 30% between 2012 and 2014, this might be cause of the new stricter treatment recommendations for the use of prophylaxis which was implemented in 2012. A big increase was seen for clindamycin between 2001 and 2011. Since 2012, the trend has reversed and the prescribing of clindamycin decreased each year hereafter.

Dentists account for approximately 7% of all antibiotics prescribed in outpatient care in Sweden. The proportion varies between 4% in some counties to 7% in some counties. The total sales of antibiotics (J01 and metronidazole), measured as prescriptions per 1 000 inhabitants and year, decreased in 18 out of 21 counties in 2014 compared with 2013. Like in outpatient care, there are big differences between the counties. Dentists in Stockholm County prescribe the most (29 prescriptions/1 000 inhabitants) and Västerbotten County the least (14 prescriptions/ 1 000 inhabitants for 2014), see Figure 1.22.

FIGURE 1.21. Sales of antibiotics prescribed by dentists in outpatient care, 2009-2014.

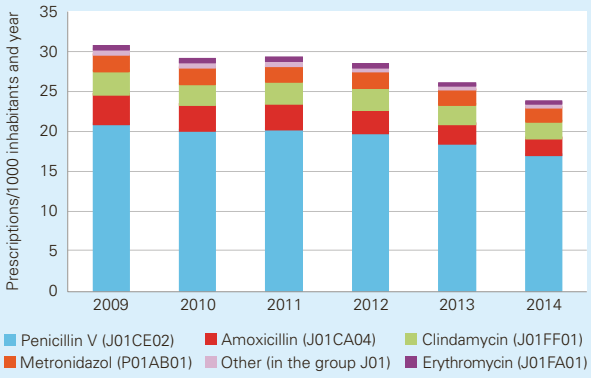
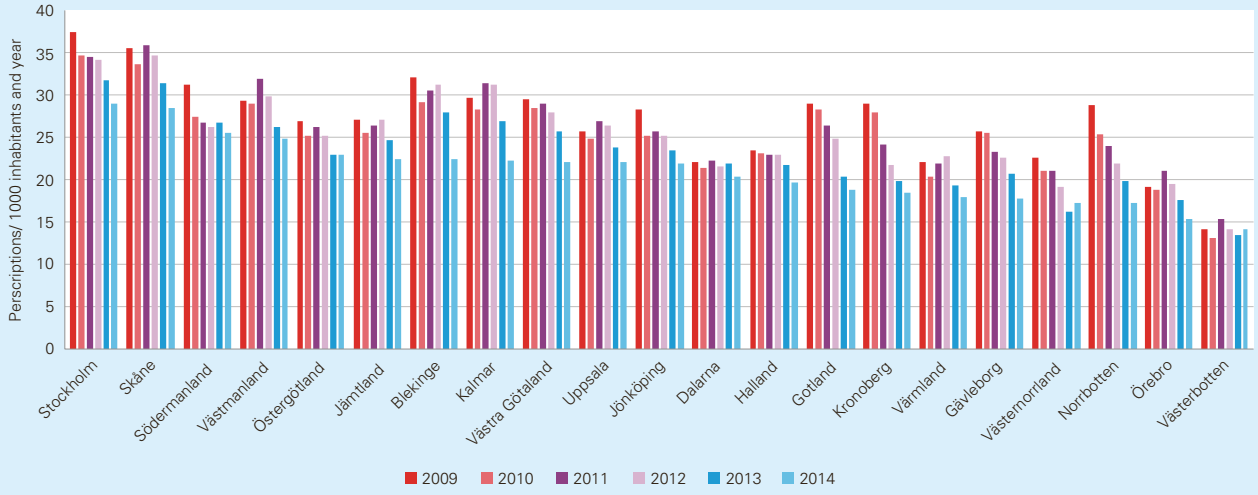


FIGURE 1.22. Sales of antibiotics prescribed by dentists in outpatient care per county, 2009-2014, Antibiotics for systemic use (J01) and metronidazol (P01AB01).



National campaign for improved patient safety

The Government and the Swedish Association of Local Authorities and Regions (SKL) agreed for the years 2011-2014 on a performance-based reimbursement to encourage, strengthen and intensify the work on patient safety efforts in the county councils. During these years just over SEK 2.2 billion was allocated to county councils as a stimulus, provided that they met certain basic requirements and implemented measures to increase patient safety in healthcare. The initiative identified antibiotic resistance and the rational use of antibiotics as central patient safety areas and a total of SEK 400 million was invested in this area. The Public Health Agency had a remit from the Government to annually evaluate the progress of the county councils to reach the goals of the antibiotics indicators.

Performance indicators

One of the basic requirements to be eligible for the performance reimbursement, was the establishment of a local Strama group (strategic programme against antibiotic resistance) in each county with a clear mission and adequate financing. All the county councils met this requirement by 2011.

Increased compliance to national treatment recommendations for common infections in outpatient care, was another key performance indicator. Furthermore a decrease in antibiotic sales towards the national target of 250 prescriptions per 1 000 inhabitants and year was rewarded each year. The national quantitative target for antibiotic prescriptions was launched by Strama in 2009, in conjunction with the European Antibiotic Awareness Day. The target was set with the knowledge that a large proportion of antibiotic use is unnecessary and was calculated based on an analysis of recorded visits for respiratory tract infections in primary care in Kalmar (Neumark T et al. 2009, Neumark T et al 2010). The target of 250 prescriptions per 1 000 inhabitants was at the launch a challenging goal given that the national average then was 382 prescriptions per 1 000 inhabitants.

During the last two years of the campaign the county councils were also required to show that at least 50 percent of the county health centers had provided the general practitioners with their personal antibiotic prescribing data. Furthermore to accomplish set targets, the prescribing of the practitioners at each health care center should in a structured manner be compared to other health centers in the county and be discussed in relation to treatment recommendations. During the last year of the patient safety initiative, in 2014, the county councils also had to assess the effects of giving feed-back on the personal prescribing patterns.

Changes in antibiotic sales 2011-2014

Significant reductions in antibiotic sales was achieved during the campaign period where it decreased among men and women and in all age groups in all counties. In Sweden in total the number of prescriptions decreased with 15%, from 381 to 325 prescriptions/1 000 inhabitants and year. The decrease in each county ranged from 8% to 20%, see Table A.

The results from the last measurement period showed that Västerbotten County was close to reaching the goal of 250 prescriptions per 1 000 inhabitants. The reduction indicates that there was a significant over-prescription of antibiotics when the campaign began in 2010, and that it is realistic and necessary to continue to work towards the 250 prescriptions-target. It´s of major importance that the decrease is established through increased compliance to national treatment recommendations. The 250 prescriptions- target must therefore be complemented by quality and safety indicators to assure development towards not only lower, but also a more appropriate prescription as well as to avoid under-prescription.

Sales statistics at the national level shows that the prescription of the 15 most commonly prescribed substances (which accounted for 98 percent of all antibiotic sales) has decreased except for pivmecillinam, nitrofurantoin and azithromycin. The first two are the recommended first-line treatment options of lower urinary tract infections in women, which suggests an increased adherence to treatment recommendation for sporadic lower urinary tract infection in women. During spring 2013, the pharmacies ran out of erythromycin (J01FA01) in Sweden and the increased sales of azithromycin can probable be explained by a shift from erythromycin to azithromycin during that period. The largest reductions was seen in antibiotics commonly used against respiratory tract infections, like penicillin V, doxycycline and amoxicillin. This suggests that adherence to guidelines for otitis media, acute bronchitis and pharyngotonsillitis improved or that less antibiotics was prescribed for viral respiratory tract infections, or a combination thereof, see Table B.

Discussion

There are several possible explanations for the decrease seen in the sales of antibiotics and the patient safety initiative is very likely to have contributed substantially. The campaign has raised increased awareness and highlighted the priority given at national level to work within the area of antibiotic resistance. This has led to reinforcement and consolidation of the existing structure of local Strama groups with close links to the national agencies in Sweden during the campaign period.

TABLE A. The sales of antibiotics in all Swedish counties, comparing the Patient safety initiative's first measurement period (1 October 2010-30 Sep 2011) with the last measurement period (1 October 2013-30 September 2014).

	Period 1 1 Oct 2010–30 Sep 2011 Prescriptions/1000 inhabitants	**Period 4** 1 Oct 2013–30 Sep 2014 Prescriptions/1000 inhabitants	**Decrease** Prescriptions	**Decrease** Per cent
Stockholm	413	356	-57	-14%
Skåne	411	351	-60	-15%
Uppsala	374	336	-38	-10%
Gotland	380	327	-53	-14%
Sweden	**381**	**325**	**-56**	**-15%**
Västra Götaland	399	320	-79	-20%
Halland	381	320	-61	-16%
Blekinge	388	316	-72	-19%
Västmanland	366	316	-50	-14%
Södermanland	345	314	-31	-9%
Östergötland	352	314	-38	-11%
Kalmar	359	312	-47	-13%
Kronoberg	370	305	-65	-18%
Örebro	336	302	-34	-10%
Västernorrland	329	299	-30	-9%
Värmland	346	298	-48	-14%
Norrbotten	349	298	-51	-15%
Jönköping	355	296	-59	-17%
Dalarna	313	288	-25	-8%
Gävleborg	337	286	-51	-15%
Jämtland	307	272	-35	-11%
Västerbotten	310	261	-49	-16%

The campaign has intensified specific activities related to the performance based indicators in the county councils during the campaign period which is one possible explanation for the decrease in antibiotic sales. Many local Strama groups have for example completed systematic work directed towards prescribers with information campaigns to the general public and activities in relation to media.

A coinciding change in the infection panorama with a reduced need for treatment may be an alternative explanation for the reduced sales of antibiotics. Another possibility could be that practitioners in general prescribe antibiotics more appropriately today. Sales data have declined in the other Nordic countries during the same period which suggests additional factors contributing to the decrease in sales. Even so, Sweden with its structure of local Strama groups systematically working with improvement of appropriate prescribing and implementation of treatment recommendations e.g. through personal feed-back is probably one important explanation to our lower prescription as compared to the other Nordic countries (Figure A).

In the impact assessment the Strama group´s unanimous interpretation was that some of the key success factors are that physicians have access to their personal antibiotic prescribing data and discuss their prescription patterns within the entire health unit staff to develop a common practice around the management of the patients. An additional success factor is considered to be the local benchmarking against other neighboring health units.

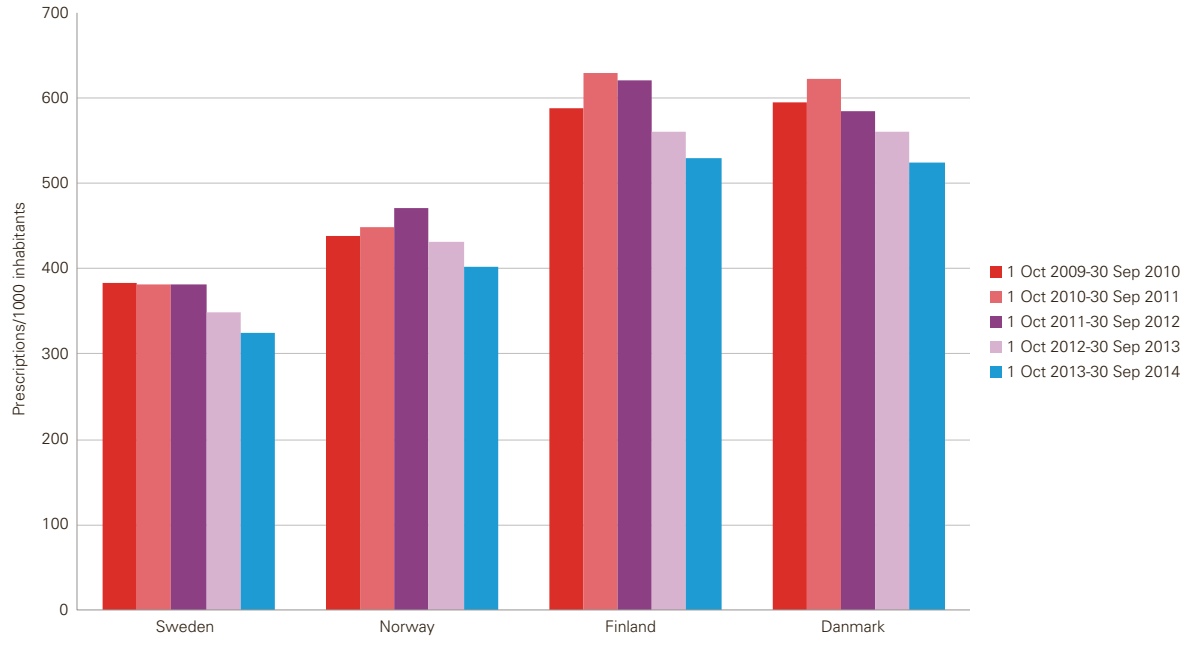
It is of great importance that the Swedish Strama model for implementing national treatment recommendations and improving antibiotic prescribing can further develop and be established as an integrated part of the local and regional health care organization. Studies have shown large differences in antibiotic prescribing between

health care units in the same area. High priority of quality improvement work at health care units has been identified as a possible factor for such variation. Strama groups are working effectively for quality improvement and appropriate antibiotic use, nevertheless it must be emphasized that it is the County Council's overall strategic responsibility to ensure that quality improvement and assurance is secured in all health units.

TABLE B. Sales statistics at the national level of the 15 most commonly prescribed preparations (which accounted for 98 percent of all antibiotic prescriptions). Comparing the Patient safety initiative's first measurement period (1 October 2010-30 Sep 2011) with the last measurement period (1 October 2013-30 September 2014).

	Period 1 1 Oct 2010-30 Sep 2011	**Period 4** 1 Oct 2013-30 Sep 2014	**Diff**	**Diff%**
Penicillin V (J01CE02)	116.7	92.1	-24.7	-21%
Flucloxacillin (J01CF05)	40.3	38.4	-1.8	-5%
Pivmecillinam (J01CA08)	33.1	33.7	0.6	2%
Doxycycline (J01AA02)	39.6	28.6	-11.0	-28%
Nitrofurantoin (J01XE01)	22.5	24.8	2.3	10%
Ciprofloxacin (J01MA02)	24.0	22.3	-1.7	-7%
Amoxicillin (J01CA04)	24.4	18.3	-6.2	-25%
Clindamycin (J01FF01)	15.9	14.9	-0.9	-6%
Lymecycline (J01AA04)	10.2	10.0	-0.2	-1%
Cefadroxil (J01DB05)	11.0	8.2	-2.8	-25%
Trimethoprim (J01EA01)	11.6	7.4	-4.2	-36%
Sulfamethoxazole and trimethoprim (J01EE01)	6.2	6.1	-0.1	-2%
Amoxicillin and enzyme inhibitor (J01CR02)	6.1	5.8	-0.3	-5%
Erythromycin (J01FA01)	8.4	5.3	-3.1	-37%
Azithromycin (J01FA10)	2.1	2.7	0.5	24%

FIGURE A. Sales statistics of antibiotic prescriptions during the patient Safety Initiatives first comparative period (1 Oct 2009-30 Sep 2010) and the four annual measurement periods October 2010 to September 2014 in the Nordic countries Sweden, Norway, Finland and Denmark.



Antibiotics in hospital care

Sales data in this chapter originates from two different sources: 1) antibiotics sold by requisitions to acute care hospitals only, Swedish acute care hospitals, for a more detailed analysis and 2) all antibiotics sold by requistions, below mentioned as hospital care, gives a general view over usage and trends.

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. It varies between nursing homes if they buy antibiotics through requisition or by prescriptions to individual residents. If antibiotics are bought on prescription, data are included in primary health care data, presented in the previous section. The way of retrieving antibiotics to nursing homes varies among counties, but on a 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 60%.

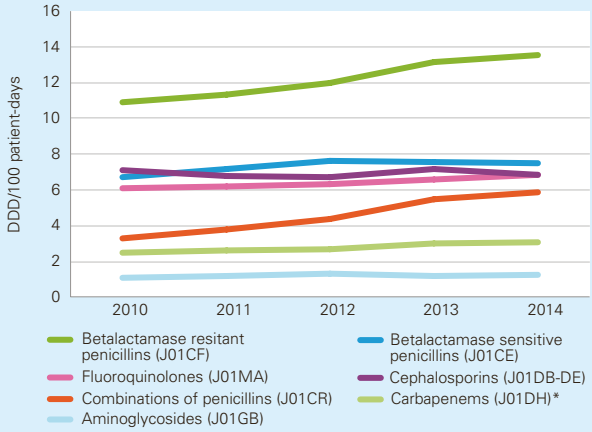
Antibiotic consumption in Swedish acute care hospitals

When analyzing data from acute care hospitals, there has been an increase in sales over the last five years (2010-2014) of 19% measured by DDD/100 patient-days and 10% measured by DDD/100 admissions. In 2014, the total consumption slightly increased compared with 2013, Table 1.3 and 1.4.

Figure 1.23 shows the most frequent groups of antibiotics used in hospital care. The consumption of betalactamase sensitive penicillins, cephalosporins and aminoglycosides did not change during the last year, and the consumption was at almost the same level as in 2013. Beta-lactamase resistant penicillins, fluoroquinolones, penicillins with enzyme inhibitor and carbapenems continue to increase as in previous years.

The use of penicillins with enzyme inhibitor have increased substantially during the latest years, while the use of carbapenems has increased marginally. These agents have in many situations replaced the cephalosporins. Piperacillin with tazobactam accounts for the majority of the sales of penicillins with enzyme inhibitor (J01CR) in acute care hospitals. In 2014 penicillins with enzyme inhibitor increased

FIGURE 1.23. Antibiotic groups often used within hospital care 2000-2014, DDD/100 patient-days in Swedish acute care hospitals.



*Includes all sales on requisition

TABLE 1.3. DDD/100 patient-days in somatic medical care in Swedish acute care hospitals 2010-2014.

	2010	2011	2012	2013	2014*
Tetracyclines (J01AA)	4.6	5.0	5.3	5.4	5.4
Penicillins with extended spectrum (J01CA)	6.0	6.5	6.9	7.5	7.7
Betalactamase sensitive penicillins (J01CE)	6.7	7.2	7.6	7.6	7.5
Betalactamase resitant penicillins (J01CF)	10.9	11.3	12.0	13.1	13.5
Combinations of penicillins (J01CR)	3.3	3.8	4.4	5.5	5.9
Cephalosporins (J01DB-DE)	7.1	6.8	6.7	7.1	6.8
Carbapenems (J01DH)**	2.5	2.6	2.7	3.0	3.1
Trimethoprim (J01EA)	0.9	0.8	0.6	0.5	0.4
Trimethoprim with sulphonamides (J01EE)	2.1	2.3	2.3	2.5	2.5
Macrolides (J01FA)	0.9	1.1	1.0	1.0	1.0
Lincosamides (J01FF)	1.7	1.7	1.9	2.1	2.0
Aminoglycosides (J01GB)	1.1	1.2	1.3	1.2	1.3
Fluoroquinolones (J01MA)	6.1	6.2	6.3	6.6	6.9
Glycopeptides (J01XA)	0.8	0.9	0.9	1.0	1.0
Imidazole derivatives (J01XD)	1.3	1.2	1.1	1.3	1.1
Nitrofurantoin (J01XE)	0.4	0.5	0.5	0.5	0.6
Methenamine (J01XX05)	0.6	0.5	0.5	0.6	0.6
Linezolid (J01XX08)	0.1	0.1	0.1	0.1	0.1
All agents (J01)	57.4	59.8	62.9	67.2	68.2

*Denominator data from 2013.
** Includes all sales on requisition

TABLE 1.4. DDD/100 admissions in somatic medical care in Swedish acute care hospitals 2010-2014.

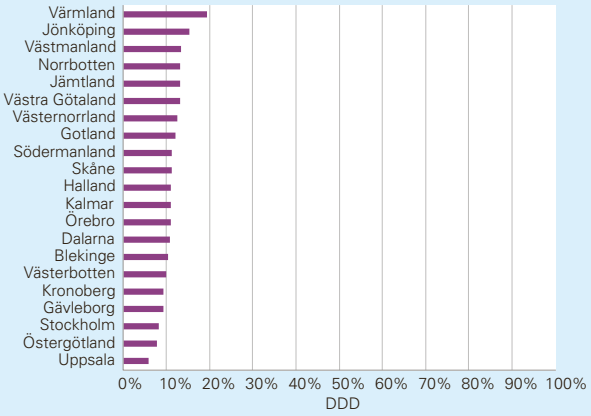
	2010	2011	2012	2013	2014*
Tetracyclines (J01AA)	21.5	22.7	23.4	24.1	24.0
Penicillins with extended spectrum (J01CA)	28.0	29.5	30.6	33.3	34.0
Betalactamase sensitive penicillins (J01CE)	31.3	32.8	33.8	33.5	33.2
Betalactamase resitant penicillins (J01CF)	51.0	51.4	53.4	58.2	59.9
Combinations of penicillins (J01CR)	15.6	17.4	19.5	24.4	26.2
Cephalosporins (J01DB-DE)	33.3	31.1	29.9	31.7	30.2
Carbapenems (J01DH)**	11.9	11.9	12.2	13.5	13.9
Trimethoprim (J01EA)	4.0	3.6	2.7	2.1	1.9
Trimethoprim with sulphonamides (J01EE)	9.9	10.3	10.2	11.0	11.0
Macrolides (J01FA)	4.1	4.9	4.2	4.5	4.4
Lincosamides (J01FF)	7.9	7.9	8.4	9.1	8.8
Aminoglycosides (J01GB)	5.0	5.3	5.7	5.4	5.6
Fluoroquinolones (J01MA)	28.3	28.3	28.1	29.2	30.4
Glycopeptides (J01XA)	3.7	4.1	4.1	4.5	4.5
Imidazole derivatives (J01XD)	6.0	5.4	5.1	5.7	4.7
Nitrofurantoin (J01XE)	2.0	2.1	2.1	2.4	2.5
Methenamine (J01XX05)	2.7	2.5	2.1	2.5	2.6
Linezolid (J01XX08)	0.4	0.3	0.4	0.5	0.6
All agents (J01)	267.5	273.2	278.9	298.1	302.2

*Denominator data from 2013.
** Includes all sales on requisition

with 7.3% measured as DDD per 100 patient-days compared to 2013. The corresponding figure for carbapenemes was 3.3%, Figure 1.23. The increase of these substances is probably a result of an increased number of infections with ESBL. Invasive infections caused by ESBL-producing Escherichia coli and Klebsiella pneumonia have increased, but the proportion of pathogens resistant to third-generation cephalosporins causing invasive infections is still very low in an European and international perspective. To minimize the selection of ESBL producing bacteria, a decreased use of 2nd and 3rd generation's cephalosporins is recommended in Sweden. Due to the decrease in the consumption of cephalosporins, the beta-lactamase resistant penicillins (J01CF) is since 2008 the largest group of antibiotics in Swedish hospital care. A large proportion of the use consists of surgical prophylaxis (even though the hospital use in Sweden to a large extent has gone from a multi-dose to a single-dose prophylaxis). The use of fluoroquinolones (J01MA) has been at almost the same level since 2008, and accounts for about 10% of all antibiotics in hospital care.

According to available data, antibiotic consumption in Swedish acute care hospitals show a wide variation between the counties in the use of narrow-spectrum penicillins, ranging from 6% to 19% of the total hospital consumption measured as DDDs, Figure 1.24. There are, however, great differences in dosages of penicillin G between the counties. DDD is 3.6 g and in Sweden the dosage varies from 1g three times a day to 3g three times a day. Type of hospital and patient composition may also influence the statistic and should be taken into account when comparing these data.

FIGURE 1.24. Percentage of narrow spectrum penicillins (penicillin V and G, J01CE) of all antibiotics in Swedish acute care hospitals 2014, per county.



Uppsala, Stockholm, Västerbotten, Västra Götaland, Skåne, Östergötland and Örebro Counties have tertiary referral hospitals.

The use of cephalosporins varied between 3.3% and 15.7%, and the corresponding figures for fluoroquinolones were 8.5% to 15.0%, and 5.5% to 13.1% for piperacillin-tazobactam, and 2.4% to 7.8% for carbapenems, Figure 1.25 and Table 1.5. Taken together, the percentage of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibioitcs in Swedish acute care hospitals varied from 28.6 percent in Värmland County to 37.6 percent in Östergötland County, Table 1.5.

TABLE 1.5. Percentage DDD of broad spectrum antibiotics (piperacillin with tazobactam, carbapenems, fluroquinolones and cephalosporins) of all antibiotics in Swedish acute care hospitals 2013-2014, per county.

	Piperacillin with tazobactam (J01CR05)		Carbapenems (J01DH)*		Fluoroquinolons (J01MA)		Cephalosporins (J01DB-DE)		All broad spectrum agents	
	2013	2014	2013	2014	2013	2014	2013	2014	2013	2014
Södermanland	7.8%	9.0%	2.7%	2.4%	14.6%	15.0%	3.9%	3.3%	29.3%	28.6%
Stockholm	5.7%	6.0%	4.6%	4.4%	9.9%	9.8%	11.1%	11.0%	29.1%	28.8%
Östergötland	4.9%	5.5%	4.3%	4.5%	9.1%	8.6%	16.1%	15.7%	27.6%	29.2%
Skåne	5.0%	5.7%	2.7%	2.8%	8.9%	9.1%	11.3%	11.5%	27.9%	30.0%
Västra Götaland	6.9%	7.5%	2.6%	3.3%	8.9%	8.8%	8.7%	8.2%	30.2%	30.4%
Kalmar	11.3%	13.1%	5.6%	5.9%	9.5%	9.1%	6.6%	10.0%	28.4%	30.8%
Norrbotten	7.7%	8.7%	4.2%	4.8%	8.5%	8.5%	7.1%	7.5%	29.5%	31.1%
Gotland	4.9%	7.0%	4.8%	3.9%	9.1%	8.5%	8.7%	9.5%	31.1%	31.2%
Jönköping	1.7%	7.8%	4.0%	4.0%	3.6%	10.2%	16.8%	9.9%	31.4%	31.3%
Värmland	6.3%	6.7%	3.3%	2.9%	9.4%	9.4%	10.9%	10.0%	29.7%	31.4%
Örebro	6.2%	8.1%	3.9%	3.4%	12.0%	11.4%	10.3%	9.1%	31.9%	31.4%
Halland	4.7%	5.7%	3.1%	3.5%	9.4%	10.8%	11.0%	10.8%	25.1%	31.4%
Kronoberg	5.9%	6.9%	2.6%	4.0%	13.4%	13.4%	11.8%	10.6%	30.3%	32.1%
Uppsala	8.6%	9.4%	3.8%	3.6%	10.3%	10.8%	10.7%	9.9%	32.3%	32.2%
Västerbotten	6.1%	5.7%	4.9%	4.4%	10.6%	10.3%	11.3%	12.0%	32.0%	32.4%
Blekinge	6.2%	6.9%	5.8%	5.6%	10.3%	10.3%	11.3%	10.9%	32.4%	32.4%
Västmanland	6.8%	7.7%	3.6%	3.7%	12.7%	3.4%	6.9%	7.3%	32.8%	33.3%
Västernorrland	5.8%	6.7%	3.0%	4.0%	11.9%	12.5%	11.6%	10.4%	34.6%	33.8%
Jämtland	6.6%	7.9%	3.6%	3.2%	11.4%	10.8%	9.5%	8.5%	34.7%	34.1%
Dalarna	4.9%	5.9%	4.8%	6.1%	11.7%	11.9%	10.6%	10.2%	34.4%	36.2%
Gävleborg	7.6%	8.2%	8.0%	7.8%	11.3%	10.6%	12.7%	11.1%	38.1%	37.6%

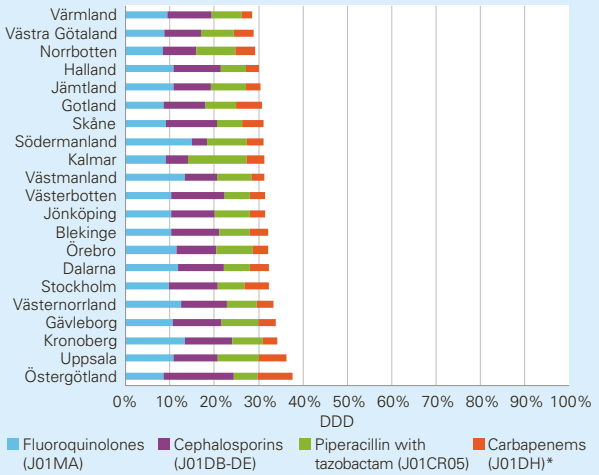
* Includes all sales on requisition

Antibiotic consumption in hospitals

The total antibiotic sale on requisition has increased in Sweden during 2000-2007 and has since then been on a quite stable level. During the last year the consumption did not change and the levels for 2014 corresponds with those in 2013. Even though we have not seen any increase since 2012, the consumption has still increased with 33% since the year 2000, from 1.18 to 1.60 DDD/1 000 inhabitants and day, Table 1.6.

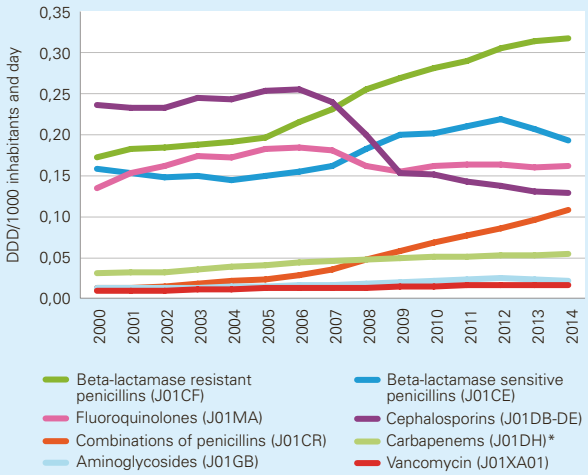
Figure 1.26 is the same as Figure 1.23, the difference is only that this includes all sales on requisition (hospitals, nursing homes and other units order of antibiotics on requisition). The figure shows the clear shift from high use of broad spectrum antibiotics to narrow spectrum antibiotics. The consumption of cephalosporins, fluoroquinolones, aminoglycosides and vancomycin did not change during the last year. Beta-lactamase resistant penicillins, penicillins with enzyme inhibitor and carbapenems continues to increase like previous years.

FIGURE 1.25. Percentage of broad spectrum antibiotics (fluoroquinolones, cephalosporins, piperacillin with tazobactam and carbapenems) of all antibiotics in Swedish acute care hospitals 2014, per county.



*Includes all sales on requisition

FIGURE 1.26. Antibiotic groups often used within hospital care 2000-2014, DDD/1 000 inhabitants and day.



*Includes all sales on requisition

A national IT tool for surveillance of healthcare-associated infections and antibiotic use

The "Anti-infection Tool" has previously been presented in Swedres-Svarm 2013. It is a national IT support tool for surveillance of healthcare-associated infections and the use of antibiotics. Every time antibiotics are prescribed through the electronic medical record system the doctor is forced to indicate the reason for the prescription. In addition, data is also transferred back from the patient´s medical record to the "Anti-infection Tool", providing information on diagnoses, microbiology results (only for C. difficile) and other medical procedures.

Since 2014, the "Anti-Infection Tool" is fully implemented in practically every Swedish hospital.

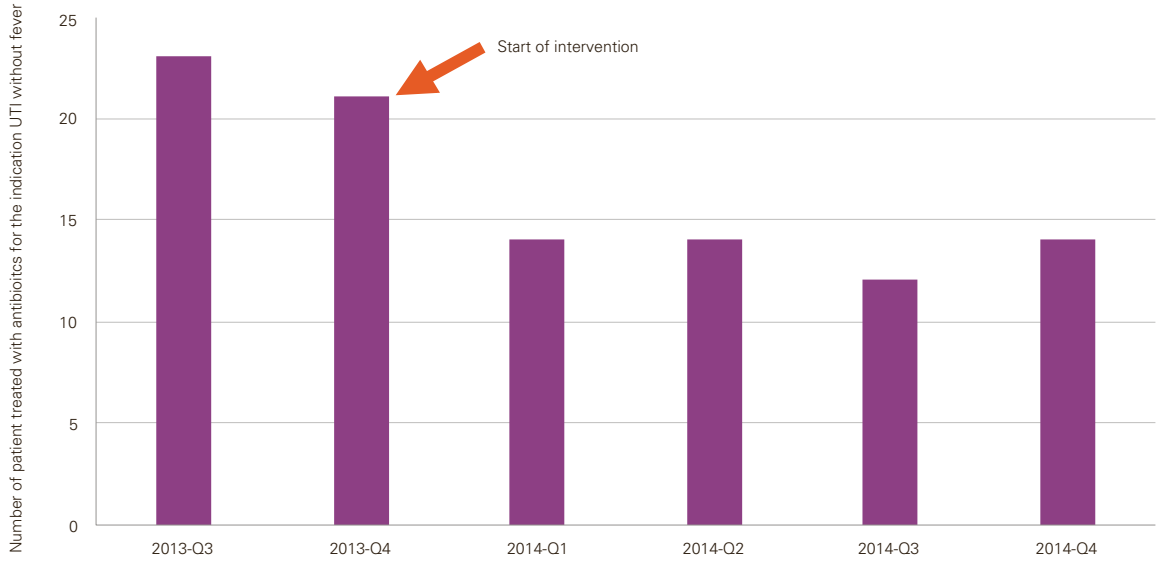
Through the reporting tool it is easy to get an exact overview of the usage of different antibiotics in each specific unit in the hospital. A validation study in Kalmar County shows that the quality of registrations differs between the predetermined diagnoses, however, the impact of error in registration decrease over time. It is important to keep in mind that the present version of the tool doesn´t measure the total amount of antibiotics used, just the type of antibiotic.

Example from Kalmar County

At the three hospitals in Kalmar County, the Anti-infection Tool was introduced during the summer 2013. Below you will find examples on how the "Anti-infection Tool" has been implicated in small clinical projects by the local Strama (the Swedish Strategic Programme against Antibiotic Resistance) group in Kalmar County.

In Kalmar County, urinary tract infections without fever is the most common indication for antibiotic treatment in hospitals. In addition, the prevalence of asymptomatic bacteriuria increase with rising age, especially among women. Tiredness, occasional confusion and other diffuse symptoms are often misinterpreted as symptoms of urinary tract infection. In combination with signs of bacteria in the urine this often leads to unnecessary antibiotic treatment. The "Anti-infection Tool" easily identifies wards with a questionable high use of antibiotics among elderly women with this diagnosis. In Kalmar County, three wards with high consumption were identified, and data was confirmed by examination of the patients' medical records. The results were pre-

FIGURE A. Number of patients treated with antibiotics for the indication urinary tract infection without fever at the geriatric clinic in Kalmar County (July 2013- December 2014). The intervention was started in quarter 4 2013 (November), marked with red arrow in the figure.



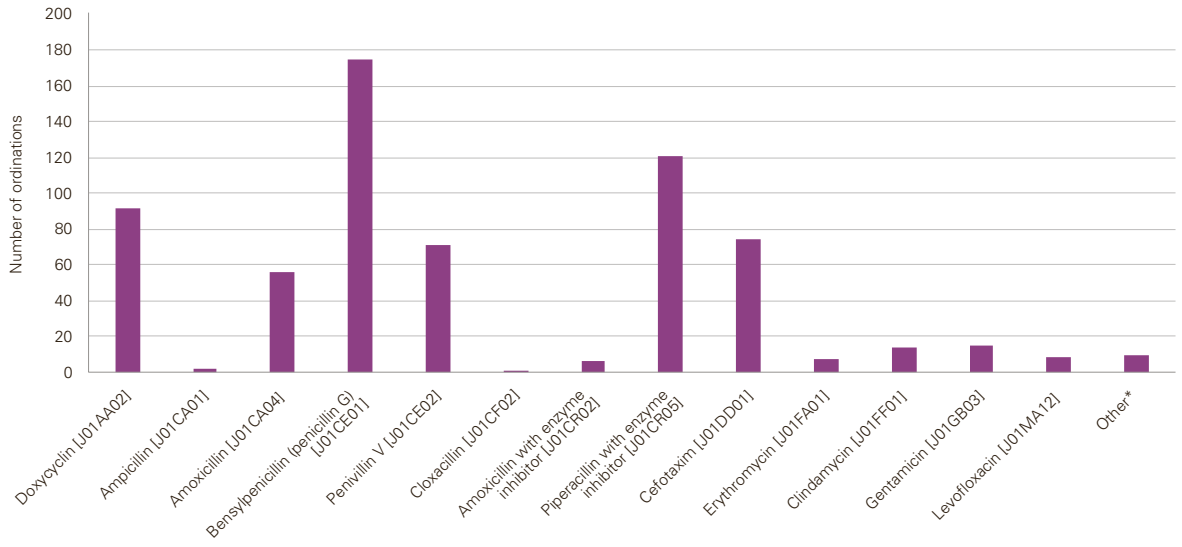
sented for the ward staff together with a short lecture on the subject. The use of antibiotics for urinary tract infections has decreased at the identified wards since the start of the intervention, Figure A.

In the reporting tool, there is a function which gives access to the personal identity numbers of the patients contributing to the statistics, facilitating a deeper analysis through the medical record. The Strama group in Kalmar County looked at the diagnostic quality in the emergency unit. The aim of the project was to evaluate if the preliminary diagnosis of pneumonia reported to the "Anti-Infection Tool" correspond to the final diagnosis, i.e was it safe to always start with narrow spectrum antibiotic such as bensylpenicillin on these patients? A selected population on 20 patients who received narrow spectrum antibiotics on admission were included in the project. One of the patient were later diagnosed with pyelonephritis, however, the rest did not change from pneumonia. One patient required a broader antibiotic after 3 days. The results shows that it was safe to start with narrow spectrum antibiotics for the preliminary diagnosis pneumonia. In Kalmar County bensylpenicillin was the most used antibioitc for community-acquired pneumonia, Figure B. However, Piperacillin/tazobactam was the second most commonly used antibiotic. The results from the project mentioned above indicates that there might be an opportunity for improvement regarding choice of antibiotics for treatment of mild-moderate severe community-acquired pneumonia in Kalmar County.

Another area of application is as part of antibiotic stewardship by infectious disease consultants. From the tool the consultant can get information about all patients who have started a certain antibiotic treatment within the entire county. Based on the information in the medical record the infection specialist, working at any hospital in the county, could write a recommendation to all hospitals on what antibiotic to use in a particular patient. The aim would be to identify unnecessary treatment with broad-spectrum antibiotics and to advice on further infection treatment strategies.

The "Anti-infection Tool" has great potential for development and the quality in registration by the doctors can be improved. Yet it is already a valuable tool for optimizing antibiotic treatment in hospitals. The future challenge is to engage more clinicians in the use of this tool.

FIGURE B. Antibiotics prescribed for the indication community-acquired pneumonia in emergency unit in Kalmar County during July 2013 to December 2014.



*[J01DB05, J01DD02, J01DD14, J01DH02, J01EA01, J01EE01, J01MA02 and J01MA14]

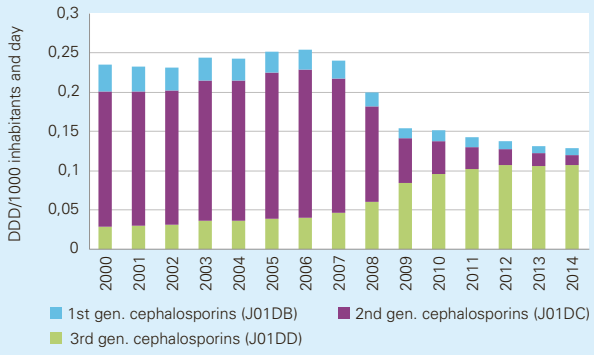
TABLE 1.6. Antibiotic consumption in hospital care 2000-2014, DDD/1 000 inhabitants and day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
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	1.60
Methenamine (J01XX05)	0.03	0.03	0.02	0.05	0.07	0.07	0.07	0.07	0.05	0.03	0.03	0.02	0.02	0.02	0.02
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	1.62

Figure 1.27 shows that the consumption of cephalosporins increased until 2006 when it peaked. After 2006 there has been a drastic change, and between 2006 and 2014 the consumption of cephalosporins decreased by 50% from 0.26 to 0.13 DDD per 1 000 inhabitants and day. Consumption of 3rd generation cephalosporins, mainly cefotaxim and ceftazidime, have replaced the use of 2nd generation cephalosporins (cefuroxime). The decrease in DDD can partly be explained by the shift from cefuroxime to cefotaxime, since the previously recommended standard doses do not conform to the WHO definitions. In Sweden, the previously recommended standard doses of cefuroxime was 1.5g x 3 = 4.5 g/d and cefotaxime 1g x 3 = 3 g/d compared to the WHO definition of DDD; 3 g/day and 4 g/day respectively. The overall decrease in the consumption of cephalosporins in hospital care indicates that these substances has been replaced by other antibiotics.

The Strama network, together with local drug and therapeutic committees have promoted the following changes in antibiotic policy in Swedish hospitals: 1) moderately severe (CRB-65 0-1) community acquired pneumonia (CAP) should be treated with narrow-spectrum penicillins; 2) surgical prophylaxis should normally be given as one dose except in high-risk situations where 24 h is a maximum with few exceptions; 3) uncomplicated lower urinary tract infections in women should be treated with pivmecillinam or nitrofurantoin, including hospital inpatients, whereas the use of fluoroquinolones should be restricded; 4) extended-spectrum cephalosporins and fluoroquinolones should not be used in situations where treatment with a narrow-spectrum penicillin is an alternative (Hanberger H et al., 2014). This can be reflected in the statistic.

FIGURE 1.27. Cephalosporins in hospital care, 2000-2014, DDD/1 000 inhabitants and day.



Adverse reactions related to antibiotic use

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 during the last five years, 2010-2014, 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=829), gastrointestinal disorders (n=273), hepatobiliary disorders (n=99), general disorders (n=149), blood disorders (n=86), neurological reactions (n=116), respiratory disorders (n=106), immune system disorders (n=130), musculoskeletal disorders (n=81), psychiatric disorder (n=50) and renal and urinary disorders (n=67).

The majority of the reports (57%) 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. 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 2010-2014.

Antibiotic	Total number of adverse drug reaction reports	Number of 'serious' reports	Number of fatal cases
Ciprofloxacin	202	114	2
Flucloxacillin	180	115	7
Phenoxymethyl-penicillin	158	70	0
Sulfamethoxazole and trimethoprim	130	80	1
Clindamycin	121	70	2
Nitrofurantoin	120	73	2
Amoxicillin	99	43	0
Doxycycline	92	43	0
Cefotaxime	88	41	1
Piperacillin and enzyme inhibitor	82	43	0

TABLE 1.8. Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2010 – 2014.

	2010	2011	2012	2013	2014	2010-2014
Fluoroquinolones (J01MA)						
Total no of reports	28	25	19	28	46	146
Number of reactions						
Musculoskeletal	3	3	4	10	12	32
tendinitis	3	2	3	3	1	12
tendon rupture	2	3	3	3	1	12
Skin- and sub-cutaneous tissue	11	5	4	5	13	38
Psychiatric disorders	5	4	0	7	7	23
Nitrofurantoin (J01XE01)						
Total no of reports	24	25	30	20	21	120
Number of reactions						
Respiratory system	6	4	16	8	7	41
dyspnoea	3	1	4	5	4	17
interstitial pneumonia	2	0	2	1	0	5
pulmonary fibrosis	0	0	3	0	3	6
Skin- and subcutaneous tissue	10	10	17	6	4	47
General disorders	7	6	3	10	2	28
Fever	3	3	2	4	1	13

Consumption of systemic antifungals

Hospital care

Compared to 2013 the total consumption of antifungal drugs for systemic use is unchanged, with a national average of 61 DDD per one million inhabitants and day. Every year since 2000 except for 2011 and 2014 there has been a small but steady increase. Since the year 2000 when the total consumption was 40 DDD per one million inhabitants and day, the increase has been 50%. Meanwhile there has been a 38% increase in the consumption 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 per 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 with an average of 149 DDD per one million inhabitants and day. Historically those two counties have had the highest consumption since 2000. The lowest use was in Jönköping County with 12 DDD per one million inhabitants and day.

Fluconazole still constitutes the majority of the antifungals consumed, 65% or 39.5 DDD per one million inhabitants and day. Amphotericin B is the second most consumed compound. The consumption increased 28% compared to 2013, and now stands for 16% of the total consumption in 2014. 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 consumption was 30 DDD per one million inhabitants and day, representing 74% of the total consumption. Fluconazole is a narrow spectrum antifungal with effect towards Candida species (excluding among others *Candida krusei* and most strains of *Candida glabrata*). 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.

Among antifungals with a broader spectrum, including both Candida glabrata and Aspergillus sp two new classes of antifungals have been introduced since 2000; the echinocandins and azoles with an enhanced efficacy. The echinocandins as a group today stands for 12% of the total consumption. Amphotericin B that in the year 2000 was the only broad-spectrum antifungal available and then constituted 20% of the total consumption, remains an important compound with todays 16%.

Among the azoles with broadspectrum there has been a shift from itraconazole that in 2000 represented 3% of all antifungals to voriconazole and posaconazole that in 2014 stands for 7.5% of the total consumption. In 2014 itraconazole was hardly used at all.

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 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 consumption of voriconazole is low in absolute numbers (1.83 DDD per one million inhabitants and day), and is virtually unchanged since 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. The total sales of voriconazole in outpatient settings is almost three times higher than in hospital care (4.5 DDD per one million inhabitants and day). However, since the absolute majority of voriconazole therapies is initiated and monitored by hospital physicians, it is probably more correct to confer those data to hospital use rather than primary health care use. The amount of voriconazole on prescription have slightly decreased compared to previous years.

Posaconazole can also be given orally, 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 hematologic units. During 2014 a new formula was released, enterocapsule, which will have an improved resorption and the increased

use in 2014, up 32% from 2.2 DDD per one million inhabitants and day to 2.9 DDD per one million inhabitants and day might be explained by this novelty and 5.9 DDD per one million inhabitants and day are sold in outpatients settings. 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 consumption of the echinocandins. In 2014 the consumption increased by 11%, making the total amount 7.3 DDD per one million inhabitants and day, and the group now constitutes 12% of all systemic antifungals consumed in hospitals. Caspofungin which has been available in Sweden since 2002 has seen its market share diminish for every year. It now constitutes 44% of the echinocandins. Anidulafungin increased its share from 30% to 38% last year. The third member of the group micafungin that for the first time appeared in the statistics in 2012 now constitutes 18%. There are no evidence for a shift in the distribution of, or in the pattern of resistance among invasive candida species in Sweden. The increased use of both anidulafungin and micafungin is probably due to their lower cost. The new indication for anidulafungin – empiric treatment of patients with neutropenia and fever – has probably resulted in an increased use of anidualfungin. Early preclinical trials of micafungin indicated an increased risk of livertumor among rats. An extended worldwide use of the compound has not showed an increased risk among humans, but the EMA still issues a warning label. 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.

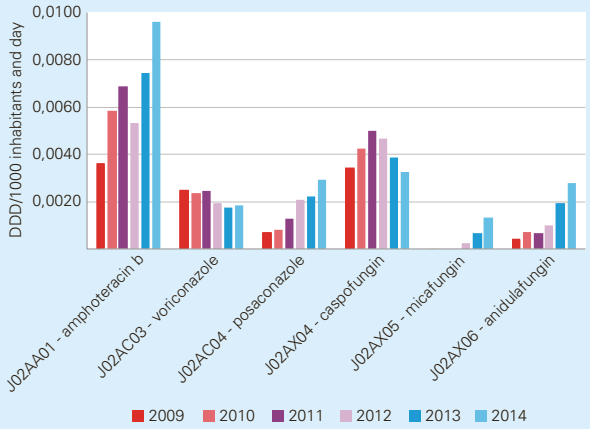
Amphotericin B has for a long time been considered the golden standard for treatment of invasive fungal infection due to its broad spectrum and well documented effect against most yeasts and molds. However the tolerability is a problem. Side effects are common with nephrotoxicity and electrolyte imbalance as the most severe. Therefore amphotericin B is now mostly used in its liposomal form, which improves tolerability. Since 2009 there has been an increased use of amphotericin B for five out of six years. Last year's increase was 28%, and amphotericin B now constitutes 44% of all broad spectrum antifungal use, Figure 1.28.

In outpatient care

Seventy-eight percent 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 (86%), mainly for mucocutaneus infections.

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

FIGURE 1.28. Sales of broad spectrum antifungals in hospital care 2009-2014. DDD/1 000 inhabitants and day.



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 sales are comparably low (European Centre for Disease Prevention and Control, 2014).

Consumption of antibiotics in animals

Statistics on total consumption of antibiotics for use in animals in Sweden are available since 1980. For a review of data from 1980-2000, see Svarm 2000 and for the follwing years the relevant Svarm- and Swedres-Svarm-reports. Data are derived from sales statistics. In the following, the term consumption will be used for sales from pharmacies to private and professional animal care-takes as well as to veterinary clinics. The consumption represents an approximation of the use of antibiotics, assuming that the amount sold is also used during the observation period. Details on data source and inclusion criteria are given in Materials and methods, consumption of antimicrobials.

Completeness of data

Until 2009, statistics on consumption of antibiotics was assumed to be complete. Since, the Swedish pharmacy market has been reregulated and concerns have been raised that data on consumption of veterinary medicinal products with a general marketing authorisation from recent years are less complete than before the reregulation. It is assumed that the problem mainly or only concerns products sold on requisition to veterinarians (i.e. for use in their practice), mostly injectables. Expressed as kg active substance, sales to pharmacies were 8% higher than from pharmacies for 2013 and 14% higher for 2014. For further information on the lack of completeness of data from recent years, see Materials and methods, consumption of antimicrobials.

Most of the trends identified in the data presented below have been observed before 2010. There are known expla-

nations relating to e.g. changes in prescribing behaviour or improved animal health that support the view that there is a true decrease in antibiotic consumption. The exception is sales of benzylpenicillin where sales have decreased from 2010. The latter trend is corroborated by data from other sources indicating a true decrease (see Comments on trends by animal species, Dairy cows).

Taken together, the lack of completeness of data from 2010 should be kept in mind when interpreting the data from recent years. From 2010 and onwards the magnitude of the changes cannot be assessed for classes with injectable products. Products for oral medication of individuals or groups are not likely to be affected to a significant degree.

Trends in animal populations

Changes in the numbers of animals may affect trends in statistics on consumption of antibiotics. The number of pigs slaughtered has decreased by 13% in five years, while the number of broilers was 14% higher in 2014 than in 2010. The number of dairy cows has been unchanged over the same time-period. 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 Demographics and denominator data.

Overall consumption

Of the overall consumption 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). In 2014, the total reported sales from Swedish pharmacies of antibiotics for animals were 10 271 kg, of which 53% was benzylpenicillin. The corresponding overall figures for 2005 and 2010 were 16 389 kg and 14 117 kg, respectively. When interpreting the figures, the mentioned decrease in numbers of pigs slaughtered as well as the uncertainty of data from recent years must be borne in mind. Still, there is most likely a true decrease over time but as data from recent years are uncertain its magnitude cannot be estimated.

Because of the indications of lack of completeness discussed above, more detailed data on overall consumption of antibiotics (e.g. by class) are not presented in this report. Information on overall consumption previous years can be found in Swedres-Svarm 2013 and earlier reports.

Consumption of antibiotics for parenteral use

The consumption of antibiotic products formulated for injection is presented in Table 1.9. Trends from 2010-2014 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). Antibiotics in these classes 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. Unfortunately, for reasons explained above, the magnitude of the effect of the regulation cannot be assessed directly from the consumption data.The decrease in consumption, however, of these antibiotics is larger than the estimated lack of completeness. Further, an increase in consumption of trimethoprim-sulphonamides from 2012 to 2014 probably reflects a switch to this class in situations when fluoroquinolones would have been used before the regulation.

TABLE 1.9. Yearly consumption of antibiotic drugs for parenteral use (injections), expressed as kg active substance and proportion sold on requisition to veterinarians. Figures are uncertain because of indications of lack of completeness.

ATCvet code	Antimicrobial class	2006	2007	2008	2009	2010	2011	2012	2013	2014	Percent sold on requisition 2014
QJ01AA	Tetracyclines	564	588	557	527	492	471	422	424	396	*53*
QJ01BA	Amphenicols							0	3	7	*4*
QJ01CE, -R, QJ51	Benzylpenicillin	7 778	7 505	7 674	7 641	7 492	6 627	6 290	5 901	5 455	*63*
QJ01CA, QJ01CR	Aminopenicillins	134	142	143	152	144	146	143	131	145	*34*
QJ01DD	Cephalosporins	26	26	25	21	13	13	8	4	2	*63*
QJ01G, -R	Aminoglycosides	345	343	318	301	272	246	210	104	145	*44*
QJ01E	Trimethoprim & sulphonamides	804	685	691	669	685	667	699	857	849	*30*
QJ01F	Macrolides & lincosamides	241	216	136	118	101	95	95	95	90	*3*
QJ01MA	Fluoroquinolones	132	125	118	113	105	83	69	29	25	*73*
QJ01XX92, - 94	Pleuromutilins	39	36	36	28	17	13	14	17	13	*6*
Total		**10 064**	**9 666**	**9 699**	**9 568**	**9 322**	**8 362**	**7 950**	**7 565**	**7 125**	**57**

TABLE 1.10. Yearly consumption of antibiotic drugs for oral medication of individual animals, expressed as kg active substance and proportion sold on requisition to veterinarians.

ATCvet code	Antimicrobial class	2006	2007	2008	2009	2010	2012	2013	2014	Percent sold on requisition 2014
QJ01AA	Tetracyclines	45	44	47	48	46	50	47	38	*1*
QJ01CA, QJ01CR	Aminopenicillins	775	756	681	650	598	501	500	460	*3*
QJ01DB	Cephalosporins	1 186	924	792	714	562	402	325	297	*2*
QA07AA	Aminoglycosides	131	126	131	118	109	102	77	61	*12*
QA07AB, QJ01E	Trimethoprim & sulphonamides	2 189	2 179	2 028	1 838	1 670	1 442	1 169	1 164	*24*
QJ01FF	Lincosamides	176	194	216	214	210	178	164	159	*2*
QJ01MA	Fluoroquinolones	59	52	46	46	39	32	22	18	*5*
Total		**4 559**	**4 276**	**3 941**	**3 630**	**3 234**	**2 706**	**2 304**	**2 198**	**14**

Consumption of antibiotics for oral medication of individual animals

In Table 1.10, the sales of products formulated for oral medication of individual animals are presented. For this category, the completeness of data is likely to be high and trends can be assessed.

For all classes except trimethoprim-sulphonamides and aminoglycosides, this category of antibiotics consists of tablets sold for companion animals. The aminoglycosides also include products authorised for farm animals while the trimethoprim-sulphonamides are mostly products for horses.

The sales of fluoroquinolones have decreased gradually since 2006 (- 69%). A more pronounced decrease is noted from 2012 to 2014 (- 43%). This is probably a reflection of the above mentioned regulation restricting veterinarians' prescribing of fluoroquinolones.

Major downward trends from 2010-2014 are noted for all classes. For further comments see Comments on trends by animal species, Horses and Dogs.

Consumption of antibiotics for oral medication of groups of animals

Data on consumption of antibiotics formulated for medication of groups of animals are given in Table 1.11. Data for 1984 are given as historical reference. As for products for oral medication of individual animals, completeness is likely to be high. Today, the consumption 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 for treatment of pigs. There has been an overall decrease by 55% of consumption of such products since 2010 (Table 1.11). The consumption of pleuromutilins has decreased since the mid 90s and were 64% lower in 2014 than in 2010. 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

TABLE 1.11. Yearly consumption of antibiotic 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	2014
QA07A	Intestinal anti-infectives			163	170	158	106	107	119	77	75	76	80
QJ01A	Tetracyclines	12 300	712	934	903	1 217	1 040	594	575	552	408	463	352
QJ01C	Penicillins incl. aminopenicillins				11	28	111	266	164	36	5	13	30
QJ01F	Macrolides & lincosamides	607	713	680	837	1 107	744	657	427	361	359	305	235
QJ01MA	Fluoroquinolones		7	5	5	3	5	5	4	2	6	1	2
QJ01MQ	Quinoxalines[b]	9 900											
QJ01XX91	Streptogramins[c]	8 800											
QJ01XX92, -94	Pleuromutilins		355	309	420	471	536	370	157	127	85	109	101
QP51AA	Nitroimidazoles	1 440											
	Feed additives[d]	700											
Total		**33 747**	**1 787**	**2 091**	**2 346**	**2 984**	**2 543**	**1 999**	**1 447**	**1 154**	**937**	**968**	**800**
QP51AH	Ionophoric antibiotics (coccidiostats)[d]	7 900	10 486	11 095	12 335	12 527	13 376	12 471	15 325	14 693	12 860	12 489	14 194

[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)

dysentery, reflected in overall declining consumption figures. The continued drop in consumption of macrolides for group medication (55% lower in 2014 than in 2010) is likely to reflect improved knowledge on how to manage problems with concomitant infections in herds with postweaning multisystemic wasting syndrome and the introduction of vaccination strategies.

Consumption of antibiotics for intramammary use

In 2014, a total sales from pharmacies of 79 790 dose applicators for use in lactating cows were reported. The two products on the Swedish market contain either procaine benzylpenicillin or procaine benzylpenicillin combined with dihydrostreptomycin.

The sales of intramammary products for use at drying off were 231 520 dose applicators in 2014. The two products on the Swedish market contain prodrugs of benzylpenicillin combined with either framycetin or dihydrostreptomycin.

The figures above include only products with general marketing authorization. In addition a limited number of dose applicators with special marketing authorization were sold.

Comments on trends by animal species

Dairy cows

Växa Sweden publishes a yearly report related to the livestock organisations' work to improve animal health and welfare in dairy cows (Växa Sverige, 2014). For statistics on incidence of antibiotic 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 (2014), 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 antibiotic for this condition will have a noticeable influence on the statistics on sales of antibiotics. The reported incidence of treatment of clinical mastitis in dairy cows has decreased over the last ten years and was 10.7 recorded treatments per 100 completed/interrupted lactations in 2013/2014. Treatment with benzylpenicillin was by far the most common (89%).

As mentioned, a total of 231 520 dose applicators of intramammaries for use at drying off were sold from Swedish pharmacies in 2014. Assuming that all cows were treated in four teats, this corresponds to 57 880 treated cows. That figure has been stable over the last five years.

Pigs

Antibiotics 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).

TABLE 1.12. Consumption of antibiotics for pigs in 2014 expressed as mg per kg slaughtered pig and percentage change since 2010.

	Individual medication		Group medication	
Antimicrobial class	**2014**	**Change since 2010 (%)**	**2014**	**Change since 2010 (%)**
Aminoglycosides	0.23	-38		
Aminopenicillins	0.38	-15	0.08	-75
Amphenicols	0.01			
Cephalosporins 3gen	0.00			
Fluoroquinolones	0.01	-79	0.00	
Macrolides & lincosamides	0.36	9	0.89	-37
Benzylpenicillin	5.51	10		
Pleuromutilins	0.05	-22	0.43	-29
Polymyxins			0.34	-5
Tetracyclines	0.34	45	1.29	-30
Trimethoprim-sulphonamides	2.32	26		
Total	**9.23**	**12**	**3.03**	**-33**

In 2010 and 2014 the consumption of antibiotics for pigs was 3 369 and 2 883 kg active substance, respectively, or 12.8 and 12.3 mg/kg slaughtered pig. Of the total consumption in kg active substance during 2014, 75% were products for injection, and of those 60% were products containing benzylpenicillin. The consumption of fluoroquinolones for pigs was 3.2 kg and there was no consumption of third generation cephalosporins for pigs.

In Table 1.12, the consumption of antibiotics for pigs expressed as mg per kg slaughtered pig is shown. The overall consumption has been stable over the last five years but the consumption of products for individual medication have increased and products for group medication have decreased (see Consumption of antibiotics for group medication). Benzylpenicillin is by far the most commonly sold substance (45% of the total, expressed as mg per kg slaughtered pig) and consumption has increased over time. Analysis of trends in consumption of antimicrobials for pigs between 2006 and 2010 (see Highlight in Svarm 2011) showed a similar pattern.

A shift from products for medication of groups of animals via feed or water towards medication of individual animals, preferably with narrow spectrum substances such as benzylpenicillin is observed over the last ten years. This is well in line with guidance on appropriate use of antibiotics.

Poultry

Antibiotics 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 0.5 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 4 of 3138 broiler flocks (0.13%) were treated with phenoxymethylpenicillin in 2014. This corresponds to 0.08 mg active substance/kg slaughtered chicken. In addition, 21 out of 249 grandpartent and parent flocks were treated with penicillins, mostly phenoxymethylpenicillin.

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

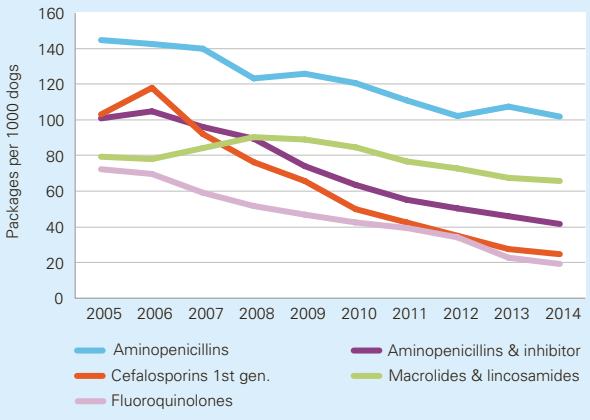
Around two thirds of the consumption of trimethoprim-sulphonamides are products for oral use in horses (paste or powder). The consumption of such products increased steadily until 2006 but from 2010, there has been a decrease by 29%. Among the indications for trimethoprim-sulphonamides in horses are reproductive disorders and various conditions in foals. Since 2009, the number of mares covered and number of foals born has decreased (Anonymous, 2014). Thus, it is probable that the decrease in consumption of trimethoprim-sulphonamides is explained by the lower number of mares covered and a lower number of foals born.

The consumption of other antibiotics for horses is difficult to estimate, as they are frequently sold on requisition and administered by the veterinarian in connection with an examination, either in ambulatory practice or in clinics or hospitals.

Dogs

Data on outpatient consumption of antibiotics authorised for medication of dogs have a high degree of completeness. In 2014, the overall consumption of products for oral medication of dogs was 881 kg compared to 1 348 kg in 2010. Aminopenicillins, first generation cephalosporins and lincosamides were by far the classes with largest consumption in 2014 (300, 278 and 151 kg, respectively).

FIGURE 1.29. Consumption of the five largest antibiotic classes among antibiotics for oral medication of dogs expressed as packages per 1000 dogs. Data include antibiotics authorised for veterinary use as well as antibiotics for human use.



In 2006, the total consumption of antibiotics for oral use in dogs, both veterinary antibiotics and those authorised for use in humans, corresponded to 563 packages per 1000 dogs. Since then, the consumption has decreased to 282 packages per 1000 dogs (-50%). Trends over time for the five largest classes (90% of the total sales) are illustrated in Figure 1.29. The most prominent changes relative to 2006 are noted for cephalosporins (-79%), fluoroquinolones (-73%) and aminopenicillins with clavulanic acid (-60%).

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 antibiotics for dogs.

Comparison of antibiotic consumption in human and veterinary medicine

Data included and calculations

The figures on total amount of antibiotics consumed for systemic use of antibiotics 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 antibiotics for use in animals (QJ01 and QJA07AA, total sales) are those presented in "Consumption of antibiotics 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 biomass 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 biomass of major animal populations, excluding dogs and cats.

Comparison of consumption in tonnes active substance

In 2014, a total of 60.5 and 10.2 tonnes of antibiotics in included ATC classes were consumed in human and veterinary medicine, respectively. It should be noted that there is a lack of completeness of 5-10% of the sales of antibiotics for animals (See Completeness of data in Consumption of antibiotics for animals). Figure 1.30 displays the consumption of beta-lactam antibiotics. These substances are by far the most used antibiotics in both human and veterinary medicine and also represent the largest amounts measured as kilograms. Penicillins ((Q)J01C) represent most of the amount in kg active substance of antibiotics for both humans and animals; 76 and 60% respectively. The substances shown in

Figure 1.31 are consumed 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 antibiotics consumed in a total quantity exceeding 1 000 kg during 2014 are included. The only class where use in animals outweighs human consumption is trimethoprim-sulphonamides, of which two thirds are sold for horses.

FIGURE 1.30. Consumption of beta-lactam antibiotics in human and veterinary medicine, kg active substance, 2014. Please note the difference in indexation of the x-axis between figures 1.30 and 1.31.

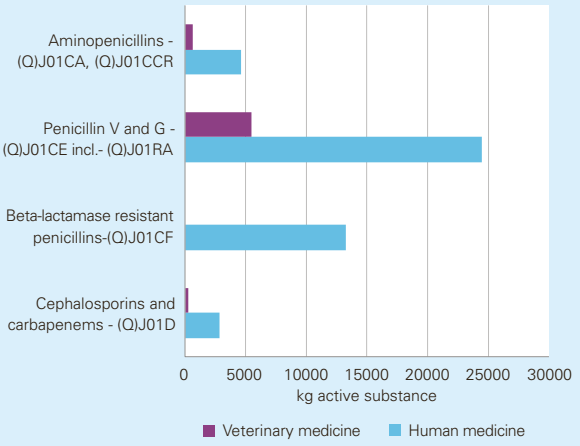
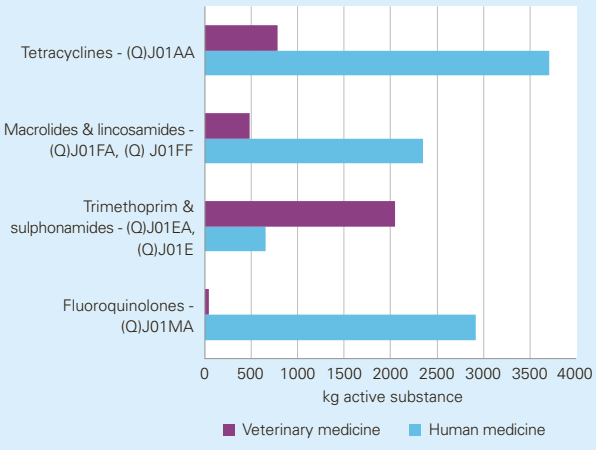


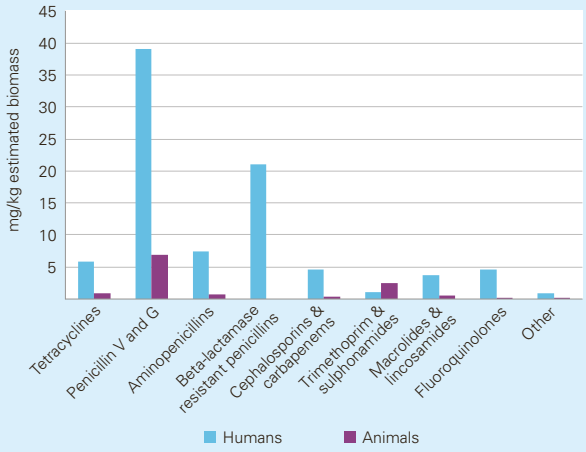
FIGURE 1.31. Consumption of fluoroquinolones, macrolides, lincosamides, trimethoprim and suphonamides, and tetracyclines in human and veterinary medicine, kg active substance, 2014. Please note the difference in indexation of the x-axis between Figure 1.30 and 1.31.



Comparison of consumption expressed as mg per estimated kg biomass

In 2014, the sales were 96.4 and 12.7 mg active substance per estimated kg biomass in human and veterinary medicine, respectively. In Figure 1.32 a comparison of consumption of antibiotics for use in humans and animals are shown expressed as mg per estimated kg biomass. Only classes where the total consumption exceeded 1000 kg active substance are shown. Data on the total consumption does not take the heterogeneity of the likelihood of exposure within the population into account. This is especially true for data on consumption for use in 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 consumption in humans is 83 times higher than in animals.

FIGURE 1.32. Consumption of antibiotics in humans and animals expressed as mg active substance per estimated kg biomass in 2014.



Antibiotic resistance

Notifiable diseases

For humans four bacterial types of antibiotic resistance are included in the Swedish Communicable Diseases Act. 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 *Enterococcus faecium* with resistance to vancomycin (VRE), and Enterobacteriaceae carrying ESBL or $ESBL_{CARBA}$. As in previous years, the reports of ESBLs have outnumbered the other three types 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.

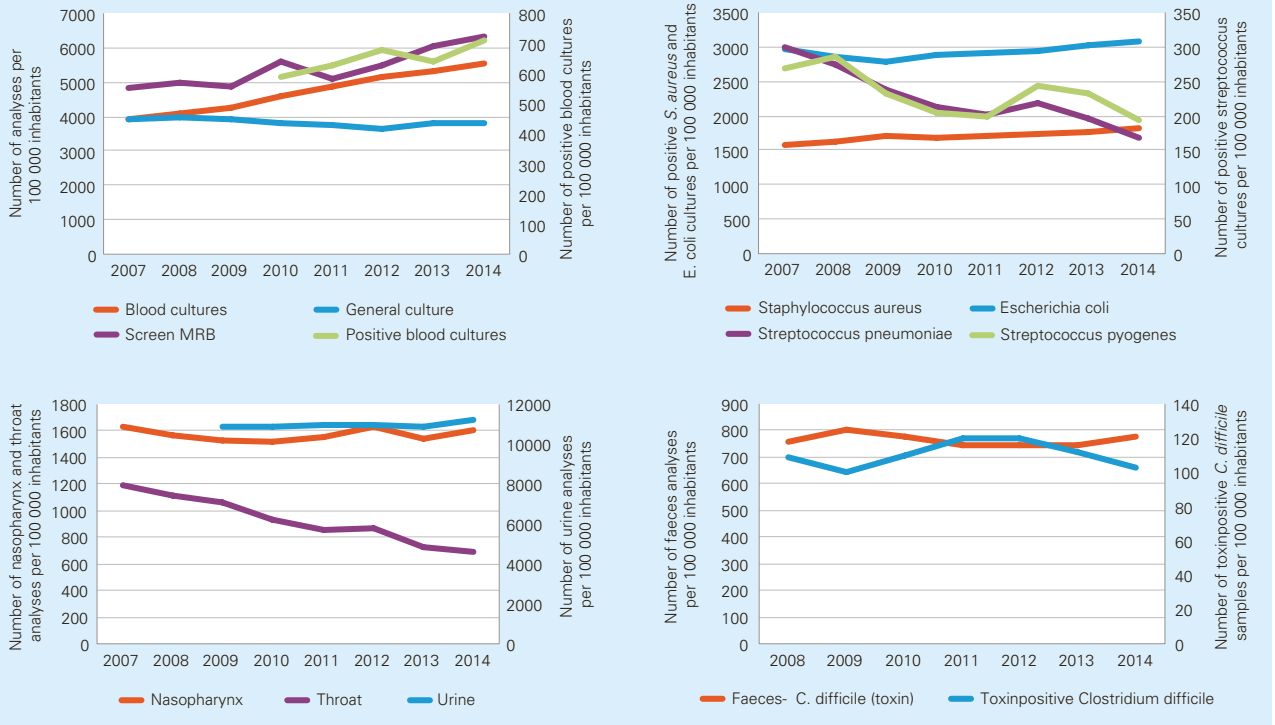
Overview of sampling and culture results in humans

Denominator data has been collected since 2001 on a voluntary basis from the microbiology laboratories in Sweden and reported each year in Swedres-Svarm as background data. The reporting laboratories, this year 24 out of 25, cover more than 95% of the population. Some modifications of the data collection has been made during the years, for instance were analyses of toxinpositive *C.difficile* included year 2008, urine cultures analyses included year 2009 and positive blood culture analyses included year 2010. Complete data for 2014 are given in the section Demographics and denominator data.

In the following figures the annual numbers of requested analyses per 100 000 inhabitants are presented for: blood culture, MRB screening culture, general culture, throat culture, nasopharynx culture, urine culture, and *C. difficile*. Number of positive blood cultures per 100 000 inhabitants and number of isolated *S. aureus*, *E. coli*, *S. pneumoniae*, and *S. pyogenes* in all specimen types per 100 000 inhabitants are also given.

In the last eight years the number of blood cultures, and MRB screening cultures requested annually per 100 000 inhabitants increased. The trends for number of positive blood cultures, and isolated *E. coli* and *S. aureus*, regardless of specimen type, were also increasing. Throat cultures and the isolation of *S. pyogenes* decreases, likely due to an increased use of near patient testing for streptococcal tonsillitis.

FIGURE 2.1. Denominator data for humans. Number of requested analyses, and number of positive analyses or isolates. All per 100 000 inhabitants.



ESBL-producing Enterobacteriaceae

ESBL-producing Enterobacteriaceae in humans

Background

ESBL-producing Enterobacteriaceae has been notifiable by clinical laboratories according to the Communicable Diseases Act since February 2007. As there is no clinical reporting, information on ESBL cases is limited to data on age, gender and sample type. From 2010, the definition of 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, additionally contact tracing became mandatory.

TABLE 2.1. Distribution of species among human cases of ESBL-producing Enterobacteriaceae 2014.

Species	Number of cases	Proportion, %
Escherichia coli	8161	89.2
Klebsiella pneumoniae	668	7.3
Proteus mirabilis	72	0.8
Citrobacter species	40	0.4
Shigella species	23	0.3
Salmonella species	16	0.2
Enterobacteriaceae (not specified or species not reported)	166*	1.8
Total number reported	**9146****	

* Distinction between an ESBL and a chromosomally mediated AmpC was not made for these bacteria.
**In 239 patients two or more ESBL-producing species were reported resulting in a higher number of isolates than number of cases reported.

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

A total of 8902 cases were notified in 2014, an increase with 9% compared to 2013. Since 2007 the number of cases has increased continuously each year with 9-33%. The national incidence was 91 cases per 100 000 inhabitants. An increased incidence was seen in 15 out of 21 Swedish counties, with the highest incidence found in Jönköping county (120 cases per 100 000 inhabitants; Figure 2.2). There was a 4-fold difference in incidence between the counties. In part the large variation in incidence between counties could be explained by different screening and contact tracing practices.

The most commonly reported species was *Escherichia coli* found in 89% of all cases, followed by *Klebsiella pneumoniae* with 7% (Table 2.1). ESBL-producing *Salmonella* species and *Shigella* species were reported in 16 and 23 cases respectively in 2014.

ESBL-producing bacteria were most often found in urine samples (59%). The second and third most common sources were fecal and rectal samples with 19% and 9% respectively. Fecal and rectal samples are usually screening samples and in recent years screening has increased. Isolates from blood and wound samples constituted 4% and 3%, respectively, and isolates were from other samples in 7% of the cases. Age, gender and sample type distribution are given in Figure 2.3. During 2014, 520 cases with ESBL-producing bacteria were reported as invasive infections (all in blood). This is an increase of 29% compared to 402 persons reported in 2013. Among these, 435 were new cases for 2014 and 85 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. The incidence (cases per 100 000 inhabitants) of ESBL-producing Enterobacteriaceae in Swedish counties 2010-2014, arranged according to incidence figures 2014.

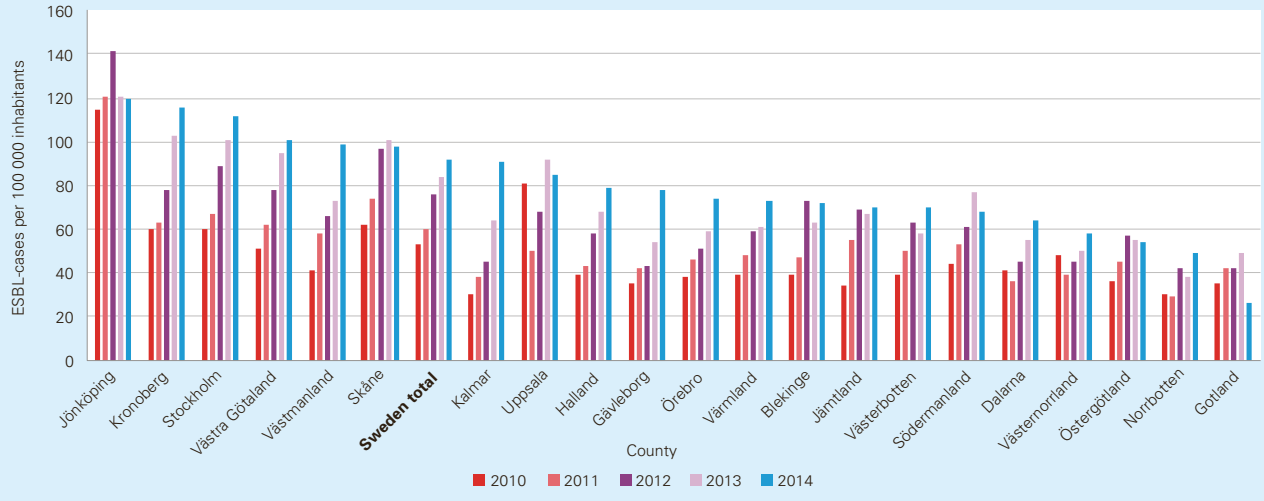
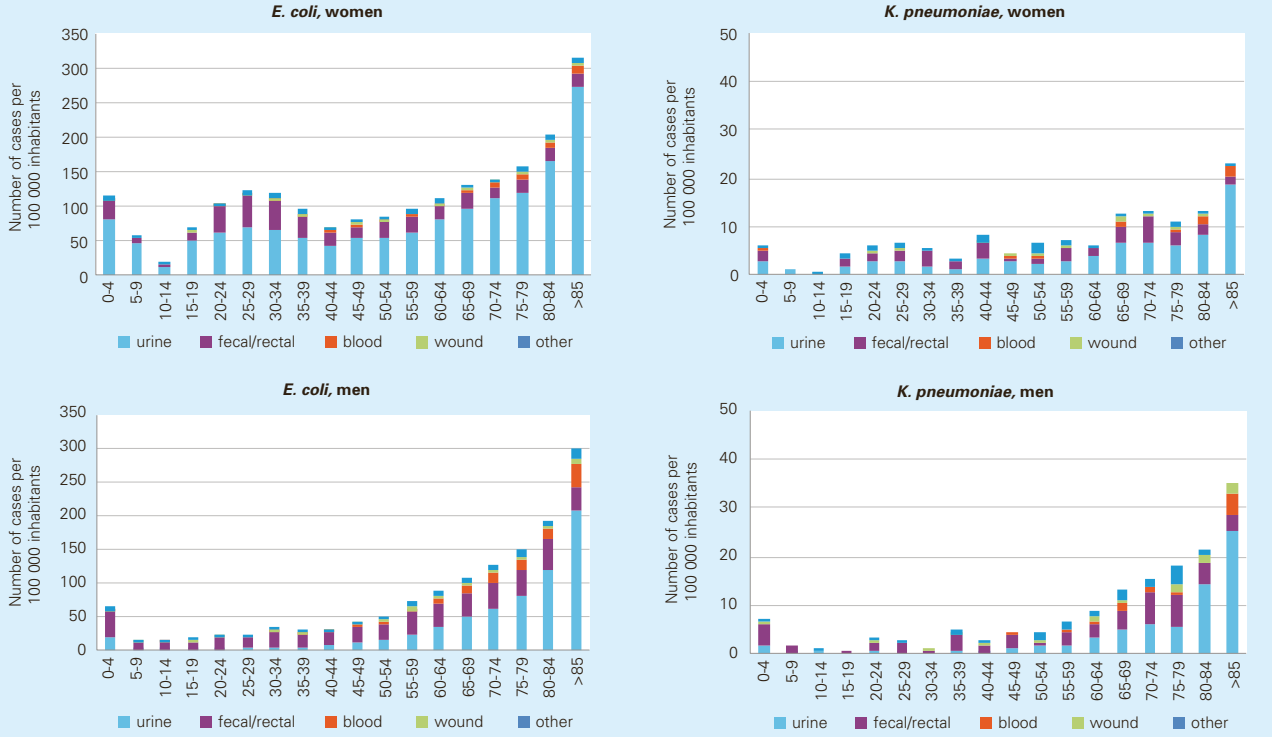


FIGURE 2.3. Age, gender and sample type distribution of human cases of ESBL-producing *E. coli* and *K. pneumoniae* 2014.



The incidence in age groups and gender differed between species (Figure 2.3). ESBL-producing *E. coli* were derived from women in 65% of the cases. They had a median age of 51 years compared to 62 years for men. The *K. pneumoniae* ESBL cases were more equally distributed between sexes, with median ages of 57 years for women and 64 years for men.

Enterobacteriaceae with carbapenemases ($ESBL_{CARBA}$)

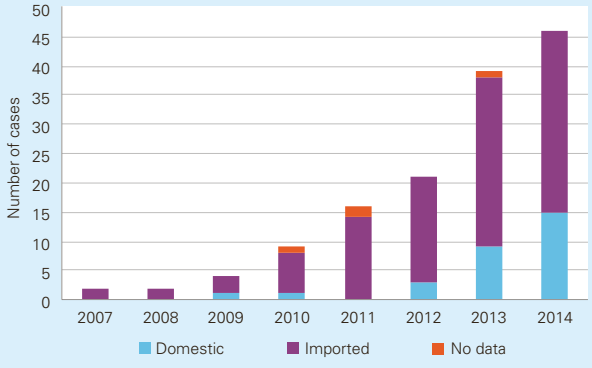
From the 15th of March 2012 Enterobacteriaceae producing carbapenemases ($ESBL_{CARBA}$) became notifiable for both physicians and laboratories. Before this date Enterobacteriaceae with an $ESBL_{CARBA}$ had been notified from the laboratories only and additional information about the cases had been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

The rationale behind the strengthened notification was that $ESBL_{CARBA}$, pose an even greater threat because of the further limited treatment options. $ESBL_{CARBA}$ of clinical importance belong to one of three kinds, either KPC (*K. pneumoniae* Carbapenemase), MBLs (Metallo-betalactamases, i.e. NDM, VIM and IMP) or certain OXA-enzymes. In Sweden, all enzymes with carbapenemase activity are denoted $ESBL_{CARBA}$ (Giske et al., 2009). A total of 141 cases with $ESBL_{CARBA}$ have been reported in Sweden 2007-2014.

In 2014, 46 new cases with an $ESBL_{CARBA}$-producing Enterobacteriaceae were reported, compared to 39 new cases in 2013. Cases were reported from twelve Swedish counties with almost half of the cases being reported from Stockholm and Skåne. Fifteen cases were reported as domestic and thirty-one cases were acquired abroad. (Figures 2.4). The five most common countries for imported infections were India (5 cases), Spain (4), Egypt (3), Greece (2) and Iraq (2).

A majority of the domestic cases, twelve cases, were detected by clinical symptoms, two were found by contact tracing and one was found by screening. Of the imported cases, twenty-three were detected through targeted screening and seven due to clinical symptoms. The way of acquisition for the domestic cases were community acquired infections (2 cases), by household contacts (1 case), or related to hospital care (2 cases) or care outside hospital (1 case). For nine domestic cases there was no information of acquisition. Among the imported cases hospital acquired infection dominated (23 cases). The other ways of acquisition for the imported cases in 2014 were, community acquired infections (3 cases), infections related to healthcare/care outside hospital (2 cases), and for one case the infection was stated to be food-and waterborne related. For two of the imported cases there was no information of acquisition.

FIGURE 2.4. Number of human cases of $ESBL_{CARBA}$ annually notified in Sweden 2007-2014.



ESBL producing *Escherichia coli* – food as a potential dissemination route to humans

This is a summary of a joint project 2009-2014 between Public Health Agency of Sweden, National Veterinary Institute and National Food Agency. The project was performed between 2009-2014 and financed by the Swedish Civil Contingencies Agency.

In Sweden, ESBL producing Enterobacteriaceae, including *Escherichia coli*, is the most commonly reported resistance type, with 8 902 cases in 2014. The main aim of this study was to investigate food as a potential source and dissemination route for ESBL-producing *E. coli* to humans. A further aim was to examine how this type of resistance is distributed in humans, foods, farm animals and the environment. By investigating the prevalence and genetic similarities between ESBL-producing *E. coli* from the different categories, an indirect measure of dispersion between settings was obtained. Such information is important for future risk management of foodstuffs in relation to ESBL-producing *E. coli*.

The study used analytical data on approximately 5 300 samples taken from foods (domestic and imported), farm animals, healthy volunteers, severely ill patients, the environment and sewage water. All samples were collected in Sweden. Except for the human clinical samples, the prevalence of ESBL-producing *E. coli* was determined by selective cultivation. To investigate similarities between ESBL-producing *E. coli* from different sample groups, molecular typing and antibiotic susceptibility testing followed by descriptive statistics were used. *Escherichia coli* producing ESBL were frequently found on chicken meat, regardless of country of origin.They also occurred to a lesser extent on imported foods: pork, beef, leafy vegetables and farmed fish foodstuffs. ESBL-producing *E. coli* isolated from imported foods and foods from other EU countries differed from those isolated from foods, only chicken meat, produced in Sweden (Figure).

In many countries, carriage of ESBL-producing bacteria is widespread and the results from this study confirm previous findings that travelling outside the Nordic countries increases the risk of becoming a carrier. The same types of ESBL-producing *E. coli* found in severely ill patients and community carriers were also found in the Swedish environment and sewage water (Figure).

A limited number of the isolates of ESBL-producing *E. coli* found in imported foods (n=5) and farm animals (n=7) were of the same type (identical MLST, plasmid replicon type and gene encoding ESBL) as those found in severely ill patients (n=1) and healthy individuals (n=4).

In conclusion, the study indicated that food on the Swedish market is a limited contributor to the occurence of ESBL-producing *E. coli* within the healthcare sector. When comparing the genes encoding ESBL there are three separate populations in Sweden today, one in Swedish foods and farm animals, one in imported foods, and one in humans and the environment. The results provide a picture of the current Swedish situation regarding occurrence of ESBL-producing *E. coli*. However, antibiotic resistance is dynamic. The national setting is influenced by changes in global epidemiology and the situation can change rapidly. Therefore, continuous monitoring of the prevalence of ESBL-producing bacteria in foods and in the environment, as well as in humans, is needed so that future risks can be assessed and management plans updated. Limiting the spread of resistance and maintaining the efficacy of antibiotics is a major challenge in the world today.

FIGURE. Distribution of ESBL-genes.

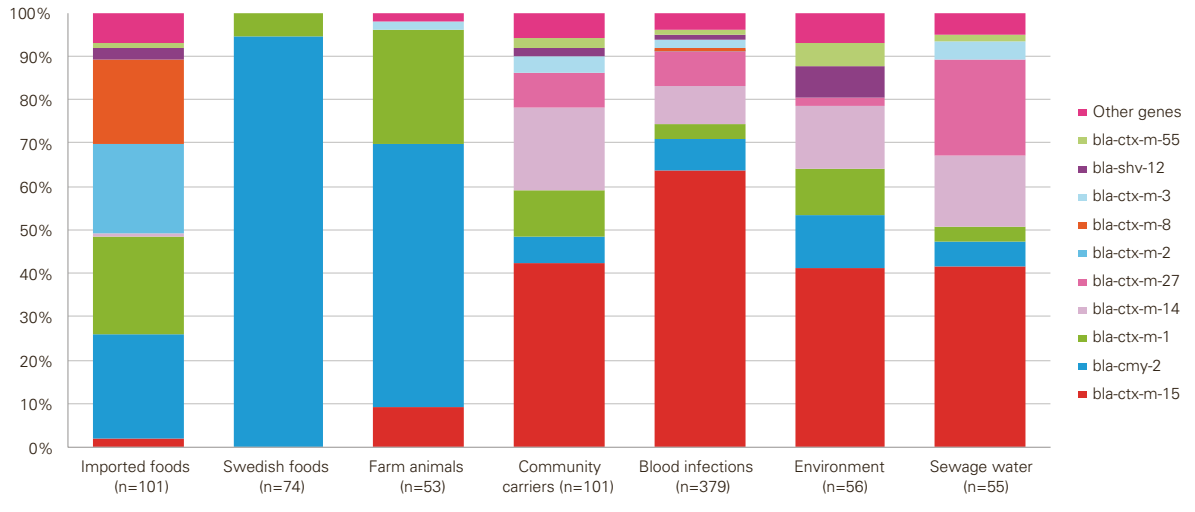


FIGURE 2.5. Number of cases and types of $ESBL_{CARBA}$ in Enterobacteriaceae in Sweden 2009-2014. In samples from two persons in 2013, and in three persons 2014 two different enzyme types were detected in the same isolate, and in samples from five persons in 2013 and in six persons in 2014 the same enzyme type was detected in more than one bacterial species.

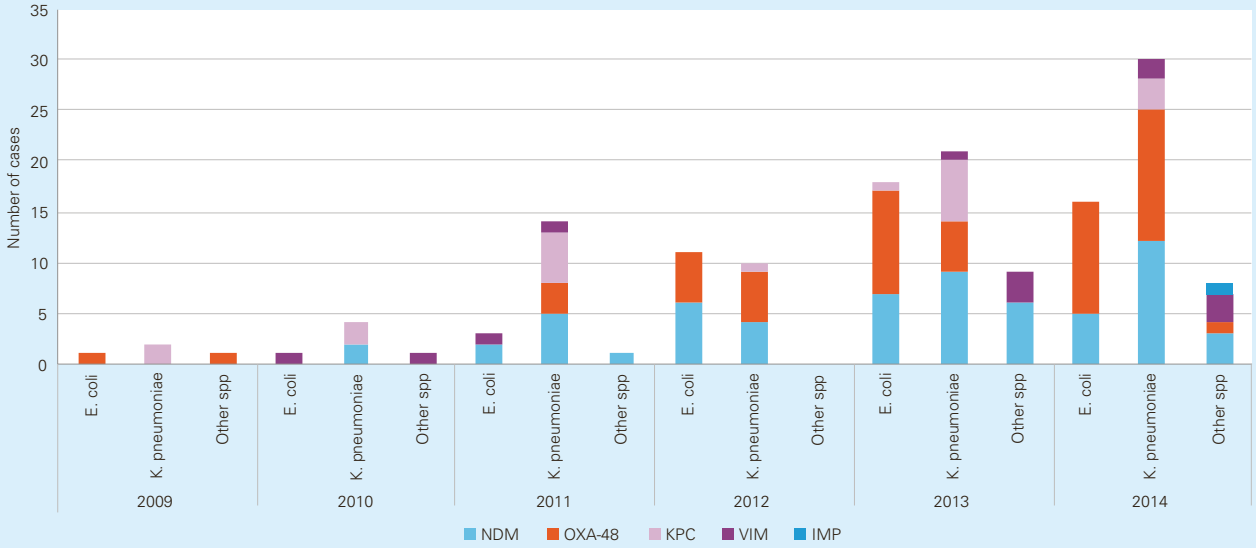
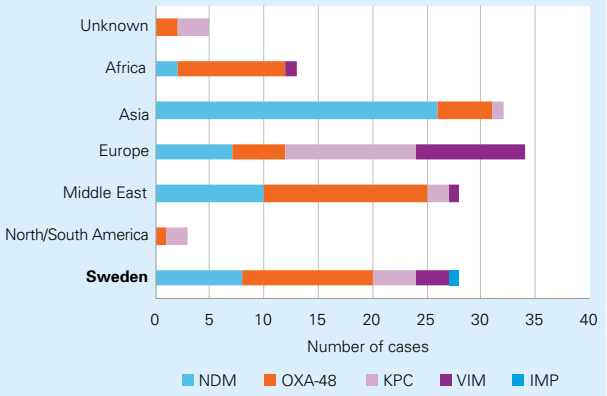


FIGURE 2.6. Carbapenemase subtypes isolated from human cases of $ESBL_{CARBA}$ notified in Sweden 2007-2014, presented in relation to region of acquisition.



The $ESBL_{CARBA}$-producing Enterobacteriaceae were identified in fecal/rectal samples (20), urine (18), wound (5), respiratory samples (1), blood (1), and one biopsy sample. Two cases of invasive infection with $ESBL_{CARBA}$ were notified in 2014. For one of the invasive cases $ESBL_{CARBA}$ was first isolated from a wound sample. The cases were almost equally distributed between the sexes and the median ages were 64 and 58 years for women and men, respectively.

In 2014 the most common carbapenemase-producing Enterobacteriaceae was *K. pneumoniae* (28 isolates) followed by *E. coli* (15 isolates). Genes coding for carbapenem resistance have also been detected in several other species of Enterobacteriaceae (Figure 2.5). In 2014 an isolate producing Imipenemase Metallo-beta-lactamase (IMP) was identified for the first time in Sweden. The IMP-producing carbapenem-resistant *Citrobacter* species isolate was recovered from a urine sample from a domestic patient with no information on way of acqusition. With the IMP-isolate five different types of $ESBL_{CARBA}$ have been identified so far. The enzyme types OXA-48 and NDM continues to dominate in 2014. Both these types of enzymes were detected in *E. coli* and *K. pneumoniae* isolates, in most cases together with CTX-M (=$ESBL_A$) and/ or pAmpC CIT (=$ESBL_M$) enzymes. In Figure 2.6 all $ESBL_{CARBA}$ enzymes isolated from cases notified in Sweden 2007-2014 are presented in relation to region of acquisition. All isolates with $ESBL_{CARBA}$ were multiresistant, leaving very few options for antibiotic treatment.

ESBL-producing Enterobacteriaceae in animals

Farm animals

In Svarm, active screening for ESBL-producing *E. coli* (including plasmid-mediated AmpC) in healthy farm animals using samples collected at slaughter for the studies of indicator bacteria has been performed since 2008. During 2014, caecal samples from healthy broilers (n=200) and healthy turkeys (n=60) were screened for *E. coli* resistant to ESCs. Isolates with reduced susceptibility were further investigated by molecular methods for presence of transferrable genes coding for ESC resistance (for details see Material and methods, resistance in bacteria from animals). In Sweden, carbapenemase producing Enterobacteriaceae ($ESBL_{CARBA}$) in animals are notifiable but this is not the case for classical ESBLs ($ESBL_A$) or plasmid-mediated AmpC ($ESBL_M$).

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. In 2014, $ESBL_A$ or $ESBL_M$ were detected in 71 (36%) of the caecal samples from broilers, but in none of the caecal samples from turkeys.

One isolate from broilers carried the gene $bla_{CTX\text{-}M\text{-}1}$ (i.e. $ESBL_A$) and 70 isolates a gene of the CIT-group (i.e. $ESBL_M$). The gene belonging to the CIT-group in those isolates has not been sequenced, but historically such isolates

have always carried the gene bla_{CMY-2}. This has also been the dominating gene among broilers in Sweden since the high occurrence was discovered in 2010.

The majority (68%) of the $ESBL_A$ or $ESBL_M$ from broilers was only resistant to betalactams. Other existing resistance traits were resistance to sulphonamides (19%), tetracycline (10%), ciprofloxacin (10%) and nalidixic acid (7%). Seven isolates (10%) were multiresistant and all of these had, in addition to resistance to betalactams, resistance to sulphonamide and tetracycline in their phenotype.

Among the 71 isolates with $ESBL_A$ or $ESBL_M$ from broilers, there were 8 that had decreased susceptibility to ertapenem

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

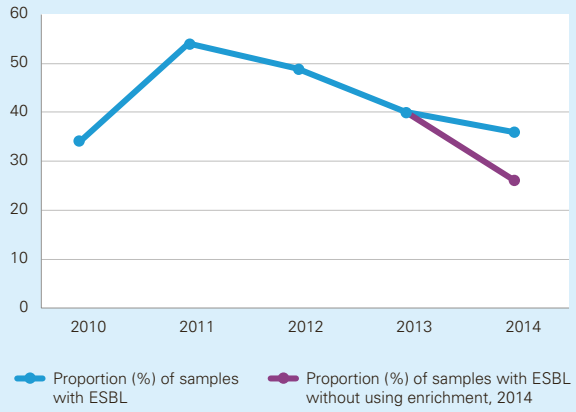
Animal species	Broilers	Calves	Dogs	Horses	Laying hens	Pigs	Turkeys
Year	2014	2013	2012	2010	2012	2011	2014
Number of samples	200	202	84	431	69	184	60
Percent (%) $ESBL_A$	<1	<1	0	1	4	2	0
Percent (%) $ESBL_M$	35	0	1	0	9	0	0

TABLE 2.3. Clinical isolates of different bacterial species of Enterobacteriaceae, producing $ESBL_A$ or $ESBL_M$ enzymes, from companion animals and horses submitted 2008-2014.

Animal species	$ESBL_A$ or $ESBL_M$	Bacterial species	2008	2009	2010	2011	2012	2013	2014
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				
	CMY-16	*Escherichia coli*							1
	unknown	*Escherichia coli*				1			
Dogs	CTX-M-1	*Enterobacter cloacae*							4
	CTX-M-1	*Escherichia coli*			1		1	1	3
	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	6
	CTX-M-15	*Escherichia coli*	1			2	3	2	
	CTX-M-15	*Klebsiella pneumoniae*		1					
	CTX-M-27	*Escherichia coli*				3		1	1
	SHV-12	*Escherichia coli*							2
	CMY-2	*Escherichia coli*			1	9	4	5	5
	CMY-2	*Proteus mirabillis*				1			
	unknown	*Escherichia coli*		1	1				
Horses	CTX-M-1	*Enterobacter* spp.						1	
	CTX-M-1	*Escherichia coli*		2	9	8	3	3	2
	CTX-M-1	*Klebsiella oxytoca*							1
	CTX-M-1	*Serratia odorifera*			1				
	CTX-M-9	*Escherichia coli*							1
	CTX-M-14	*Escherichia coli*				1			
	CTX-M-15	*Escherichia coli*		1	1				
	CTX-M-15	*Klebsiella pneumoniae*		1					
	SHV-12	*Citrobacter braakii*			1				
	SHV-12	*Enterobacter amnigenus*							1
	SHV-12	*Enterobacter cloacae*							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	
	SHV-12	*Klebsiella pneumoniae*							1
	unknown	*Enterobacter cloacae*							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.

FIGURE 2.7. Proportion (%) of samples from broilers positive for $ESBL_A$ or $ESBL_M$ from 2010 to 2014.



(MIC 0.12 – 0.25 mg/L), but no isolates with decreased susceptible to imipenem or meropenem. Two of the isolates with decreased susceptibility to ertapenem, including the one with MIC of 0.25, were further investigated with PCR but no genes conferring resistance to carbapenems were detected. Ertapenem is known to have lower specificity to detect carbapenemase producing Enterobacteriaceae than imipenem and meropenem (Cohen Stuart et al., 2010).

Since 2011, there has been a gradual decrease in the proportion of samples from broilers that are positive for $ESBL_A$ or $ESBL_M$ (Figure 2.7), and the difference between the occurrence in 2012 and in 2014 is statistically significant ($p<0.01$, X^2). Furthermore, in 2014 the screening method was altered compared to 2013 and pre-enrichment in MacConkey broth with cefotaxime was included before the samples were cultured on MacConkey agar with cefotaxime (for details on methodology see Material and methods, resistance in bacteria from animals). The samples were also cultured in duplicate according to the previous method and if only that had been used, $ESBL_A$ or $ESBL_M$ would have been isolated from 52 (26%) of the samples. When that figure is compared to figures from 2013, the difference is significant ($p=0.01$, X^2).

The occurrence of $ESBL_A$ or $ESBL_M$ in turkeys has been investigated in two consecutive years, 2013 and 2014, and a total of 115 samples have been analysed. No such resistance has been found even though 28 (24%) isolates have shown phenotypical ESC resistance. Furthermore, in 2014 phenotypical resistance to ESC was detected in one isolate of indicator *E. coli* from a turkey, but genes conferring transmissible $ESBL_A$ or $ESBL_M$ resistance were not detected.

Companion animals and horses

During 2014, a total of 30 isolates of Enterobacteriaceae with phenotypic resistance to ESCs were confirmed to produce $ESBL_A$ or $ESBL_M$ at SVA (Table 2.3). The isolates were from cat (n=1), dogs (n=21) and horses (n=8), and the majority was isolated from wounds or from the urogenital tract.

TABLE 2.4. Notifications of human cases of MRSA according to the Communicable Disease Act 2010-2014 by county.

County	2010		2011		2012		2013		2014	
	No	Inc *	No	Inc*	No	Inc*	No	Inc*	No	Inc*
Blekinge	8	5.2	17	11.1	24	15.8	32	20.9	37	24.0
Dalarna	27	9.7	38	13.7	33	11.9	35	12.6	61	21.9
Gotland	5	8.7	9	15.7	11	19.2	15	26.2	17	29.7
Gävleborg	26	9.4	36	13.0	35	12.7	51	18.3	50	17.9
Halland	40	13.4	51	16.9	47	15.5	58	18.9	55	17.7
Jämtland	28	22.1	19	15.0	33	26.1	54	42.7	51	40.2
Jönköping	54	16.0	61	18.1	82	24.2	126	36.9	118	34.3
Kalmar	72	30.8	45	19.3	72	30.8	82	35.1	140	59.4
Kronoberg	23	12.5	40	21.7	40	21.5	54	28.9	89	47.1
Norrbotten	21	8.4	20	8.0	31	12.5	39	15.6	73	29.2
Skåne	313	25.2	369	29.5	384	30.4	394	30.9	488	37.9
Stockholm	412	20.0	502	24.0	589	27.7	623	28.8	685	31.2
Södermanland	30	11.1	34	12.5	32	11.6	50	18.0	66	23.5
Uppsala	41	12.2	42	12.4	80	23.4	76	22.0	98	28.1
Värmland	28	10.2	48	17.6	40	14.6	80	29.2	66	24.0
Västerbotten	39	15.0	20	8.0	21	8.1	34	13.0	40	15.2
Västernorrland	30	12.4	24	9.9	35	14.5	40	16.5	56	23.0
Västmanland	32	12.7	28	11.0	31	12.1	50	19.3	68	26.0
Västra Götaland	264	16.7	347	21.8	360	22.5	439	27.2	463	28.4
Örebro	40	14.3	44	15.6	55	19.4	50	17.5	106	36.8
Östergötland	47	10.9	71	16.5	62	14.3	72	16.4	94	21.3
Total	**1580**	**16.8**	**1884**	**19.9**	**2097**	**21.9**	**2454**	**25.4**	**2921**	**30.0**

*=Incidence (cases per 100 000 inhabitants)

Zoonotic aspects on ESBL-producing Enterobacteriaceae

In 2011, the European Food Safety Authority (EFSA) concluded that there was 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. Both of these aspects has also been investigated in a recent publication by deBeen et al. (2014).

The 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 6% are of the $ESBL_M$ type. Furthermore, a recent Swedish study investigating the potential overlap between clinical human isolates and isolates from healthy farm animals and food concluded that the overlap was limited and that food in Sweden was not a source for ESBLs for humans (see In focus ESBL producing *Escherichia coli* – food as a potential dissemination route to humans for more details). Nevertheless, continued vigilance towards development of reservoirs of ESBL-producing Enterobacteriaceae in animals is warranted.

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 notifications have been reviewed and complemented with available relevant epidemiologic information from investigations around each case in collaboration with the CMOs. This has been performed the last eight years.

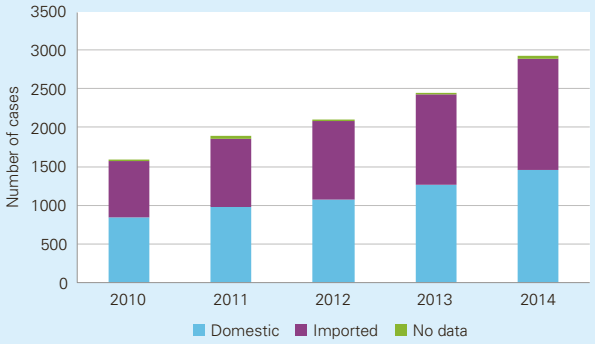
Notifications of MRSA according to the Communicable Disease Act

In 2014 a total of 2921 cases of MRSA were notified, an increase by 467 cases (19%) compared to 2013 (Figure 2.8). The average national incidence was 30 cases per 100 000 inhabitants with higher than average incidence figures in Kalmar (59.4), Kronoberg (47.1), Jämtland (40.2), Skåne (37.9), Örebro (36.8), Jönköping (34.3) and Stockholm (31.2) counties.

In 2014, 50% (n=1452) of all reported MRSA were domestic cases and 49% (n=1428) were acquired abroad. Syria (183 cases), Iraq (97), Philippines (76), Eritrea (64) and Egypt (44) made up the five most common countries for imported MRSA. For approximately one percent country of infection was missing ("No data").

Among the domestic MRSA cases 2014, the incidence was highest in the age group 0-6 years, followed by the age group 80 years and older (Figure 2.9). The incidence of MRSA among the very old and the very young was substantially higher (≥ 23) than in the other age groups. In the other age groups the incidence remained at a low but slightly increasing level, in 2014 reaching 10-14. Among children (0-6 years), the infants (0 years) had by far the highest incidence (Figure 2.10). Infant MRSA cases were mainly detected through contact tracing (56%), 24% by screening and 19% by clinical symptoms. Of 160 cases among infants, 29 (18%) were hospital related, 18 of these were part of neonatal outbreaks comprising three or more cases, 116 cases (72%) were community acquired.

FIGURE 2.8. Number of human cases of MRSA notified annually by country of infection, Sweden 2010-2014.



In 2014, 43% of the domestic cases were identified through contact tracing, 10% in targeted screening, and 45% during investigations of clinical symptoms (Figure 2.11 A). For imported cases the corresponding figures were 17%, 48%, and 33%, respectively (Figure 2.11 B). The majority of samples from investigations of clinical symptoms were wound samples (62%). Invasive MRSA infection was reported in 39 cases 2014 compared to 42 cases 2013. Thirty of those were newly notified cases 2014 and nine occurred in patients already known to carry MRSA in previous years.

Epidemiological classification of the acquisition of MRSA was based on information in the clinical notifications and from subsequent investigations by the CMOs, Figures 2.11, A and B. Community-acquired infections dominated among domestic cases 2014 and comprised 76% (n=1100) of all domestic cases, Figure 2.12 A. Among the imported cases the proportion of community acquired infections was 50% (n=707), Figure 2.12 B. Hospital acquired MRSA was comparatively more common in imported cases, 28% (n=393), than among domestic cases, 8% (n=109). The number of domestic cases with hospital acquired MRSA decreased from 147 (2013) to 109 (2014). On the other hand, the number of domestic cases with MRSA acquired in healthcare/care outside hospital increased slightly to 112 in 2014 compared to 91 in 2013. In addition, the number of imported cases with MRSA acquired in healthcare/care outside hospital increased to 113 (8%), from 65 (6%) in 2013.

Outbreak investigations

During 2014, twenty outbreaks (three or more cases/outbreak) were reported in nine different counties. These outbreaks comprised 100 cases, representing 3% of all cases of

FIGURE 2.9. Incidence per age group of all notified domestic human cases of MRSA in Sweden 2010-2014.

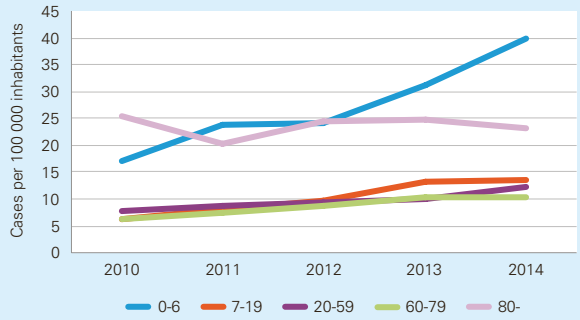


FIGURE 2.10. Incidence of notified domestic human cases of MRSA in the age group 0-6 years in Sweden 2010-2014.

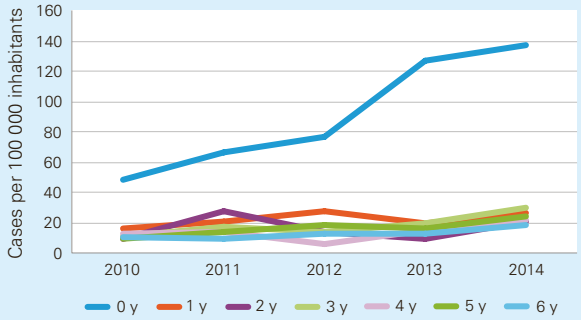


FIGURE 2.11, A AND B. Indications for sampling of domestic (A, top) and imported (B, bottom) MRSA cases in Sweden 2010-2014. Number of reported human cases each year is shown in brackets.

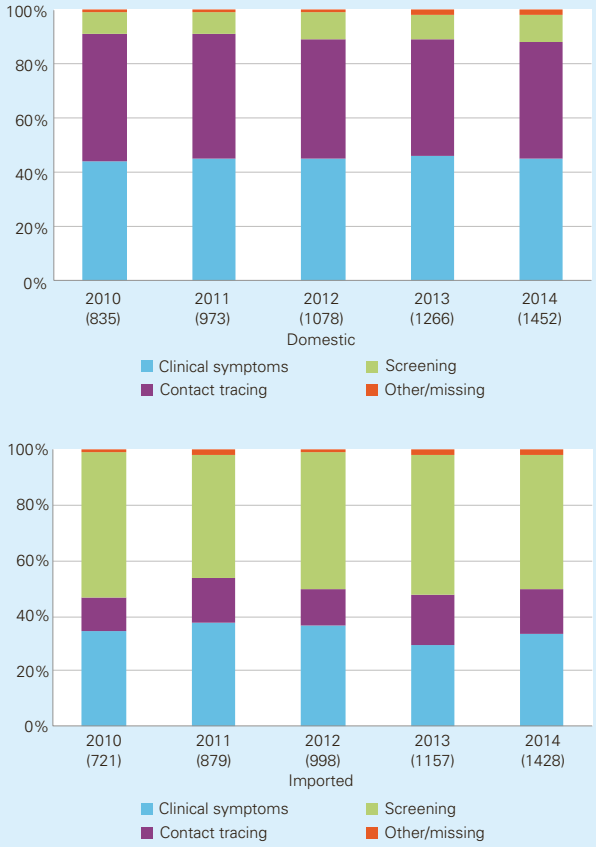
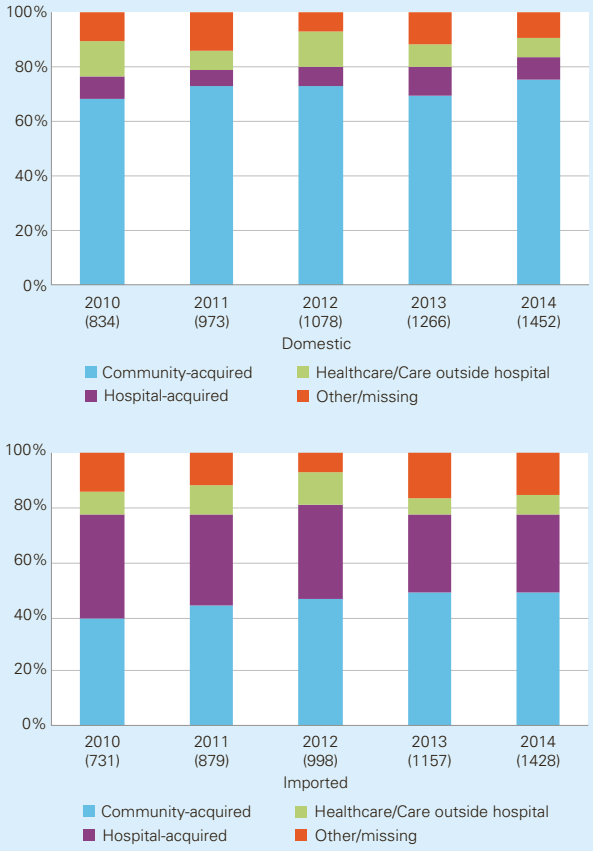


FIGURE 2.12, A AND B. Epidemiological classification of human cases of MRSA, A, top: domestic, and B, bottom: imported , Sweden 2010-2014. Number of reported cases each year is shown in brackets.



MRSA in 2014. The three most common *spa*-types were t790, t002 and t2958. Fourteen outbreaks were reported from healthcare institutions outside hospitals, whereas four were hospital outbreaks. One of the outbreaks in 2014 was connected to sport.

Epidemiological typing of MRSA

The primary method used for epidemiological typing of MRSA isolates sent to the Public Health Agency of Sweden is *spa*-typing. This is a DNA sequence based method with a standardized, unambiguous and internationally well recognized nomenclature (http://spaserver.ridom.de/). In addition, PVL status (absence/presence of genes coding for PVL) of each isolate is determined and used as an epidemiological marker that differentiates MRSA variants within *spa*-types.

In 2014, *spa*-typing results were available for MRSA isolates from 98% of the notified cases. All but 13 of the 2856 isolates were typable, and a total of 402 *spa*-types were recorded. The ten most common *spa*-types in 2010-2014 are listed in Table 2.5. In 2014, 46% of the cases (n=1322) had an MRSA with a top ten *spa*-type. Seven of these *spa*-types have been among the top ten during 2010-2014; t223, t008, t044, t002, t127, t019 and t437. Three of the top ten *spa*-types in 2010, t032, t015 and t021, were not seen among the top ten

TABLE 2.5. The ten most common *spa*-types among MRSA from notified human cases in 2010 - 2014. Number of notifications per *spa*-type and percent PVL-positive isolates are shown for 2013 and 2014.

2010	2011	2012	2013			2014		
spa-type	*spa*-type	*spa*-type	*spa*-type	No.	PVL-pos (%)	*spa*-type	No.	PVL-pos (%)
t008	t008	t002	t008	176	88	t223	232	3
t002	t002	t008	t002	166	29	t008	186	81
t044	t019	t019	t223	139	1	t044	178	94
t019	t044	t223	t044	121	93	t002	172	32
t223	t223	t044	t127	104	27	t127	127	38
t437	t127	t127	t019	93	94	t304	120	10
t127	t437	t437	t304	59	8	t019	116	91
t032	t690	t015	t437	47	77	t690	71	72
t015	t015	t304	t690	46	46	t437	69	62
t021	t790	t690	t386	32	0	t386	51	6
			t688	32	0			

in 2014, and three of the top ten *spa*-types in 2014, t304, t690 and t386, were not seen among the top ten in 2010.

Table 2.6 shows the top ten *spa*-types seen among isolates from cases with domestically acquired MRSA (n=680) and MRSA acquired abroad (imported, n=633), respectively, for 2014. Eight of the *spa*-types were present among the top ten in both groups; t002, t223, t008, t044, t127, t304, t019 and t690. The two *spa*-types seen only among the top ten in the domestic group were t267 and t790, and the two seen only among the top ten in the imported group were t437 and t386.

In 2014, 35% of the cases (n=1011) had PVL-positive MRSA, compared to 37% in 2013. The most common MRSA variants seen during 2014 were t223, PVL-negative (n=225), t044, PVL-positive (n=167), t008, PVL-positive (n=151), t002, PVL-negative (n=117), t304, PVL-negative (n=108), t019, PVL-positive (n=106), t127, PVL-negative (n=79), t002, PVL-positive (n=55), t690, PVL-positive (n=51), t386 PVL-negative (n=48) and t688, PVL-negative (n=48).

TABLE 2.6. The ten most common spa-types among MRSA from notified human cases with domestically acquired MRSA and MRSA acquired abroad (imported), respectively, for 2014. 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 (%)
t223	109	5	t223	118	2
t002	106	32	t008	86	80
t008	100	82	t044	79	90
t044	96	97	t019	71	90
t304	64	8	t127	65	43
t127	59	34	t002	64	31
t019	44	95	t304	52	10
t690	38	87	t437	36	61
t267	32	0	t386	32	6
t790	32	0	t690	30	50

MRSA in animals

In Sweden, MRSA in animals was first verified in 2006 and was made notifiable in 2008. During 2014, 18 new cases of MRSA were detected; 9 horses, 3 dogs, 3 hedgehogs, 2 cats and 1 dairy cow. Up to and including 2014, a total of 80 cases in animals have been confirmed (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 or cefoxitin were further analysed with confirmatory tests. Screening studies for active monitoring have been performed in pigs, cattle, horses and dogs during different years (see below).

Farm animals

During 2014, a screening study in nucleus and multiplying pig herds was performed (see In focus: MRSA in pigs in Sweden). MRSA was not detected. Screening studies have previously been performed four times in pigs since 2006, with only one positive sample from pigs at slaughter in 2010. In dairy cattle, active monitoring of selected isolates of beta-lactamase producing *S. aureus* from milk samples has been ongoing since 2010, and 702 isolates have been tested up to and including 2014. One isolate from each submission of beta-lactamase producing *S. aureus*, if present, is tested. In this monitoring, PVL-negative MRSA with *mecC* was detected four times in 2010-2011 (Unnerstad et al., 2013), and once in 2013. PVL-positive MRSA with *mecA* was detected in 2012 and PVL-negative MRSA with *mecA* in 2014. During 2013, 513 isolates without beta-lactamase production were part of the monitoring as well, without any findings of MRSA. The above mentioned monitoring is performed on isolates with anonymized origin. In addition, PVL-positive MRSA with *mecA* was isolated from milk and body samples of cattle on the same dairy farm in 2012, 2013 and 2014 (see Zoonotic aspects on MRSA).

Companion animals and horses

In dogs, cats and horses, there was no active monitoring of MRSA during 2014. 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 2014, MRSA was detected in clinical samples, mostly from wound infections, from three dogs, two cats and nine horses.

Since the first finding of MRSA in companion animals, *spa*-type t032 has been most common (Table 2.8), and in isolates from horses *spa*-type t011, CC398, has dominated. Most isolates from horses have been from clinical cases with postoperative wound infections (Table 2.7), and all isolates from both companion animals and horses have been PVL-negative.

Wild animals

In 2012, two MRSA-isolates were confirmed retrospectively from hedgehogs sent in for post mortem investigation in 2003 and 2011. In 2014, MRSA was isolated from three more hedgehogs. Two isolates came from post mortem investigations and one from a live animal with skin wounds. All isolates from hedgehogs were MRSA with *mecC* (Table 2.7). The isolate from 2003 was retrospectively found to be the first known isolate of MRSA from animals in Sweden, although not confirmed until 2012.

Zoonotic aspects on MRSA

Zoonotic transmission of MRSA occurs by direct or indirect contacts, making farmers, animal caretakers, 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 livestock-associated MRSA CC398 in many countries.

So far, there is no indication of zoonotic transmission of MRSA of importance in Sweden. However, sporadic transmission from humans to animals probably occurs, in particular concerning companion animals.

MRSA CC398

Internationally, 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 screening study in 2014, MRSA was not detected in Swedish pigs, indicating a favourable situation, see In Focus: MRSA in pigs in Sweden. In Sweden, MRSA CC398 occurs among horses with *spa*-type t011 as the most common type (Table 2.7).

In humans, PVL-negative MRSA of five CC398-associated *spa*-types (t034, t011, t571, t108 and t1606) were detected in 70 human cases in 2006-2014. The two dominating *spa*-types were t011 (n=34) and t034 (n=30). Twenty-one of the 70 cases were from 2014, fifteen with *spa*-type t011, five with t034 and one with t1606. *Spa*-type t011 was seen in both humans and horses. There is, however, no known indication of transmission between animals and humans, but the epidemiological information on these cases is 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). In Sweden, MRSA with *mecC* has been isolated from milk from dairy cows, from hedgehogs and from cats (Table 2.7 and 2.8).

MRSA with *mecC* has been found in 64 human cases 2011-2014. In total, 15 *spa*-types were seen among human isolates. The two most common were t373 (16 cases) and t843 (16 cases). Five *spa*-types have been seen among isolates from both humans and animals, t843 (dairy cows and hedgehog), t978 (hedgehog, cats), t3391 (hedgehog), t5771 (hedgehog) and t9111 (dairy cows). No epidemiological link is, however, known between the animal and human cases.

Potential transmission from humans to animals

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.

In 2012, PVL-positive MRSA of *spa*-type t002 was isolated from a dairy farmer and from several of the dairy cows and a few other cattle in the farm. 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 cattle on the farm both in 2013 and 2014.

In 2014, MRSA of *spa*-type t127 was detected in a milk sample with anonymized origin. Because this *spa*-type is common in humans, transmission from humans to cow can be suspected. There is, however, no epidemiological information available about this case.

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). Once a carrier, an animal can act as a source of MRSA for other humans. 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, but in 2014 it was only found in 27 isolates. In later years, isolates with other *spa*-types have been detected in dogs, some of these types being common in humans.

TABLE 2.7. Large animals and wildlife. Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in Swedish horses, pigs, cows and hedgehogs up to and including 2014. All isolates were positive for the *mecA* or *mecC* and *nuc* genes by molecular methods. Shaded areas indicate MIC above EUCAST cut-off values.

Animal species	Year	Clinical background/ Sampling site	Antimicrobial													*spa*-type	*mec*-gene
			Oxa[a]	Fox	Pen	Cet	Cli	Ery	Tet	Fus	Gen	Kan	Cip	Tmp	Chl		
Horse	2007	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	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	8	>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	abscess	>16	4	>4	>8	≤0.25	1	64	1	>64	>32	1	>32	16	t011	*mecA*
Horse	2014	wound	>16	>16	>4	4	≤0.25	1	64	0.25	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	post-op wound	>16	>16	>4	1	≤0.25	≤0.25	32	0.12	16	>32	0.25	>32	8	t011	*mecA*
Horse	2014	wound	>16	>16	>4	1	≤0.25	≤0.25	32	≤0.06	8	>32	0.25	>32	8	t011	*mecA*
Horse	2014	wound	>16	>16	>4	4	≤0.25	≤0.25	32	0.12	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	wound	>16	>16	>4	4	≤0.25	≤0.25	32	≤0.06	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	unknown	>16	>16	>4	2	≤0.25	≤0.25	32	0.12	32	>32	0.25	>32	8	t011	*mecA*
Horse	2014	post-op wound	>16	>16	>4	2	≤0.25	≤0.25	32	0.12	64	>32	0.12	>32	8	t011	*mecA*
Horse	2014	umbilical wound	>16	>16	>4	2	≤0.25	≤0.25	16	≤0.06	64	>32	0.25	>32	8	t011	*mecA*
Horse	2014	post-op wound	16	>16	>4	4	≤0.25	≤0.25	32	≤0.06	64	>32	>4	>32	8	t011	*mecA*
Pig	2010	snout	>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*
Cow	2014	milk screening	>16	>16	>4	2	≤0.25	>32	16	0.25	≤0.5	>32	0.25	2	8	t127	*mecA*
Hedgehog	2003	kidney	16	16	2	2	≤0.25	1	≤0.5	1	1	8	0.5	4	8	t5771	*mecC*
Hedgehog	2011	skin infection	4	16	2	1	0.5	1	≤0.5	1	1	8	0.5	2	8	t843	*mecC*
Hedgehog	2014	lung	16	>16	2	1	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	0.25	1	8	t978	*mecC*
Hedgehog	2014	spleen	16	>16	2	2	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	0.25	0.5	8	t3391	*mecC*
Hedgehog	2014	skin infection	16	>16	2	2	≤0.25	≤0.25	≤0.5	0.5	≤0.5	4	0.5	1	16	t6300	*mecC*

[a] Tested with 2% NaCl

TABLE 2.8. Companion animals. Isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in Swedish dogs and cats up to and including 2014. All isolates were positive for the *mecA* or *mecC* and *nuc* genes by molecular methods. Shaded areas indicate MIC above EUCAST cut-off values.

Animal species	Year	Clinical background/ Sampling site	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*
Dog	2014	wound	16	>16	>4	2	≤0.25	1	16	0.5	1	8	0.5	4	8	t325	*mecA*
Dog	2014	unknown	>16	>16	>4	8	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	2	>4	1	8	t032	*mecA*
Dog	2014	unknown	>16	>16	>4	1	≤0.25	>32	≤0.5	≤0.06	≤0.5	2	0.25	1	8	t002	*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															
Cat	2014	wound	8	>16	1	2	≤0.25	≤0.25	≤0.5	0.25	≤0.5	2	0.25	0.5	8	t978	*mecC*
Cat	2014	unknown	8	>16	2	1	≤0.25	≤0.25	≤0.5	≤0.06	≤0.5	1	0.25	0.5	8	t978	*mecC*

[a] Tested with 2% NaCl; [b] The isolate was not available for further laboratory analyses.

MRSA in pigs in Sweden

MRSA in pigs

MRSA of clonal complex 398 (CC 398) is widespread in pigs in many countries and pigs are mostly carriers without clinical symtoms. The bacteria are spread by direct or indirect contact and therefore trade of live pigs is an obvious risk factor for occurrence of MRSA in pig herds (Crombé et al., 2013). Use of antibiotics and large herd size are also associated with a higher risk of MRSA (Crombé et al., 2014).

Hitherto few efforts have been made to mitigate or control MRSA in pigs. An exception is Norway where MRSA is controlled by depopulation of positive farms and cleaning and desinfection of premeses before restocking. (http://www.mattilsynet.no).

In Sweden, the aim is so far to counteract introduction and spread of MRSA in pig herds. To this end pig farmers and their employees have been informed on MRSA CC398 and adviced on biosecurity measures to mitigate its introduction to pig herds. Also, breeding pigs traded from other countries are quarantained and tested for MRSA before introduced to herds in Sweden. Similarly, semen traded from other countries is tested for MRSA.

Screening studies in Swedish pigs

Five screening studies have been performed in different categories of pigs in Sweden:

- 100 herds producing pigs for slaughter were sampled in 2006-2007.
- 208 production herds and breeding herds were sampled in an EU baseline study in 2008.
- Pigs from 191 herds were sampled at slaughter in 2010.
- All 53 nucleus and multiplying herds were sampled in 2011.
- All 39 nucleus and multiplying herds were sampled in 2014.

Of all samples taken, MRSA was only found in one pooled sample from five pigs from one herd at slaughter in 2010. Since the sampling was performed blindly, the herd was not known and no measures were taken.

Nucleus and multiplying herds are selling live animals to several other herds further down in the pig production pyramid. Since trade of live animals is an important risk factor for transmission of MRSA, these types of herds are of key importance for controlling spread of MRSA in pigs. All Swedish nucleus and multiplying herds present were subjected to sampling, 53 herds in 2011 and 39 herds in 2014. Weaned pigs in the age 5-12 weeks were sampled, 6 pigs per box, 15 boxes per herd. Sampling was done by scrubbing the skin behind one ear with a sterile compress. The same compress was used to all 6 pigs in the same box, constituting a pooled sample. In general, samples were analysed in accordance with the method in the EU basline study, in a two step selective enrichment, followed by plating on selective media and blood agar plates. MRSA was not found in any sample.

Hence, there are reasons to believe that the MRSA situation in the Swedish pig population still is favourable. The low number of notified human cases of MRSA CC398 (21 cases in 2014) supports this opinion. However, continuous monitoring in pigs is of importance as the situation can change rapidly.

Consequences of MRSA in pigs

The problem with MRSA CC398 in pigs is not primarily infections in pigs, but instead that the pig population may constitute a reservoir with risk of spread to humans. People in direct or indirect contact with live pigs carrying MRSA CC398 are at risk to become carriers of such bacteria. In regions where MRSA is prevalent among pigs, pig farmers and their employees, veterinarians, animal transporters and slaughter house workers may therefore be considered a risk group for MRSA carriage. This applies also to household members of these professional categories.

Carriage of MRSA CC398 in humans implies a risk for infections that are difficult to treat, but may also cause anxiety and stigmatisation. Moreover, colonized and infected people in contact with health care may generate increased societal costs if precautionary measures to prevent further spread are taken.

Societal benefits from preventing MRSA in pigs

In a scenario were MRSA has been introduced, spread and established in the Swedish pig population, it is likely that people with professional contact with live pigs would be classified by the health care as a risk group for MRSA carriage. This would imply societal costs in the health care. A study was performed in order to estimate these costs, and also to estimate the costs for preventing introduction of MRSA to Swedish pigs through import of breeding pigs (Höjgård et al., 2015).

The risk group was estimated to about 6 000 persons. The extra costs these persons would generate in contact with primary care and in-patient care due to MRSA sampling, precautionary measures, contact tracing and treatment were calculated. These costs would be the potential societal benefits from preventing introduction of MRSA to pigs. Likewise, the costs for preventing introduction through sampling of imported breeding animals and destruction of positive animals were calculated. The societal benefits were estimated to between € 871 000 and € 1 233 000 and the costs to € 211 000, giving a net societal benefit of between € 660 000 and € 1 022 000 annualy.

As there were several factors that were not known, the calculations were partly built on assumptions, but the results indicate that under Swedish conditions the societal benefits exceed the costs for preventing introduction of MRSA CC398 through import of pigs.

The future

When first detected in 2004, MRSA CC398 was already widely spread among pigs in several countries. However, there are indications that the situation in the Swedish pig population still is favourable, as stated above, and efforts to mitigate spread among pis in Sweden may therfore be relevant and warranted. Hence, from a public health perspective there would be good reasons to prevent spread of MRSA to pigs in Sweden.

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP)

MRSP in animals

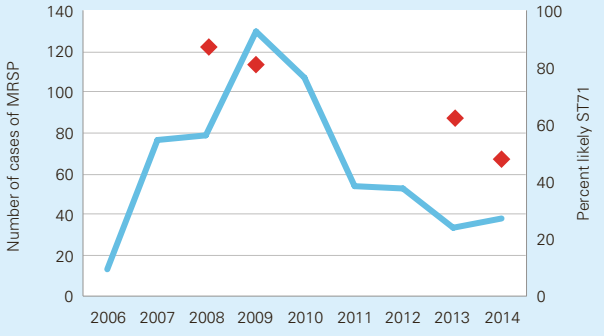
Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) was first isolated in Sweden from a healthy dog in 2006. Therafter a large increase in the numbers of notified MRSP cases was observed and the highest number was observed in 2009 with 130 cases (Figure 2.13). However, since 2010 the number of cases has dropped successively with only 33 cases notified in 2013, but in 2014 the reported cases increased to 39. In 2014 the isolates were from 36 dogs, 2 cats and 1 horse.

In 2014, 34 of the 39 notified MRSP isolates were available at SVA for further epidemiological typing and antimicrobial susceptibility testing. The origins of isolates were unknown in 8 of the cases, 11 were from wounds, 7 from skin including ears. The remaining isolates were from, ungual crest (n=2), urine (n=2), eye (n=1), milk sample (n=1), tonsil (n=1) and lung (n=1).

Based on *spa*-typing 47% of the isolates were shown to belong to the European clone ST71-J-t02-II-III, described by Perreten et al. (2010), belonging to *spa* type t02. Of the remaining isolates 35% was nontypeable and three isolates belonged to t05, two to t10 and one to a new *spa*-type. All nontypeable isolates were subjected to MLST, two isolates were shown to be ST71, four belonged to ST258, one to ST45, one to ST298 and four belonged to new MLSTs. The ST258 is of specific interest because it has been described as an emerging clone in Denmark and Norway (Osland et al., 2012; Damborg et al., 2013). After MRSP was first detected in Sweden the occurrence was dominated by the European clone ST71-J-t02-II-III, but during the last couple of years the occurrence of this clone has decreased and the diversity of MRSP has increased.

All isolates were defined as multi-resistant, but 91% were susceptible to fusidic acid, 32% to gentamicin and 100% to tetracycline and nitrofurantoin. The isolates belonging to the ST71-J-t02-II-III clone were all susceptible to fusidic acid, with the exception of one isolate, one of the ST71 nontypeable by *spa*-typing.

FIGURE 2.13. Blue line represents the number of cases with methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) in Sweden notified to the Swedish Board of Agriculture 2008-2014. In 2006-2007 the numbers represent the isolates that were sent to SVA and confirmed as *mecA*-positive. Red squares represent the percent of isolates likely belonging to the European clone ST71-J-t02-II-III, complete data only available for 2008-2009 and 2013-2014.



Zoonotic aspects on MRSP

Staphylococcus pseudintermedius is not considered to be a zoonotic pathogen, but there are several reports of MRSP infections in humans with a varying degree of severity. Furthmore, in a recent study it was shown that out of 101 isolates defined as *S. aureus* from infected dog bites by clinical microbiology laboratories, 13% were actually *S. pseudintermedius* (Börjesson et al., 2015). One of the isolates was multi-resistant belonging to ST118.

In 2011 there were four cases of MRSP infections in hospitalised patients at Uppsala University hospital without any established animal-human contact (Starlander et al., 2014).

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

VRE in humans

Background

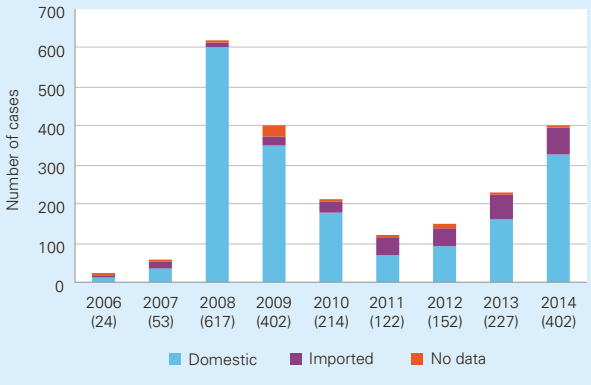
Vancomycin resistant enterococci (VRE) are important causes of nosocomial infections in many parts of the world, usually involving high-risk populations such as immunocompromised and intensive care patients. Like MRSA, VRE were made notifiable according to the Swedish Communicable Disease Act in the 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 relevant epidemiologic information from investigations around each case in collaboration with the CMOs. 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).

Notifications of VRE according to the Communicable Disease Act

During 2014 a total of 402 cases were reported, an increase by 77% compared to 2013 (Table 2.9). Although VRE cases were reported from 19 of the 21 Swedish counties the increase was largely due to one major hospital outbreak in Gävleborg that started in 2013 and continued during 2014. The average national incidence of VRE was 4.1 with higher than average incidence figures in Gävleborg (76.4), Uppsala (10.9) and Kronoberg (7.4) counties. Of all cases, 330 (82%) were reported as domestic (Figure 2.14), and of those 311 were healthcare related. In 69 cases (17%) VRE had been acquired abroad. The most common countries for imported VRE infection were Serbia (11 cases), Turkey (9), Greece (8) and Germany (4). Sixty-three (91%) of the imported cases were healthcare related.

The domestic VRE cases were detected through contact tracing (71%), screening (18%) or clinical symptoms (4%). For six percent of the domestic cases, indication for sampling was not stated. The majority of the imported cases (90%) were detected through screening, four percent due to clinical symptoms and none due to contact tracing. Accordingly a majority of the isolates (92%) in the first laboratory notifications were from feces and rectum, and only four percent from urine, wound or other clinical samples. More cases were notified from men (55%) than from women (45%), with the median age for women 76 years and for men 75 years.

FIGURE 2.14. Number of human cases of VRE annually notified in Sweden 2006-2014 by country of infection. Numbers of reported cases are shown in brackets.



The median age was lower for imported (66 years) than for domestic cases.

In 2014, isolates from 394 cases carried *E. faecium* and isolates from 9 cases *E. faecalis*. In a sample from one case both *E. faecium* and *E. faecalis* could be isolated. As in 2013, the dominating resistance gene 2014 was *vanB* (Table 2.9). Invasive VRE infection was reported in seven cases in 2014. All were in newly notified persons.

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 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 2014, thirteen healthcare related outbreaks of *E. faecium* were reported from six counties; seven outbreaks with *vanA* gene and six with *vanB* gene. The seven *vanA* outbreaks affected 2-19 patients each, and six *vanB* outbreaks affected 2-225 patients. The largest outbreak started in Gävleborg county in september 2013, and lasted to the end of 2014. A total of 314 cases have been reported from this outbreak caused by a strain typed as SE-EfmB-1308. http://www.folkhalsomyndigheten.se/amnesomraden/beredskap/utbrott/utbrottsarkiv/vankomycinresistenta-enterokocker-gavleborg-2013-2014/

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.

TABLE 2.9. VRE-notifications according to the Communicable Disease Act 2007-2014 by species and van-gene.

Species and R-gene	2007	2008	2009	2010	2011	2012	2013	2014
E. faecium vanA	12	96	61	63	39	97	93	110**
E. faecium vanB	38	505	326	135	70	26	126	281**,***
E. faecalis vanA	2	4	6	3	8	5	1	3
E. faecalis vanB				1	2			5***
Not specified	1	12	9	12	3	24	7	6
Total	**53**	**617**	**402**	**214**	**122**	**152**	**227***	**402**

*In one case in 2013 a strain of *E. faecium* with both *vanA* and *vanB* gene was detected.
**In two cases in 2014 a strain of *E. faecium* with both *vanA* and *vanB* gene was detected.
***In one case in 2014 both *E. faecium vanB* and *E. faecalis vanB* could be isolated.

VRE in animals

No specific screening for vancomycin resistant enterococci (VRE) was performed in 2014. 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 2014, samples from broilers were investigated and one isolate of *E. faecium* had MIC above ECOFF (8 mg/L). The isolate was further investigated by PCR but *vanA* or *vanB* genes were not detected (see 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 are present among Swedish broilers. There is a potential risk for transfer of these VRE to humans. However, in studies comparing PFGE-patterns from human and broiler isolates no common type has been found. 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 2014 a total of 70 PNSP cases were reported in Sweden. Forty-six percent of the cases had been infected domestically and 31% of the cases in a foreign country. For the remaining 16 cases (23%) no country of acquisition was given.

The incidence of PNSP in Sweden 2014 was 0.7 cases per 100 000 inhabitants. The majority of PNSP cases (34% in 2014), independent of year observed, are found in the age group 0-4 years. Of the reported cases in 2014, 60% have been male, 40 % female.

PNSP were reported from 16 of 21 Swedish counties, with Stockholm (17 cases), Kalmar (8 cases) and Skåne (6 cases) accounting for 44% of all notifications. The remaining 13 counties reported 1-5 cases each.

PNSP, were most often found in cultures from the nasopharynx. In 33 cases (47%) the detection of PNSP was due to clinical infection. Seven cases were detected through contact tracing and 6 cases through targeted screening. In the remaining cases another reason for sampling was stated (7 cases) or the information was missing (17 cases).

Serotype distribution

In 2014, three cases of invasive PNSP infection, with bacteria isolated from blood were reported (MIC > 1 mg/L). These were of serotypes 6B, 9N and 11A. For all cases of PNSP with MIC ≥ 0.5 mg/L (227 isolates serotyped so far) the most common serotypes were in descending order: 19F (24%), non-typable (NT) (17%), 35B (12%), 19A (9%), 23F (6%), 14 (5%), 11A(4%), 6B(4%) and 9V(4%).

Zoonotic pathogens

Zoonoses are diseases and infections that can be naturally transmitted between animals and humans. Antibiotic 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 2014 we used the complete data sets of positive blood cultures from seven laboratories (see background information) as one source of information on antibiotic susceptibility in *Salmonella*. In 2014, 61 isolates of *Salmonella* were found among a total of 12609 blood cultures. The most common serovars were *S.* Typhi (14), *S.* Enteritidis (8), *S.* Panama (3), and *S.* serogroup C and D, *S.* Typhimurium (3) with 3 isolates from each (Table 3.1). Nineteen of the cases were reported as travel associated, with Thailand, India, Africa (north or central regions), Turkey, Bali and Nepal being the countries/regions mentioned.

TABLE 3.1. *Salmonella* from blood cultures in Sweden 2014. Data collected from reporting laboratories covering apporximately 48 % of the Swedish population.

Salmonella serovar	No of isolates	No of isolates tested for Cip	No of Cip-R	No of isolates tested for Tsu	No of Tsu-R	Countries reported (no)
S. Typhi	14	13	9	14	2	India (3), Nepal (1), Thailand (1), Zambia (1)
S. Enteritidis	8	8	3	8		
S. Panama	3	3		3	3	Thailand
S. Serogroup C	3	2		3		Ghana
S. Serogroup D	3	2	1	3	1	Unspecified travel
S. Typhimurium	3	2		3		
S. Heidelberg	2	2		2		
S. Stanley	2	2	2	2		
S. other serovars	23	20	5	22	6	Africa (1), Bali (1), India (1), Kenya (1), Marocko (1), Sri Lanka (1), Thailand (3), Turkey (1)
Total	**61**	**54**	**20**	**60**	**12**	

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 12 isolates (20%) and resistance to ciprofloxacin in as many as 19 (37%). Nine of 13 *S.* Typhi isolates tested for ciprofloxacin susceptibility were resistant to ciprofloxacin (MICs 0.25-32 mg/L) but resistance was also found among isolates of other serovars (Table 3.1).

Salmonella in animals

Findings of *Salmonella* in animals are notifiable in Sweden. In Svarm, antibiotic susceptibility is determined in one isolate from each warm-blooded animal species (wild and domesticated) involved in incidents notified 2014. Isolates from incidents previously notified but still under restrictions in 2014 are also included. In incidents involving more than one serovar, one isolate of each serovar is tested. As from 2014 phage typing is not performed on isolates of *Salmonella* from animals. For details on methodology see Materials and methods, resistance in bacteria from animals.

All animals 2014

Altogether, 77 isolates were tested of which 21 were *S.* Typhimurium (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 (75%) were susceptible to all antimicrobials tested, but 19 isolates were resistant to at least one substance and five isolates (6%) were multiresistant.

Two isolates of *S.* Typhimurium from wild birds were phenotypically resistant to ESC. In both isolates the MIC of ceftazidime was 2 mg/L and in one of the isolates the MIC of cefotaxime was 1 mg/L. Ampicillin MIC was 32 mg/L in both isolates. However, on testing with PCR no genes coding for transferable ESC resistance were detected.

The five multiresistant isolates were *S.* Typhimurium from cattle (Table 3.5). One of the isolates was resistant to ampicillin, ciprofloxacin, chloramphenicol, florfenicol, gentamicin, streptomycin, sulphonamide and tetracycline. *Salmonella* with this phenotype has previously not been isolated from animals in Sweden (Table 3.6) and it is an uncommon phenotype also in other countries in EU (EFSA & ECDC, 2015). Three isolates were resistant to ampicillin, streptomycin, sulphonamide, tetracycline and in addition to quinolones (ciprofloxacin and nalidixic acid). One of the isolates from 2014 was from an incident notified in already in 2013 and still under restrictions. Hence, *Salmonella* with this phenotype has been isolated only from three incidents in animals in Sweden (Table 3.6). This resistance phenotype is uncommon also in other countries in EU (EFSA & ECDC, 2015). One isolate was resistant to ampicillin, chloramphenicol, florfenicol, streptomycin, sulphonamide and tetracycline. This is one of the most common MDR-phenotypes of *S.* Typhimurium in EU and is often associated with *S.* Typhimurium of phage type DT 104 (EFSA & ECDC, 2015). Such strains have on several occasions been isolated from cattle, pigs and sheep in Sweden (Table 3.6).

TABLE 3.2. Number of *Salmonella enterica* isolates tested for antibiotic susceptibility, 2014.

Serovar	Cattle	Poultry	Horses	Dogs	Cats	Wild birds	Wild mammals	Total
S. Derby				1				**1**
S. Dublin	13							**13**
S. Duesseldorf							2	**2**
S. enterica subsp. *diarizonae* (IIIb)							4	**4**
S. Enteritidis							7	**7**
S. Infantis	1							**1**
S. Mbandaka	1	1						**2**
S. Newport				1				**1**
S. Poona		1						**1**
S. Typhimurium	6	5			15	11	6	**43**
S. enterica subsp. *enterica* (I)			1			1		**2**
Total	**21**	**7**	**1**	**2**	**15**	**12**	**19**	**77**
Percent of total	27%	9%	1%	3%	19%	16%	25%	100%

Farm animals 2000-2014

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 2000-2014, isolates from the vast majority of notified incidents in farm animals were tested in Svarm, in total 622 isolates. About half of the isolates, 306 (49%), were *S.* Typhimurium and of these 38% were from pigs, 33% from cattle, 27% from poultry and 2% from sheep.

The majority (73%) of *S.* Typhimurium isolates from the incidents in farm animals has been susceptible to all antibiotics tested but 34 (11%) were multiresistant (Table 3.6). The most common resistance traits were ampicillin, streptomycin, tetracycline, sulphonamide, chloramphenicol and florfenicol. Resistance to third generation cephalosporins has not been found and resistance to ciprofloxacin has been confirmed in isolates from only five incidents. Six isolates (2%) of other serovars than Typhimurium have been multiresistant.

The 34 multiresistant isolates of *S.* Typhimurium in the period 2000-14 were from 32 separate incidents of which 21 involved cattle, 6 pigs, 2 poultry and 1 incident involved both

TABLE 3.3. Distribution of MICs and resistance (%) in *Salmonella enterica* (n=77) from all animals, 2014.

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	9								89.6	1.3				2.6			6.5			
Cefotaxime	1		1.3	7.8	36.4	45.5	6.5	1.3	1.3											
Ceftazidime	3						51.9	33.8	9.1	2.6	2.6									
Chloramphenicol	3									26.0	68.8	2.6				2.6				
Ciprofloxacin	5	1.3	40.3	13.0	40.3	1.3		3.9												
Colistin	5							35.1	44.2	15.6	3.9	1.3								
Florfenicol	3										72.7	24.7			2.6					
Gentamicin	1						1.3	76.6	18.2	2.6				1.3						
Kanamycin	0											100								
Nalidixic acid	4									7.8	83.1	5.2		3.9						
Streptomycin	18									1.3	1.3	1.3	77.9	11.7		2.6		3.9		
Sulphamethoxazole	8												1.3	16.9	48.1	24.7	1.3	1.3		6.5
Tetracycline	6								90.9	2.6				1.3			5.2			
Trimethoprim	0					1.3	61.0	33.8	2.6	1.3										

TABLE 3.4. Distribution of MICs and resistance (%) in *Salmonella* Typhimurium (n=43) from all animals, 2014.

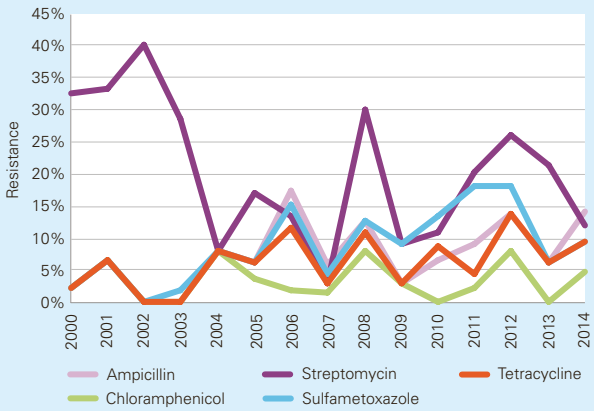
Antimicrobial	Resistance %	Distribution (%) of MICs (mg/L)																	
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	16								83.7					4.7			11.6			
Cefotaxime	2					44.2	46.5	4.7	2.3	2.3										
Ceftazidime	5							41.9	39.5	11.6	2.3	4.7								
Chloramphenicol	5									25.6	69.8					4.7				
Ciprofloxacin	9		41.9		16.3	32.6	2.3		7.0											
Colistin	0							37.2	53.5	9.3										
Florfenicol	5										83.7	11.6			4.7					
Gentamicin	2							79.1	18.6					2.3						
Kanamycin	0											100								
Nalidixic acid	7									2.3	88.4	2.3		7.0						
Streptomycin	14												86.0	2.3		4.7		7.0		
Sulphamethoxazole	12													9.3	46.5	30.2	2.3			11.6
Tetracycline	12								88.4					2.3			9.3			
Trimethoprim	0						60.5	39.5												

TABLE 3.5. MICs (mg/L) in *Salmonella enterica* resistant to three or more antibiotics, 2014. Shaded fields indicate resistance.

Source	Serovar	Amp	Ctx	Caz	Cip	Nal	Chl	Flo	Col	Gen	Kan	Str	Sul	Tet	Tmp
Cattle	*S.* Typhimurium	>128	0.25	1	0.12	8	>64	>32	1	>16	≤8	128	>1024	>128	0.5
Cattle	*S.* Typhimurium	>128	0.12	0.5	0.06	4	>64	>32	2	1	≤8	128	>1024	32	0.5
Cattle	*S.* Typhimurium	>128	0.06	1	0.5	32	4	8	1	1	≤8	>256	>1024	>128	0.25
Cattle	*S.* Typhimurium	>128	0.06	0.5	0.5	32	4	8	≤0.5	0.5	≤8	>256	>1024	>128	0.25
Cattle	*S.* Typhimurium	>128	0.12	0.5	0.5	32	4	8	1	1	<8	>256	>1024	>128	0.25

pigs and cattle. Of the two remaining incidents, one was in sheep and one in ducks in a hobby flock. Three incidents in 2004 involved cattle and 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, 2000-2014. The number of isolates each year varies (n=31-85).



In 2014 monophasic *S.* Typhimurium I (O 4,5,12:i- /O 4,5:i:- / O 4:i:-) was not isolated. However, nine incidents of monophasic *S.* Typhimurium 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

Occurrence of *Salmonella* among farm animals, as well as among other animals, is low in Sweden and few incidents involve multiresistant strains. Notably, transferable ESC resistance has never been found. Resistance to fluoroquinolones is rare but it is worrying that in the last two years three incindents in cattle involved multiresistant *S.* Typimurimum with a resistance phenotype that includes fluoroquinolones. The overall situation is however still favorable. This is largely due to the effective strategies in the Swedish salmonella control programme initiated in the 1950-ies.

TABLE 3.6. Resistance phenotypes of *Salmonella* Typhimurium (n=305) from incidents in farm animals, 2000-2014. All isolates were tested for susceptibility to ampicillin, florfenicol, gentamicin, chloramphenicol, ciprofloxacin, 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**
AmpStrSulTetCip-NalChlFlo	**Pigs**											1													**1**
AmpStrSulTetCipChl-FloGen	**Cattle**																						1		**1**
AmpStrSulTetChlFlo	**Cattle**											6		1									3		**10**
AmpStrSulTetChlFlo	**Pigs**											4											1		**5**
AmpStrSulTetChlFlo	**Sheep**											1													**1**
AmpStrSulTetChl	**Cattle**											1													**1**
AmpStrSulTetCipNal	**Cattle**																						3		**3**
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**																1			1					**2**
StrSul	**Poultry**																							2	**2**
SulTm	**Cattle**						2																		**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	10	1	**63**
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	9		**40**
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**	**48**	**9**	**305**

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, of the most common serovars from human invasive infections in 2014 (Table 3.1) *S.* Typhi is a serovar that is not associated with animals. Also, other serovars from human invasive infections e.g. *S.* Enteritidis, are most rare in animals in Sweden.

Moreover, over one third of the human isolates from the reporting laboratories in 2014 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

Data on antibiotic resistance in *Campylobacter* from humans is largely lacking. During 2014 29 cases of *Campylobacter* were reported from five laboratories delivering data from blood cultures. Resistance to erythromycin was found in one case and resistance to ciprofloxacin in four cases. None of the isolates tested were resistant to both of these antibiotics.

Campylobacter in animals

The isolates of *Campylobacter jejuni* tested are from caecal content of broilers collected at abattoirs and were isolated within the framework of the Swedish Campylobacter control programme. For details on methodology see Materials and methods, resistance in bacteria from animals.

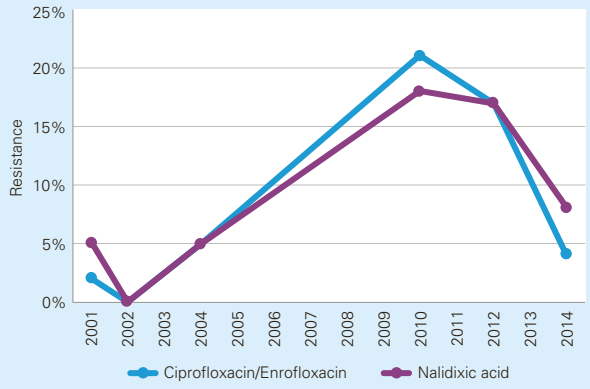
Of the 102 isolates tested, 92 were susceptible to all six antibiotics. Resistance to fluoroquinolones only (ciprofloxacin and nalidixic acid) was the most common phenotype (Table 3.7). Four isolates were resistant to nalidixic acid but not to ciprofloxacin, however the MIC of ciprofloxacin was slightly elevated for these isolates (0.5 mg/L). This has been described previously and in one study the majority of the isolates with the same phenotype had an Thr-86 →Ala mutation in *gyrA* instead of the more common Thr-86 → Ile mutation (Griggs et al., 2005).

In comparison to previous years quinolone resistance increased notably in 2010 and 2012 but has declined 2014 (Figure 3.2). The reasons for this are not known but selection through use of antibiotics is unlikely as a single explanation since fluoroquinolones are seldom used in broiler production in Sweden. Further monitoring to follow up the finding is needed as well as further studies to elucidate the epidemiology of fluoroquinolone resistant *C. jejuni*.

TABLE 3.7. Distribution of MICs and resistance (%) for *Campylobacter jejuni* from broilers, 2014.

Antimicrobial	Resistance (%) n=102	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Ciprofloxacin	4	89.2	2.9	3.9			1.0	1.0	2.0				
Erythromycin	0				99.0	1.0							
Gentamicin	0	1.0	24.5	71.6	2.9								
Nalidixic acid	8				1.0	2.9	70.6	17.6			3.9	3.9	
Streptomycin	1		1.0	4.9	73.5	16.7	2.9				1.0		
Tetracycline	1			99.0						1.0			

FIGURE 3.2. Ciprofloxacin and nalidixic acid resistance (%) in *Campylobacter jejuni* from broilers years 2001, 2002, 2004, 2010, 2012 and 2014. In years 2001-2002 enrofloxacin was tested instead of ciprofloxacin. The number of isolates per year has varied (n=38-102).



Zoonotic aspects on *Campylobacter*

Data for 29 isolates of *Campylobacter* from humans were available 2014 and of these only five were resistant to either erythromycin or fluoroquinolones. However this is a small number of isolates and in Swedres 2011 (data for 2002-2011) 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 broilers 2014. Notably, resistance to erythromycin, the drug of choice for treatment of human campylobacteriosis, has only been found in two isolates from Swedish broiler meat (Svarm 2013) and never in isolates coming directly from animals in Sweden. 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.

Comparisons between data for *Campylobacter* from animals and humans are 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.

Clinical isolates from humans

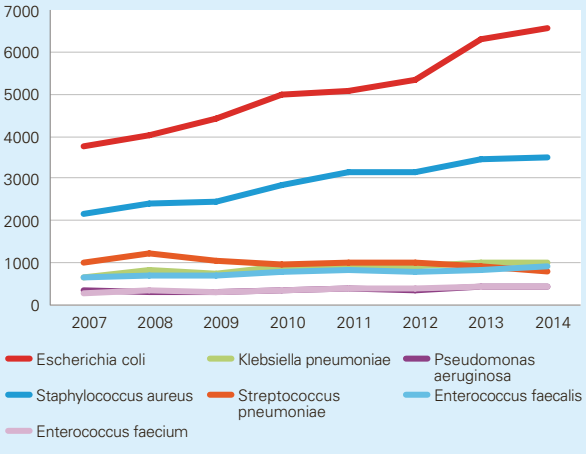
Swedish surveillance of antimicrobial resistance is based on the routine testing of clinical samples in microbiology laboratories. In these laboratories the majority of tests for antibiotic susceptibility are performed using the standardized disk diffusion method. From 2011 and onwards all laboratories 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 fifteen laboratories in 2014, together representing approximately 80% of the Swedish population. Results on eight 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, seven of these Swedish laboratories, with coverage of approximately 48 % 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).

FIGURE 4.1. Yearly number of bloodstream infections by seven pathogens reported to EARS-Net from Sweden 2007-2014 by participating laboratories. Acinetobacter species was introduced in 2014, but data not shown in figure.



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 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 most of the European countries were participating in EARSS. In 2014 *Acinetobacter* species was added to the programme.

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 participating laboratories is still managed by the Public Health Agency of Sweden, former SMI.

A summary of the data reported from Sweden 2007-2014 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 numbers for other pathogens, but they also showed increasing trends over the years, whereas the numbers of the other five pathogens were stable.

Results and comments

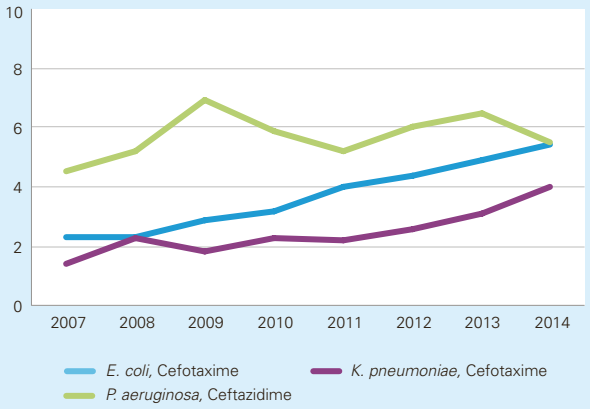
In general the proportions of resistance to clinically important antimicrobials were low, and this has been the typical situation for Sweden and its neighbouring Nordic countries all through the EARSS/EARS-Net history (www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/). However, increasing 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 for resistance to ceftazidime in *P. aeruginosa* is not ESBL-production (Figure 4.2). In *E. coli* and *K. pneumoniae* the levels of cephalosporin resistance has reached 5.4% and 4.0%, respectively (Table 4.1). Resistance to fluoroquinolones is now on a level of approximately 11.7% in *E. coli* and 5.1% in *K. pneumoniae*. During 2014 13 participating laboratories reported 59 cases of *Acinetobacter* species, with resistance to carbapenems at 3.4 % (two cases).

TABLE 4.1. Antimicrobial resistance in isolates from bloodstream infections of eight pathogens included in EARSS/EARS-Net surveillance during the years 2007-2014

		2007		2008		2009		2010		2011		2012		2013		2014		
Species	**Antibiotic**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**% R**	**n**	**n tested**	**% R***
Escherichia coli	total no of isolates	3745		4028		4423		4991		5066		5336		6323		6586		
	Ctx		2.3		2.3		2.9		3.2		4.0		4.4		4.9		6576	5.4
	Imp/Mer		0.0		0.0		0.0		0.0		0.0		0.0		0.0		6321	0.0
	Gen/Tob		2.2		2.3		3.3		4.5		5.1		5.5		4.5		6577	6.3
	Fluoroquinolones		13.3		14.4		13.7		14.0		10.4		9.9		9.9		5170	11.7
	Ptz**		nd		nd		nd		nd		nd		nd		nd		6285	2.3
Klebsiella pneumoniae	total no of isolates	649		826		755		908		934		933		1028		1009		
	Ctx		1.4		2.3		1.8		2.3		2.2		2.6		3.1		951	4.0
	Imp/Mer		0.0		0.0		0.0		0.0		0.0		0.0		0.0		984	0.2
	Gen/Tob		1.1		1.1		1.0		2.0		2.1		2.1		2.0		1008	3.2
	Fluoroquinolones		10.8		12.9		12.2		8.5		5.0		4.6		4.4		766	5.1
	Ptz**		nd		nd		nd		nd		nd		nd		nd		964	9.3
Pseudomonas aeruginosa	total no of isolates	335		309		326		337		402		350		428		432		
	Caz		4.5		5.2		6.9		5.9		5.2		6.0		6.5		437	5.5
	Imp/Mer		7.1		4.0		7.7		6.7		7.2		6.9		6.3		432	7.6
	Gen/Tob		0		0		0		3.0		1.0		1.4		2.3		445	1.8
	Fluoroquinolones		10.4		7.6		10.1		10.1		7.0		9.1		7.9		345	7.5
	Ptz**		nd		nd		nd		nd		nd		nd		nd		442	5.0
Staphylococcus aureus	total no of isolates	2163		2409		2457		2856		3143		3268		3209		3519		
	Oxa/Fox		0.5		0.7		1.0		0.5		0.8		0.7		1.2		3511	0.9
	Van		0.0		0.0		0.0		0.0		0.0		0.0		0.0		1026	0.0
Streptococcus pneumoniae	total no of isolates	1028		1213		1060		960		1019		992		861		797		
	Pen (I+R)		3.0		2.0		3.3		3.8		3.5		5.0		6.6		797	6.3
	Ery		5.2		5.2		3.9		3.9		4.5		5.1		5.8		793	6.2
Enterococcus faecalis	total no of isolates	651		720		718		776		824		779		851		912		
	Van		0.0		0.0		0.0		0.0		0.0		0.0		0.0		894	0.0
	Gen (HLAR)		16.1		20.1		18.6		15.2		16.6		14.1		13.3		673	15.6
Enterococcus faecium	total no of isolates	279		333		311		339		406		391		431		457		
	Van		0.0		1.5		0.5		0.3		0.0		0.0		0.0		456	0.7
	Gen (HLAR)		14.4		24.8		24.1		21.8		22.0		18.4		20.4		351	22.5
*Acinetobacter species****	total no of isolates															59		
	Imp/Mer		nd		nd		nd		nd		nd		nd		nd		59	3.4

*From 2014 the resistance is expressed as % of isolates tested
**Ptz was included from 2014
***_Acinetobacter species_ was included from 2014

FIGURE 4.2. Proportion of resistance to third generation cephalosporins in *E. coli, K. pneumoniae* and *P. aeruginosa*. Swedish data in EARS-Net 2007-2014, from participating laboratories, covering approximately 80% of the population



Last year was the first year that MRSA exceeded 1%, and the highest level noted for PNSP, at 6.6% I+R, in Sweden ever since the start of EARSS/EARS-Net. This year the number has stabilized at 0.9% MRSA and 6.3% nonsusceptibility to penicillin (I+R) for pneumococci. For the two enterococcal species there were three cases of VRE reported for *E.faecium* (0.7%), for *E.faecalis* there is still no report of VRE. High-level aminoglycoside resistance (HLAR) was found in both species at 16-23%, somewhat higher compared 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 seven laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is at present 4.7 million, thus representing around 48% of the Swedish population. From these laboratories data on all bacterial pathogens consecutively isolated from blood cultures are retrieved, not only those specified by EARS-Net. In previous SWEDRES reports (2008-2013) 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 2014.

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.

TABLE 4.2. Antimicrobial resistance in invasive isolates of Streptococcus pyogenes, Streptococcus agalactiae and Haemophilus influenzae during seven years (2008-2014).

		2008 (n=11.115)*		2009 (n=11.416)		2010 (n=12.296)		2011 (n=16.969)		2012 (n=18.117)		2013 (n=18.367)		2014 (n=12.609)		
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**	**n (% of tot)**	**n tested**	**% 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	149 (1.2)	149	2.0
	Tet		14.6		9.7		12.7		13.3		12.5		7.7		141	7.8
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	184 (1.5)	184	13.6
	Kli		6.5		3.8		5.4		5.8		13.7		9.3		158	10.1
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	70 (0.6)	61	14.8
	Ctx		nd		nd		nd		2.5		1.9		0		58	0.0
	Tsu		14.3		14.3		13.3		15.8		22.3		17.2		70	21.4

*Total number of positive blood isolates from participating laboratories

**from 2014 the resistance is expressed as % resistance of isolates tested

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 proportions 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 2014 six pathogens were included in the program, and the results on these pathogens are presented and analyzed in the following texts and graphs to illustrate trends.

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 2014, 24 laboratories delivered data as requested. All laboratories used EUCAST methodology, and a total of 6439 isolates were included in the analysis (Figure 4.3).

The proportion of resistance for all tested antibiotics were similar between 2013 and 2014 and only slightly increasing for ampicillin, cefadroxil and ciprofloxacin (Figure 4.3). Cefadroxil resistance is used as an indicator for presence of genes coding for ESBLs.

It should be noted that ciprofloxacin 5µg is now the recommended disk for detecting fluoroquinolone resistance, and the resistance rate 10,4 % 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.

FIGURE 4.3. Proportion, %, resistant *E. coli* isolates from urine, 2002-2014. 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.

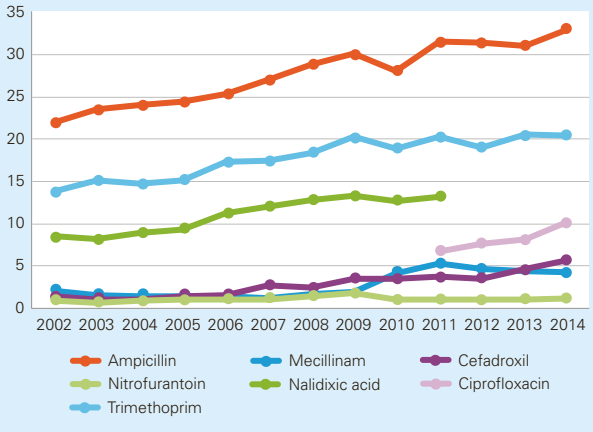
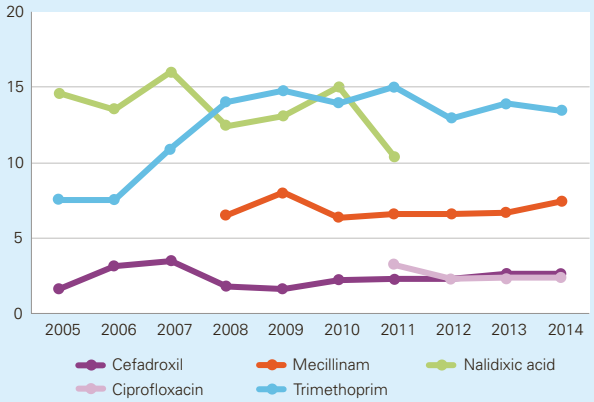


FIGURE 4.4. Proportion, %, resistant *K. pneumoniae* isolates from urine, 2005-2014. Resistance (R) to fluoroquinolones was tested by nalidixic acid (screening for I+R) 2005-2011, and by ciprofloxacin from 2011 and onwards. Zone breakpoints relevant at the time of testing were always used.



Klebsiella pneumoniae

K. pneumoniae is an important bacterial species from a hospital infection control point of view. Isolates mainly derived from urine samples have been included in the surveillance programme since 2005. In 2014, 23 laboratories delivered data according to EUCAST methodology, and 2591 isolates were included in the analysis (Figure 4.4). The results indicate that the rates of resistance to all tested antibiotics were the same in 2013 and 2014 except for a slight increase in the resistance to mecillinam.

Pseudomonas aeruginosa

Pseudomonas aeruginosa has been included in the surveillance programme on a yearly basis since 2006, with the exception of 2008. Laboratories have been asked to test 100 consecutive isolates of *P. aeruginosa* with the exclusion of respiratory isolates. In 2014, 22 laboratories delivered data according to EUCAST methodology, and 2480 isolates were included in the analysis (Figure 4.5). Aminoglycoside resistance (gentamicin and/or tobramycin tested) is around 1 %, but with a small increase for gentamicin. 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 more or less stable since 2010. For the carbapenems, resistance to imipenem continues to be higher (9 %) than to meropenem (5.1 %) in 2014. Resistance to ciprofloxacin show a slight decrease from around 10 % to 8 %.

FIGURE 4.5. Proportion, %, resistant *Pseudomonas aeruginosa* isolates for four groups of antibiotics tested, 2006-2014 (no data collected in 2008). Zone breakpoints relevant at the time of testing were always used.

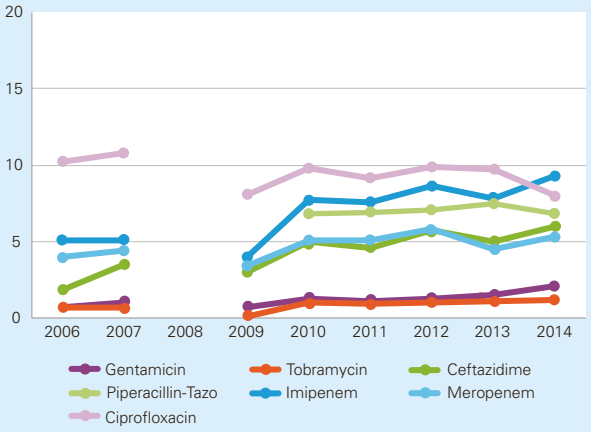
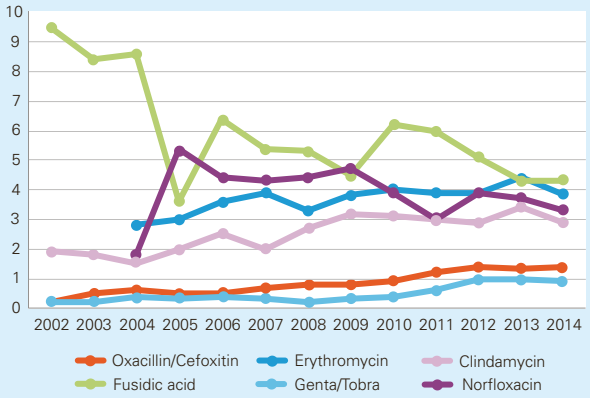


FIGURE 4.6. Proportion, %, resistant *Staphylococcus aureus* isolates from skin and soft tissue infections 2002-2014. In 2005 only results from infections in elderly (> 65 years) patients were reported.



Staphylococcus aureus

Staphylococcus aureus from skin and soft tissue infections has been included in the annual surveillance programme since 2002. In 2014, 24 laboratories delivered data. All laboratories used the EUCAST methodology, and a total of 5343 isolates were included in the analysis (Figure 4.6).

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 1.4% in 2014. The average resistance proportions for erythromycin, clindamycin, fusidic acid and norfloxacin indicates a slight decreasing trend. Resistance to aminoglycosides was still only 1%.

Streptococcus pneumoniae

Isolates collected and tested in the surveillance programme were mainly derived from nasopharyngeal cultures. Most of the years a total of approximately 2500 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, used as indicator for fluoroquinolone resistance) using the disk diffusion method. In 2014, 23 laboratories delivered data according to EUCAST methodology, and 2391 isolates were included in the analysis. The national summary of the results, as retrieved from ResNet, are shown in Figure 4.7. During the first 15 years of surveillance there had been a slow increase in the proportions of resistance for all tested antibiotics. In 2010 this successive increase stopped. In 2014 the increase in resistance continued for all tested antibiotics except norfloxacin.

Haemophilus influenzae

Haemophilus influenzae was re-introduced into the yearly surveillance programme on antibiotic resistance in 2008 after several years with no data collections. In 2014, 24 laboratories delivered data according to the new EUCAST methodology, and 2593 isolates were included in the analysis.

FIGURE 4.7. Proportion, % resistant *Streptococcus pneumoniae* isolates from respiratory tract specimens 1994-2014.

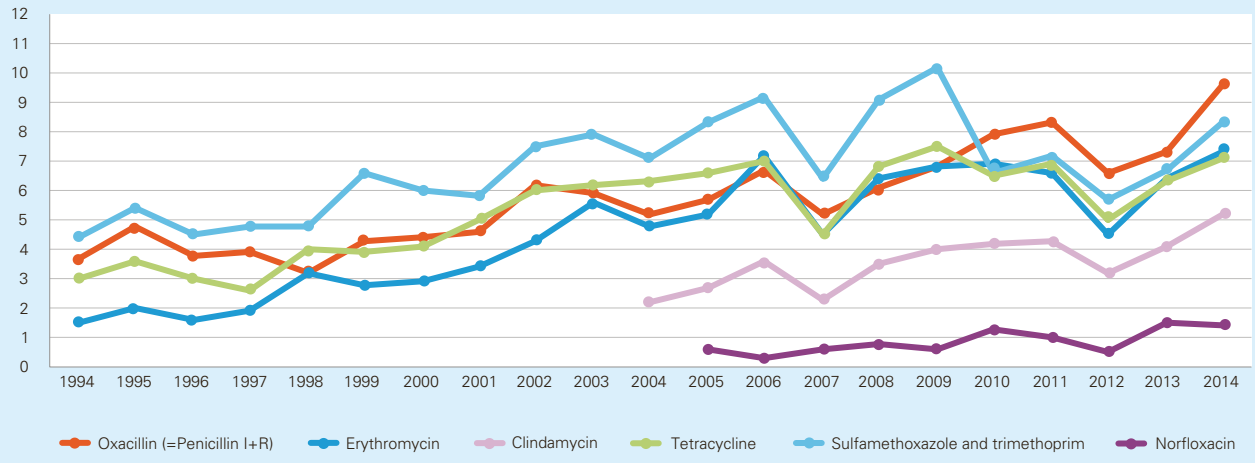
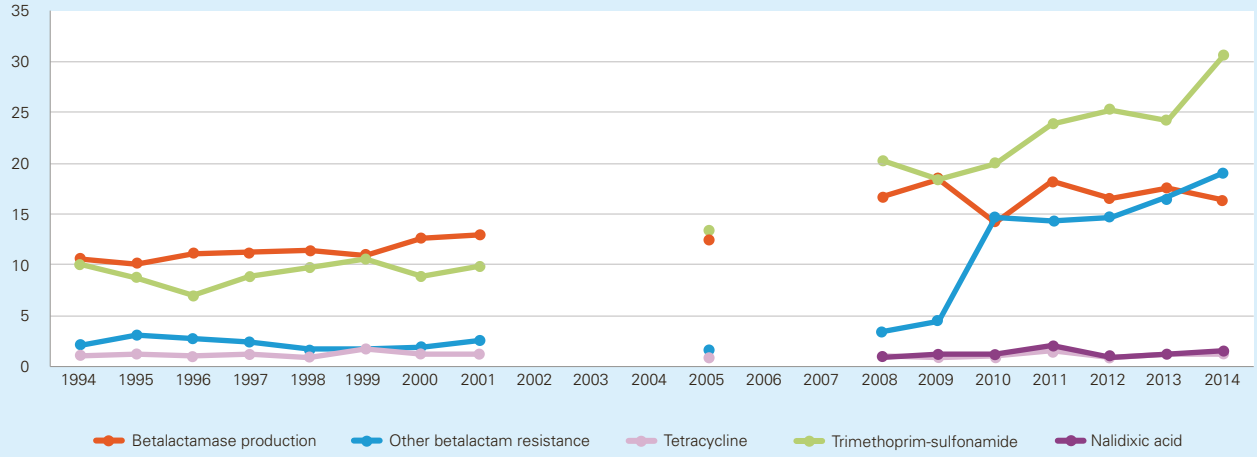


FIGURE 4.8. Proportion, %, resistant isolates of *Haemophilus influenzae* from respiratory tract specimens 1994-2014 (no data collected in 2002-2004, 2006-2007). In 2010-2014 beta-lactamase producing isolates were separated from isolates with other beta-lactam resistance mechanisms by use of penicillin G1 unit disk using the following interpretation: 6 mm = beta-lactamase production, 7-11 mm = other beta-lactam resistance.



In 2010 methodological changes were introduced (for description see www.nordicast.org) which made results for beta-lactam resistance more difficult to interpret. This was resolved by adjusting the reporting routines. Laboratories were asked to report 6 mm inhibition zones of penicillin G 1 for all beta-lactamase producing isolates, regardless of the actual zone diameter (Figure 4.8). 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 resistance due to other mechanisms of beta-lactam resistance (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 increase in resistance to trimethoprim-sulfamethoxazole slowed down. This year, 2014, a high increase in resistance to trimethoprim-sulfamethoxazole was seen again, reaching 30,7 %. The increase in resistance due to BLNAR seen from 2013 continues, while the resistance correlating beta-lactamase production is slightly decreasing. Tetracycline resistance in *Haemophilus influenzae* was still rare (1.3%) as was resistance to fluoroquinolones (1.4 %), detected by the nalidixic acid screening disk.

Clostridium difficile

The *Clostridium difficile* surveillance programme in Sweden

The national surveillance program for *Clostridium difficile* includes both a voluntary laboratory reporting system of all new cases of *C. difficile* infection (CDI) and susceptibility testing and epidemiological typing of isolates from the clinical microbiology laboratories. All *C. difficile* strains isolated during week no. 11 and 39 were sent to the Public Health Agency of Sweden for typing by PCR ribotyping and antibiotic susceptibility testing. Primarily metronidazole and vancomycin resistance was monitored, i.e. the recommended treatment choices for CDI. However, since use of antibiotics is a risk factor for acquiring CDI we also tested susceptibility to other antibiotics as an indicator of selective pressure, currently moxifloxacin, clindamycin and erythromycin. All isolates were tested using Etest on Mueller Hinton agar.

Incidence of CDI and distribution of resistant *Clostridium difficile* isolates in 2014

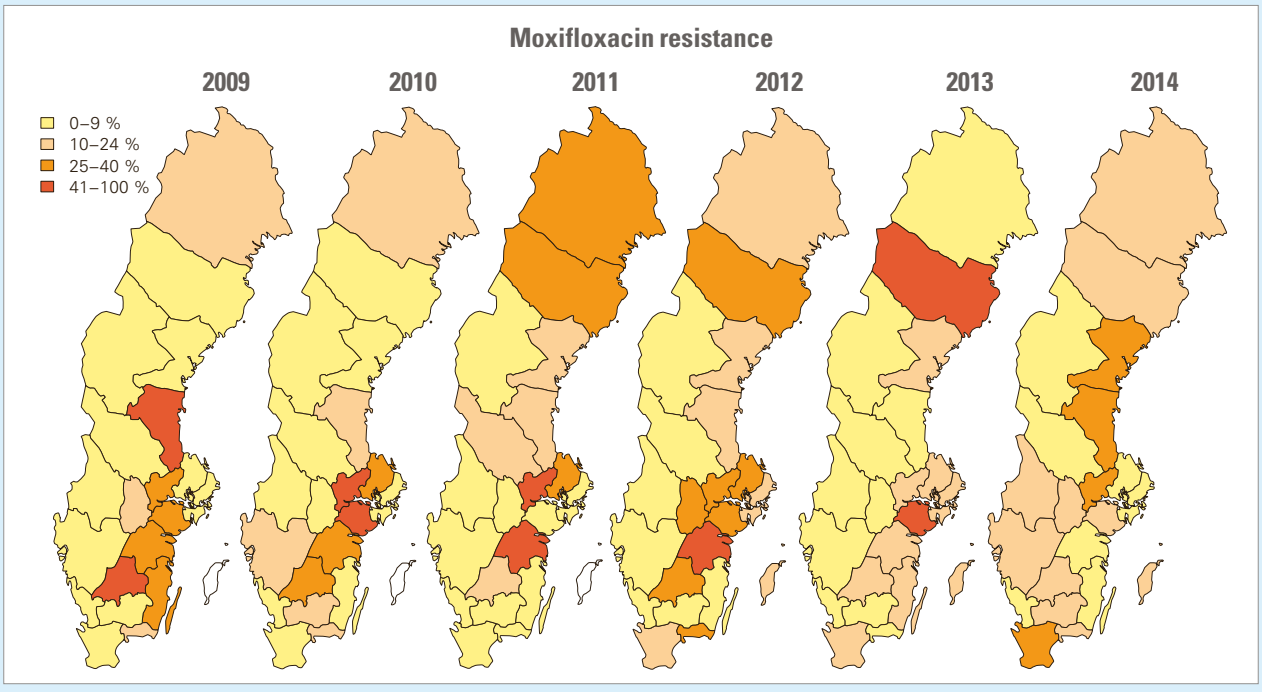
In 2014, 7691 new CDI cases were reported corresponding to an incidence 79/100,000 inhabitants, indicating that the incidence continues to fall. Also the number of collected isolates from all counties have decreased, from 491 and 458 isolates in 2012 and 2013, respectively, to 412 isolates in 2014. Three isolates in 2014 had a decreased susceptibility against the treatment option metronidazole with MICs of 4 and 2 (n=1 and 2, respectively). These isolates belonged to type 027, responsible for the outbreak in the county of Kronoberg in the beginning of 2014. The proportions of *C. difficile* isolates resistant to the indicator antibiotics erythromycin and clindamycin increased slightly during 2014 while that of moxifloxacin was the same as in 2013. (Table 4.3). Of particular interest, no resistant isolate of type 046 previously common in the county of Jönköping was detected. Also, the number of type 012 isolates with moxifloxacin resistance, common in the county of Östergötland in 2010-2013, has decreased from 32/34 isolates in 2012 to 10/18 isolates in 2014 (Fig 4.9). Also, both type 017 and 231 showed decreased in numbers in 2014 compared to 2013 but remain clustered to certain regions. Resistant type 027 increased in 2014 due to the outbreak in Kronoberg (http://www.folkhalsomyndigheten.se/documents/statistik-uppfoljning/smittsamma-sjukdomar/Clostridium-difficile-arsrapporter/Slutrapport-nationell-screening-Clostridium-difficile-typ-027-feb-2014.pdf). Type 078, commonly found also in animals, had variable resistance pattern towards the indicator antibiotics and its proportion has slowly increased from 11/491 (2.2 %) in 2012 to 21/458 (4.6 %) and 22/412 (5.3 %) in 2013 and 2014, respectively.

TABLE 4.3. *Clostridium difficile* types resistant to erythromycin, clindamycin and moxifloxacin in Sweden 2014 (n=412).

Antimicrobial	Type	% R 2014 (2013)	Distribution (no. of strains) per MIC (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
Clindamycin	012	89 (75)											1	1				16
	017	100 (79)																8
	027	50 (-)									2	1			2	1		
	046	0 (53)									1		2					
	231	100 (100)																6
	Other	13 (7)					1	2	26	45	94	99	32	27	15	4		24
	Total	**18 (15)**					**1**	**2**	**26**	**47**	**97**	**100**	**35**	**28**	**17**	**5**		**54**
Erythromycin	012	94 (75)								1		2				1		14
	107	100 (79)																8
	027	67 (-)								2								6
	046	0 (46)								1	2							
	231	100 (100)														1		**5**
	Other	13 (9)					4	40	131	116	37	3	1			4		33
	Total	**19 (16)**					**4**	**40**	**131**	**120**	**39**	**5**	**1**			**6**		**66**
Moxifloxacin	012	55 (63)							3	5					10			
	017	75 (59)								1	1				6			
	027	83 (40)								1					5			
	046	0 (27)								2	1							
	231	100 (100)													6			
	Other	9 (6)						7	70	193	66	5			30			
	Total	**14 (14)**						**7**	**73**	**202**	**68**	**5**			**57**			

The following MIC-breakpoints were used: clindamycin R > 16 mg/L, erythromycin R > 2 mg/L and moxifloxacin R > 4 mg/L.

FIGURE 4.9. Proportion of *Clostridium difficile* isolates with resistance to moxifloxacin per county 2009-2014.



Neisseria gonorrhoeae

Notifications according to the Swedish Communicable Diseases Act

Gonorrhoea is a notifiable infection and in 2014, 1336 cases (13.7 cases per 100 000 inhabitants) of gonococcal infections were reported to the Public Health Agency of Sweden. Most of these 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), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, Örebro.

In 2014, in total *N. gonorrhoeae* strains from 382 of the notified cases were fully characterised at this laboratory, representing 29% 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 β-lactamase was examined by nitrocefin discs.

The results for 2014 are compared with those from 2007 to 2013 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, however, decreased from 13% in 2013 to 9% in 2014. Nevertheless, this decrease might only reflect that only a low number of gonococcal isolates from Stockholm were analyzed at the Swedish Reference Laboratory for Pathogenic Neisseria. 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 2014, the resistance to cefixime (2%) continued to decrease and the resistance to ceftriaxone (0.3%) remained low. 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 some additional European countries. The reasons for this decline are still unknown, however, most likely the European recommendations to use ceftriaxone (500 mg) plus azithromycin (2 g) in the empiric first-line treatment 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 in most countries globally), and it is not suitable for treatment of pharyngeal gonorrhoea.

TABLE 4.4. Proportion of antibiotic resistance (%) and β-lactamase production of Swedish *Neisseria gonorrhoeae* strains 2007-2014

	2007 (n=406)	**2008** (n=447)	**2009** (n=384)	**2010** (n=618)	**2011** (n=805)	**2012** (n=877)	**2013** (n=967)	**2014** (n=384)
β–lactamase positive	30	28	44	29	23	23	18	28
Ampicillin	30	28	44	31	24	23	18	28
Cefixime	<1	1	5	6	8	10	4	2
Ceftriaxone	0	<1	0	2	2	1	<1 (0.3)	<1 (0.3)
Azithromycin	7	13	6	12	11	10	13	9
Ciprofloxacin	70	63	75	56	55	62	53	60
Spectinomycin	0	0	0	0	0	0	0	0

Neisseria meningitidis

Notifications according to the Swedish Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease, and in 2014 a total of 49 clinical cases (0.50 cases per 100 000 inhabitants) of the disease were reported. All together 45 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), 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 MIC values for penicillin G, cefotaxime, meropenem, chloramphenicol, ciprofloxacin and rifampicin. Production of β-lactamase was examined by nitrocefin discs.

Ten (22%) isolates had reduced susceptibility to penicillin G (MIC>0.064 mg/L). All isolates (100%) were susceptible to cefotaxime (MIC values of <0.002-0.016 mg/L), meropenem (MICs: 0.003-0.047 mg/L), chloramphenicol (MICs: 0.25-1.5 mg/L), ciprofloxacin (MICs: 0.002-0.006 mg/L), and rifampicin (MICs: 0.003-0.032 mg/L). None of the isolates obtained in 2014 produced β-lactamase, and in fact no β-lactamase-producing meningococcal isolate has ever been found in Sweden.

Mycobacterium tuberculosis

During 2014 in total 684 cases of tuberculosis (TB) were reported compared to 655 cases during 2013 which is a small increase.

The number and proportion of culture confirmed cases were 527 (77 %) compared to 522 (80 %) in 2013. *Mycobacterium tuberculosis* was identified in 522 cases and there was one *Mycobacterium africanum* and four *Mycobacterium bovis* diagnosed this year. The proportions of cases diagnosed with isoniazid resistant TB in 2014 were 9.8 % (51/522) and MDR 2.9 % (15/522). No XDR-TB were diagnosed during 2014.

Isolates of *M. tuberculosis* resistant to at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) were identified in 65 patients corresponding to 12.4% of the 522 with culture confirmed TB, see Table 4.5. As always isoniazid resistance was the most common resistance. Among the cases born in Sweden only two (four %) of 45 with culture confirmed diagnosis had isoniazid-resistant TB and no other resistance was found.

As much as 92 % of the TB cases reported in Sweden are born in another country. In this group 13.2 % (63/477) had some kind of resistance and 15 of those 63 had MDR-TB.

For 30 of the 522 we have information on previous treatment for TB after 1950 since when effective medication has been available. Out of these 30 cases 26 % (8/30) had some resistance and four were cases of MDR-TB. It is likely that more cases have received treatment earlier but there are no data on this.

Of the 15 cases with MDR-TB none was of Swedish origin and the majority (11/15) came to Sweden 2013 or later. In total 11 of the 15 cases had pulmonary manifestations and among them four were smear positive.

Genetic typing with MIRU-VNTR (Mycobacterial Interspersed Repetitive Units - Variable Numbers of Tandem Repeat) has been performed on 488 of the 522 isolates so far. This is done to help detect clusters which could indicate ongoing spread in Sweden. Of all 684 reported cases, 67 are considered to have been infected in Sweden. Among culture confirmed cases thought to have been infected in Sweden were the strain is unique, the majority are elderly who most likely were infected in their youth.

The proportion of patients with *M. tuberculosis* resistant against isoniazid has increased slightly in 2014 and we have seen more cases of MDR-TB but no XDR-TB as we did in 2012 and 2013.

TABLE 4.5. Drug resistant tuberculosis in Sweden 2005-2014.

Year of diagnosis	2005		2006		2007		2008		2009		2010		2011		2012		2013		2014	
Culture confirmed *M. tuberculosis*	448		395		361		434		510		523		473		498		522		522	
	No	**%**	**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	58	10.7	65	12.4
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	51	9.8
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	18	3.4
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	15	2.9
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	23	4.4
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	15	2.9

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 animals with diesase. Therefore, data may be biased towards samples from treated animals or from herds where antibiotic treatment is common. Any assessments of trends are 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 faecal samples or samples taken post mortem from the gastro-intestinal tract. During the latest years, the number of samples submitted has decreased and the sampling strategy has probably changed to some extent. This may influence the proportion of resistant isolates. Some of the isolates are tested by PCR for genes coding for the virulence factors enterotoxin (LT), heat-stable enterotoxin a and b (STa and STb), verocytotoxin (VT2e) and adhesion factors F4, F5, F6, F18 and F41. However, isolates may be susceptibility tested regardless of presence of virulence factors.

As in previous years, resistance to ampicillin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole were the most common resistance traits (Table 5.1). Resistance to ampicillin and to trimethoprim-sulphamethoxazole has increased considerably compared to previous years (Figure 5.1). Resistance to enrofloxacin has varied between 6% and 11% since 2001. In 2014, two isolates had MICs above the ECOFF for colistin. This may be true resistance or due to methodological errors, but the isolates were not available for further analyses.

Multiresistance occurred in 42% (50/118) of the isolates in 2014 which is higher than previous years (38% in 2013, 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 a regulation from 2013, susceptibility testing is generally required before ordination of fluoroquinolones for 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 between trimethoprim-sulphonamides and other antibiotics is common.

The combination of resistance to ampicillin, streptomycin and trimethoprim-sulphametoxazole was the most common trait in 2014, as in previous years, occurring in 64% of the multiresistant isolates. Seventeen percent of all isolates were resistant to four antibiotics. Three isolates were resistant to five antibiotics and one isolate to six antibiotics.

FIGURE 5.1. Resistance (%) in *Escherichia coli* from pigs 1992-2014. 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).

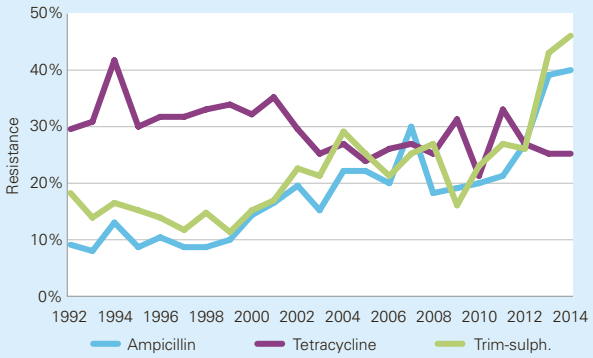


TABLE 5.1. Distribution of MICs and resistance (%) in *Escherichia coli* from pigs 2014. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2014 n=118	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	40					48.3	11.9		39.8		
Cefotaxime[a]	0		100								
Ceftiofur[b]	0		27.5	65.2	7.2						
Colistin[a]	4				81.6	14.3			4.1		
Enrofloxacin	11	89.0	3.4	4.2	0.8	2.5					
Florfenicol[b]	1					5.8	47.8	37.7	7.2	1.4	
Gentamicin	0					99.2	0.8				
Neomycin	13						83.9	3.4		1.7	11.0
Streptomycin	50							39.0	11.0	11.0	39.0
Tetracycline	25					64.4	8.5	1.7	25.4		
Trim-Sulph.[c]	46			53.4	0.8			45.8			

[a] 49 isolates tested; [b] 69 isolates tested; [c] 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 antibiotic susceptibility data from isolates of *B. hyodysenteriae* from Sweden 1990-2010 has resulted in a proposal for ECOFFs for the antibiotics 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. However, with the previously used clinical breakpoint >2 mg/L, no isolate was classified as clinically 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 antibiotics tested. As guide for the choice of antibiotic 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 58% to tylosin (Table 5.3). If the same ECOFF as for *B. hyodysenteriae* is used, 28% of the isolates are resistant to tiamulin. Tiamulin, valnemulin and tylosin are currently licensed for treatment of spirochaetal diarrhoea in pigs in Sweden and isolates with high MICs of these three substances are present.

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. 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 also 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. Antibiotic resistance is rare among isolates of *Pasteurella* spp. (Table 5.5).

Isolates from 2013-2014 (n=114) were species identified by MALDI-TOF MS and are *Pasteurella multocida*. Isolates from earlier years were identified to species with biochemical methods. Most of these isolates are *P. multocida*, but species identification is in some cases uncertain. However, ECOFFs for *P. multocida* are used in Table 5.5 for all isolates.

TABLE 5.2. Resistance (%) in *Brachyspira hyodysenteriae* from pigs 2005-2014 and distribution of MICs for isolates from 2009-2014. Clinical isolates from faecal samples.

Antibiotic	Resistance (%)			Distribution (%) of MICs (mg/L)												
	2005-06 n=54[a]	2007-08 n=38[b]	2009-14 n=62[c]	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline	9	3	3			17.7	67.7	11.3		3.2							
Tiamulin	7	18	6		41.9	37.1	14.5	3.2	3.2								
Tylosin	81	76	58								24.2	16.1	1.6			1.6	56.5
Tylvalosin	NA	93[d]	56				1.6	17.7	24.2	3.2	11.3	27.4	11.3		3.2		
Valnemulin	0	18	3	82.3	14.5			3.2									

[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, 7 isolates 2014; [d] 15 isolates tested; NA=not analysed.

TABLE 5.3 Distribution of MICs for *Brachyspira pilosicoli* from pigs 2005-2014, n=289. Clinical isolates from faecal samples. The number of isolates each year varies (n=12-67).

Antibiotic	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			39.1	48.8	4.5	2.8	4.5	0.3						
Tiamulin		33.2	26.3	12.1	8.3	6.2	1.7	0.7	2.4	9.0				
Tylosin							5.5	20.4	11.8	4.2	4.5	3.8	5.2	44.6
Tylvalosin[a]				0.8	12.7	25.4	25.4	4.8	1.6	4.0	13.5	11.9		
Valnemulin	45.7	20.1	5.9	9.3	7.3	4.2	2.4	1.4	3.8					

[a] 126 isolates tested.

TABLE 5.4. Distribution of MICs and resistance (%) in *Actinobacillus pleuropneumoniae* from pigs 2005-2014. Clinical isolates from post mortem investigations of lungs. The number of isolates each year varies (n=16-57).

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)														
	2005-2014 n=326	≤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	12.6	58.0	29.4												
Florfenicol	0									100						
Gentamicin	0							0.3	8.9	78.8	12.0					
Nalidixic acid	0							2.5	60.7	36.8						
Penicillin	0			0.3	4.9	65.0	29.8									
Streptomycin	NR[a]								0.3		1.8	46.9	49.1	1.8		
Tetracycline	<1							99.7	0.3							
Trimethoprim	0				18.7	60.7	17.2	2.5	0.9							

[a] Not relevant since the genus has inherently low susceptibility to streptomycin.

TABLE 5.5. Distribution of MICs and resistance (%) in *Pasteurella* spp. from pigs 2005-2014. Clinical isolates from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs. The number of isolates each year varies (n=10-95).

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)														
	2005-2014 n=252	≤0.008	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[a]									100							
Ciprofloxacin	0[a]	21.6	58.8	18.6	1.0												
Enrofloxacin	0[b]					98.7	1.3										
Florfenicol	1[c]										98.8	1.2					
Gentamicin	1									73.4	21.0	4.8	0.4	0.4			
Nalidixic acid	0[a]								50.5	40.2	8.2		1.0				
Penicillin	0					52.0	43.3	4.8									
Streptomycin	NR[d]										3.2	44.4	34.1	13.5	4.8		
Tetracycline	0								98.4	1.6							
Trim/Sulph	1[e]							96.4	0.7	0.7	0.7	1.4					

[a] 97 isolates tested; [b] 155 isolates tested; [c] 248 isolates tested, [d] Not relevant since the genus has inherently low susceptibility to streptomycin; [e] 138 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. 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 isolates from the period 2012-2014 resistance was higher than previous years for ampicillin, streptomycin and tetracycline (Table 5.6). Multiresistance occurred in 76% (22/29) of the isolates from 2014, compared to 70% in 2013, 50% in 2012 and 40% in 2007-2011. The reason for the observed increase is not known. However, a biased material, due to sampling in herds with therapeutic failure and to new legislation that states susceptibility testing, could have influenced the results. Moreover, the low number of tested strains in 2014 makes it difficult to draw conclusions on trends.

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 milk samples

Isolates of *E. coli* are from clinical submissions of milk samples from dairy cows. It is probable that most sampled cows had clinical mastitis. According to a regulation from 2013, susceptibility testing is generally required before ordination of fluoroquinolones for use in animals. As a consequence of this the number of isolates of *E. coli* from milk samples that are susceptibility tested has increased considerably during 2013 and 2014 compared to previous years. Although antibiotic treatment is not always indicated for *E. coli* mastitis, fluoroquinolones may be the clinically most effective group of antibiotics if treatment is required.

In the material from 2014, 32% (30/95) of the isolates were resistant to at least one antibiotic. Resistance to ampicillin, streptomycin, tetracycline or trimethoprim-sulphamethoxazole was most common and has increased compared to 2013 (Table 5.7). Multiresistance occurred in 19% (18/95) of all isolates. Resistance to ampicillin, streptomycin and trimethoprim-sulphamethoxazole were the most common traits and 16% of all isolates were resistant to all three of these antibiotics. Three isolates were resistant to five antibiotics (ampicillin, enrofloxacin, streptomycin, tetracycline and trimethoprim-sulphamethoxazole).

Klebsiella pneumoniae from milk samples

Isolates of *Klebsiella pneumoniae* are from clinical submissions of milk samples from dairy cows. Resistance was uncommon and 74% of isolates was susceptible to all tested antibiotics, excluding ampicillin, and MICs were in accordance with the results from susceptibility testing of isolates from 2002-2003 (Bengtsson et al., 2009). Resistance to streptomycin was the most common resistance trait. Multiresistance did not occur in isolates from 2014.

TABLE 5.6. Resistance (%) in *Escherichia coli* from cattle 1992-2002 and 2005-2014. Distribution of MICs for isolates from 2012-2014. Clinical isolates from faecal samples or from samples taken post mortem from the gastro-intestinal tract.

Antibiotic	Resistance (%)				Distribution (%) of MICs (mg/L)									
	1992-02 n=220	2005-06 n=63	2007-11 n=70	2012-14 n=117	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	24	32	33	55					38.5	6.0	0.9	54.7		
Ceftiofur[a]	0[g]	0	3	2		4.5	83.8	9.9	1.8					
Enrofloxacin[b]	10	13	10	12	88.0	3.4	0.9	0.9	6.8					
Florfenicol	0[g]	0	1	0						34.2	64.9	0.9		
Gentamicin[c]	5	0	1	1					86.3	12.8		0.9		
Neomycin	8	13	24	19						65.8	15.4	1.7	1.7	15.4
Streptomycin[d]	42	54	49	77							17.9	5.1	1.7	75.2
Tetracycline	31	49	64	77					20.5	2.6		76.9		
Trim/Sulph.[e,f]	11	21	17	21			77.8	0.9		0.9	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. Resistance (%) in *Escherichia coli* from dairy cows 2013-2014 and distributions of MICs for isolates from 2014. Clinical isolates from milk.

Antibiotic	Resistance (%)		Distribution (%) of MICs (mg/L)									
	2013 n=142	2014 n=95	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	14	20				5.3	44.2	28.4	2.1	20.0		
Ceftiofur	1	0		9.5	68.4	22.1						
Enrofloxacin	5	6	93.7	1.1	4.2	1.1						
Florfenicol	0	0					1.1	47.4	49.5	2.1		
Gentamicin	0	0					95.8	4.2				
Neomycin	4	1						94.7	4.2	1.1		
Streptomycin	16	25						3.2	32.6	38.9	3.2	22.1
Tetracycline	9	19				8.4	51.6	18.9	2.1	18.9		
Trim-Sulph.[a]	11	17			83.2				16.9			

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

Staphylococcus aureus from milk samples

Isolates of *Staphylococcus aureus* are from milk samples from dairy cows with clinical mastitis. Samples were submitted within a field study in which participating veterinary practices sent in milk samples from dairy cows with clinical mastitis in a randomized way.

Resistance was uncommon in this material and in accordance with the results from susceptibility testing of isolates from 2002-2003 (Bengtsson et al., 2009). Since 2002-2003, the proportion of beta-lactamase producing isolates has decreased from 7% to 1%. In order to reduce transmission of beta-lactamase producing *S. aureus* among Swedish dairy cows, it is recommended not to keep animals with mastitis caused by such bacteria in the herd. The decrease in beta-lactamase producing *S. aureus* over the last decade indicates that this strategy has been effective. However, the sampling strategy and number of sampled cows are not similar in the two studies, and conclusions on trends should therefore be drawn with caution.

For four of the isolates, MICs of oxacillin were above the cut-off value. Three of the isolates had MIC 2 mg/L and one isolate had MIC 1 mg/L (Table 5.9). These four isolates were tested for the presence of *mecA* and *mecC* genes with PCR but the genes were not detected.

TABLE 5.8. Resistance (%) in *Klebsiella pneumoniae* from dairy cows 2013-2014 and distributions of MICs for isolates from 2014. Clinical isolates from milk.

Antibiotic	Resistance (%)		Distribution (%) of MICs (mg/L)									
	2013 n=41	2014 n=39	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	NR[b]	NR[b]								100		
Ceftiofur	0	0		7.7	82.1	10.3						
Enrofloxacin	0	3	89.7	7.7	2.6							
Florfenicol	2	3					2.6	43.6	46.2	5.1	2.6	
Gentamicin	0	0					100					
Neomycin	2	0						100				
Streptomycin	7	18						71.8	10.3		5.1	12.8
Tetracycline	15	5				5.1	71.8	17.9		5.1		
Trim-Sulph.[a]	5	0			100							

[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 5.9. Distribution of MICs and resistance (%) in *Staphylococcus aureus* isolated from dairy cows in 2013-2014. Clinical isolates from milk.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)														
	2013-2014 n=74	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Cephalothin	0			9.5	45.9	43.2		1.4								
Ciprofloxacin	0				12.2	52.7	33.8	1.4								
Chloramphenicol	0									5.4	91.9	2.7				
Clindamycin	1					98.6	1.4									
Erythromycin	0					32.4	50.0	17.6								
Fucidic acid	8			17.6	17.6	12.2	44.6	6.8	1.4							
Gentamicin	0						89.2	8.1	2.7							
Kanamycin	0						5.4	13.5	56.8	16.2	8.1					
Oxacillin	5				5.4	52.7	17.6	18.9	4.1	1.4						
Penicillin[a]	1															
Tetracycline	1						93.2	5.4	1.4							
Trimethoprim	9						5.4	41.9	43.2	8.1	1.4					

[a] Denotes beta-lactamase production.

TABLE 5.10. Distribution of MICs and resistance (%) in *Pasteurella* spp. from calves 2005-2014. Clinical isolates from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2005-2014 n=293	≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Ampicillin	0					100					
Enrofloxacin	0[b]		96.6	3.4							
Florfenicol	0							100			
Penicillin	0		53.9	38.9	7.1						
Tetracycline	0					95.9	4.1				
Trim/Sulph.[a]	0				96.9	1.7	1.0	0.3			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole); [b] 268 isolates tested.

Pasteurella spp.

Isolates of *Pasteurella* spp. are from nasal swabs from calves with respiratory disease or from post mortem investigations of lungs. Isolates from 2013-2014 were species identified by MALDI-TOF MS and are *Pasteurella multocida*. Isolates from earlier years were species identified with biochemical methods. Most of these isolates are also *P. multocida*, but species identification is in some cases uncertain. However, ECOFFs for *P. multocida* are used, if possible, in Table 5.10 for all isolates.

Antibiotic resistance was 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.

Sheep

Mannheimia haemolytica and *Bibersteinia trehalosi*

Isolates of *Mannheimia haemolytica* and *Bibersteinia trehalosi* are from post mortem investigation of lungs. Resistance was uncommon in this material (Table 5.11). Since ECOFFs are rarely available for these bacteria, ECOFFs for *P. multocida* are used, when possible. Two isolates had MICs just above the ECOFF for penicillin, but these isolates were not available for further analyses.

TABLE 5.11. Distribution of MICs and resistance (%) in *Mannheimia haemolytica* and *Bibersteinia trehalosi* from sheep 2013-2014. Clinical isolates from the respiratory tract, isolated from post mortem investigations of lungs.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2013-2014 n=44	≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Ampicillin	0					100					
Enrofloxacin	5		79.5	15.9	2.3	2.3					
Florfenicol	0						100				
Penicillin	5		61.4	18.2	15.9	4.5					
Tetracycline	0					95.5	4.5				
Trim/Sulph.[a]	0				97.7		2.3				

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

Risk factors for antibiotic resistant *Escherichia coli* in faeces of preweaned dairy calves

Antibiotic resistant *E. coli* that has been selected for in the farm animal population may be transmitted to humans via the food-chain (van den Bogaard and Stobberingh, 2000). Of special concern is *E. coli* that has acquired resistance to fluoroquinolones or ESCs, which are critically important antibiotics in human medicine (WHO, 2012). Faecal *E. coli* from preweaned calves is often multiply resistant, even without exposure to antibiotics (Swedres-Svarm, 2013; de Verdier et al., 2012). To increase the knowledge about risk factors for the occurrence and dissemination of faecal resistant *E. coli* from calves and to define measures to reduce the occurrence, a PhD project was initiated in 2011. Below is a summary of the studies included in the project. The full thesis "Antimicrobial resistant *Escherichia coli* in faeces of preweaned dairy calves" is available from http://pub.epsilon.slu.se/.

In a study on 243 farms risk factors for resistant *E. coli* were sought (Duse et al., 2015). Increasing calf age was a consistent protective factor against resistant *E. coli*, with the prevalence being highest around one week of age and then gradually declining. The microbiota of the gastrointestinal tract of the new-born calf is less diverse than in older cattle (Mayer et al., 2012). Many resistant *E. coli* strains carry factors that enhance their colonization ability (de Lastours et al., 2014; de Verdier et al., 2012) and competitiveness against susceptible *E. coli* (Eberhart et al., 2014), which may explain their successful establishement in the young calf gut. The decline in resistant *E. coli* with increasing age may be due to a combination of acquired immunity to certain strains (Runnels et al., 1980) and increased competition from an increasingly diverse gastrointestinal microbiota (Mayer et al., 2012).

Feeding colostrum from cows treated with antibiotics at drying off did not affect the shedding of antibiotic resistant *E. coli* by calves. In contrast, feeding milk from cows treated with antibiotics during lactation to calves increased faecal streptomycin resistant *E. coli* and quinolone resistant *E. coli* (QREC). It can be assumed that antibiotics in milk inhibit susceptible species in the gastrointensitnal tract, and thus, disturbs the composition of the microbiota. A disturbed gastrointenstintal microbiota is tantamount to reduced colonization resistance which may ease the establishment of antibiotic resistant *E. coli*. Hence, feeding milk from antibiotic-treated cows cannot be recommended from a resistance point of view.

Treatment with broad-spectrum antibiotics in both cows and calves increased the occurrence of faecal *E. coli* with resistance to related or unrelated drugs (Duse et al., 2015). Treatment of cows may result in selection of resistant *E. coli* in their gastrointestinal microbiota, which could readily be spread by faeces in the farm environment and transferred to calves. Hence, prudent use of antibiotics likely reduces the overall burden of resistant *E. coli* on dairy farms and should include not only treatment of calves, but also treatment of cows.

Resistant *E. coli* was also more common on large than on small farms, which is a concern with the current development towards larger farms in Sweden. Calves on farms with parlour milking compared to farms with tie stall milking or automatic milking systems, and calves on farms in South and East compared to North Sweden were also more likely to carry resistant *E. coli*. The latter may be due to clonal dissemination of resistant *E. coli* between closely located farms.

The prevalence of faecal QREC from calves varied substantially between farms, and this prompted additional studies on risk factors and within-farm dissemination of QREC (Duse et al. 2015). On farms with high prevalence of faecal QREC in calves, QREC was also frequently found in calf feed, water and milk troughs, in the calving pen and in faecal samples from newly calved cows.Thus, it was assumed that QREC is maintained in the calf group by faecal-oral circulation through contamination of feed, water and milk troughs and that transit of cows and calves via the calving area may be important for the dissemination of QREC between cows and calves. On most farms, two to four genotypes were found throughout the farm, indicating within-farm clonal dissemination of QREC. Poor farm hygiene, group calving and infrequent use of the calving pen as a sick pen were risk factors for faecal QREC in cows and calves. Measures to reduce the burden of QREC on farms may be related to factors that decrease contamination and spread of faecal material, such as proper cleaning of feed, water and milk troughs as well as the use of single calving pens.

The same clone of QREC was also found on more than one farm, suggesting clonal spread between farms. Farms that were located closer to each other were more likely to share the same QREC clone, possibly due to an epidemiological connection between those farms. Quinolone resistant *E. coli* was also more common on farms that purchase cattle or share animal transporter with other farmers. A positive correlation was also found between the number of purchased cattle and the genetic diversity of QREC within the farm, suggesting that new QREC genotypes are introduced to the farm via purchase of cattle. These results indicate that QREC is spread between farms via the movement of cattle and equipment.

Farmed fish

Isolates presented are from clinical submissions of farmed fish. In 2014, data for nine isolates of *Aeromonas salmonicida* subsp. *achromogenes* and nine of *Flavobacterium columnare* were available. Data for 2009-2014 are compiled and presented as distributions of MICs in Table 5.12. In Table 5.13 MIC distributions for isolates of *Flavobacterium psycrophilum* are presented. Isolates of *F. psychrophilum* are from 22 disease outbreaks. In all but six of these samplings more than one isolate of *F. psychrophilum* were susceptibility tested. Most isolates of *A. salmonicida* and *F. columnare* are from brown trout or archtic char whereas most isolates of *F. psychrophilum* are from rainbow trout.

At present there are only published interpretative criteria for MIC data for *A. salmonicida* from aquatic animals (CLSI, 2014b). Epidemiological cut-offs of >4 mg/L and >1 mg/L was proposed by CLSI for florfenicol and oxytetracycline, respectively. Using those criteria, one isolate is interpreted as resistant to florfenicol and two to tetracycline. A bimodal distribution with deviating high MICs of the quinolone nalidixic acid indicate the presence of acquired resistance to this antibiotic as well. Recently, Smith et al. (2014) proposed ECOFFs for florfenicol, oxolinic acid and oxytetracycline for *F. psycrophilum*. These are used in the distributions in Table 5.13. Resistance to oxolinic acid and oxyteracycline was high in this material. There is a limited therapeutic use of the quinolone oxolinic acid as well as of tetracycline in aquaculture in Sweden.

TABLE 5.12. Distribution of MICs for *Aeromonas salmonicida* subsp. *achromogenes* (n=69) and *Flavobacterium columnare* (n=40) from farmed fish 2009-2014.

Bacterial species	Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)								
		2009-2014	≤0.5	1	2	4	8	16	32	64	>64
Aeromonas salmonicida subsp. *achromogenes*	Florfenicol	1			97.1	1.4		1.4			
	Nalidixic acid[a]		81.7	1.7					1.7	6.7	8.3
	Tetracycline	3	94.2	2.9		1.4		1.4			
Flavobacterium columnare	Florfenicol				100						
	Nalidixic acid[b]		77.4	12.9	3.2	3.2				3.2	
	Tetracycline		97.5	2.5							

[a] 60 isolates tested; b 31 isolates tested.

TABLE 5.13. Distributions of MICs and resistance (%) in *Flavobacterium psycrophilum* from farmed fish 2014.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)											
	2014 n=61	≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
Florfenicol	0						26.2	29.5	36.1	8.2			
Oxolinic acid	69				3.3	26.2	1.6		8.2	60.7			
Oxytetracycline	80			3.3	16.4		1.6	8.2	23.0	19.7	18	9.8	
Trim/Sulph.[a]	87				1.6	8.2	3.3	13.1	23.0	26.2	24.6		

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

Svarmpat – monitoring of resistance in pathogens from farm animals

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

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

Selected studies within Svarmpat in 2014:

Milk samples in dairy cows

- Screening for MRSA in milk samples from dairy cows 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 2010-2014, 702 isolates were tested and MRSA with *mecC* was confirmed in 3 isolates from 2010, 1 from 2011 and 1 from 2013, and MRSA with *mecA* was confirmed in 1 isolate from 2012 and 1 from 2014. In addition, 513 isolates of *S. aureus* without beta-lactamase production was tested in 2013, but MRSA was not detected. See Notifiable diseases, MRSA in animals.

- Continuous monitoring of bacterial findings in clinical mastitis in dairy cows started in 2013. Randomly collected milk samples from dairy cows with clinical mastitis are cultured and isolated bacteria are susceptibility tested. Mastitis is an important disease in dairy cows. Most bacteria causing mastsitis in dairy cows in Sweden are sensitive to penicillin and penicillin is the drug of choice for treatment if antibiotic is needed. It is, however, desirable to continuously monitor the situation concerning bacterial panorama and resistance situation. Resistance in *S. aureus* isolated in this study is presented in Clinical isolates from animals.

Respiratory tract samples in pigs, cattle and sheep

- Resistance in *Actinobacillus pleuropneumoniae* and *Pasteurella multocida* from pigs, *P. multocida* and *Mannheimia haemolytica* from cattle and *M. haemolytica* and *Bibersteinia trehalosi* from sheep are continously susceptibility tested within Svarmpat. Resistance to penicillin in these bacteria is very uncommon, supporting the recommendation to primarily use penicillin for treatment of pneumonia in pigs, cattle and sheep. For resistance results see Clinical isolates from animals.

Enteric samples from pigs

- Swine dysentery and spirochaetal diarrhoea in pigs are important diseases in many countries. The resistance situation in the causative agents, *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 Clinical isolates from animals.

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 and the work is party financed by Svarmpat. See Notifiable diseases, ESBL-producing Enterobacteriaceae.

Questionnaire about specified pig diseases

During 2014, a questionnaire about the disease syndromes head tilt and exudative epidermitis in pigs was performed with the aim to increase knowledge about occurrence and outcome of treatment. Answers were received from 186 pig veterinarians, pig farmers and pig farm workers. Results are being compiled.

Horses

Escherichia coli

Isolates of *Escherichia coli* are from clinical sampling of the genital tract of mares. As in previous years, resistance to trimethoprim-sulphametoxazole and streptomycin was most common in 2014 (Table 5.14). Since 2004, the rate of resistance has differed somewhat between the years, but the figures seem to decline (Figure 5.2).

Multiresistance was detected in 5 % (12/229) of the isolates, which is comparable to the figures in 2013 (4%) and 2012 (6%), but less than 2011 (11%). Ten of the isolates were resistant to three substances and one to four substances, including ampicillin, trimethoprim-sulphametoxazole and/or different aminoglycosides, but also to tetracycline and enrofloxacin. However, no dominant trait was oserved. One isolate was resistant to six substances; ampicillin, enrofloxacin, gentamicin, neomycin, streptomycin, tetracycline and trimethoprim-sulphametoxazole.

No ESC resistant *E. coli* was isolated from this material. For more information of ESBL in horses, see ESBL-producing Enterobacteriaceae in animals.

FIGURE 5.2. Resistance (%) in clinical isolates of *Escherichia coli* from the genital tract of mares 2004-2014. The number of isolates each year varies (n=124-273).

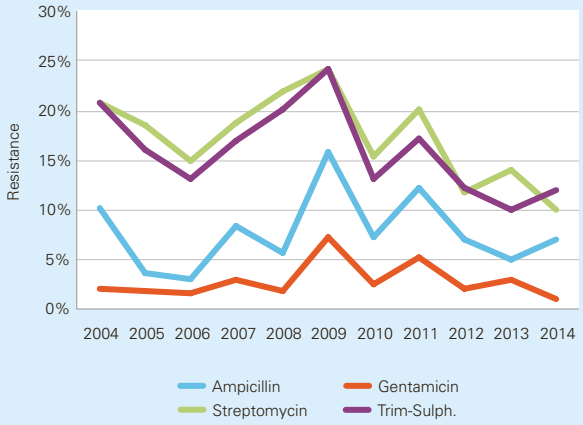


TABLE 5.14. Distributions of MICs and resistance (%) in *Escherichia coli* from horses in 2014. Clinical isolates from the genital tract of mares.

Antibiotic	Resistance (%) 2014 n=229 [b]	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64
Ampicillin	7					44.1	48.5	0.9	6.6		
Cefotaxime	0		100								
Colistin	4				67.4	28.9	2.8	0.5	0.5		
Enrofloxacin	2	98.3	1.3	0.4							
Gentamicin	1					98.3	0.4	0.4		0.9	
Neomycin	1						98.7				1.3
Streptomycin	10							72.1	18.0	0.4	9.6
Tetracycline	3					91.7	4.8	0.4	3.1		
Trim-Sulph.[a]	12			88.2			11.8				

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphametoxazole); [b] n=229 for all substances except cefotaxime and colistin with 218 tested isolates respectively.

TABLE 5.15. Distribution of MICs and resistance (%) in *Streptococcus zooepidemicus* isolated from horses in 2014. Clinical isolates from the respiratory tract.

Antibiotic	Resistance (%) 2014 n=129	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0				100						
Enrofloxacin	NR [b]	0.8	0.8		53.5	45.0					
Florfenicol	0					98.4	1.6				
Gentamicin	NR [b]					0.8	1.6	45.0	47.3	5.4	
Penicillin	0	100									
Spiramycin	0						100				
Tetracycline	2				41.9	47.3	9,3		1.6		
Trim-Sulph.[a]	5			82.2	10.1	3.1		4.7			

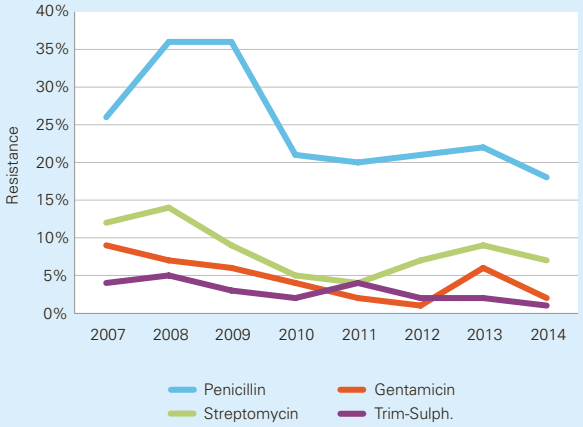
[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphametoxazole); [b] NR= Not relevant as the inherent susceptibility is above concentrations that can be obtained during therapy.

TABLE 5.16. Distribution of MICs and resistance (%) in *Staphylococcus aureus* from horses 2014. Clinical isolates from the skin.

Antibiotic	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2014 n=132	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ceftiofur	0		1.5	2.3	77.2	18.9					
Enrofloxacin	3	36.4	55.3	5.3	2.3	0.8					
Florfenicol	2					3.0	65.9	28.8	2.3		
Gentamicin	2					97.8	0.8	1.5			
Oxacillin	0			100							
Penicillin[a]	18										
Spiramycin	<1						15.2	75.0	9,1		0.8
Streptomycin	7						24.2	47.0	22.0	3.8	3.0
Tetracycline	3				97.0	0.8	0.8	1.5			
Trim-Sulph.[b]	<1			99.2	0.8						

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

FIGURE 5.3. Resistance (%) in clinical isolates of *Staphylococcus aureus* from skin of horses 2007-2014. The number of isolates each year varies (n=96-145).



Streptococcus zooepidemicus

Isolates of *Streptococcus zooepidemicus* are from clinical sampling of the respiratory tract. Resistance to antibiotics was rare in 2014 (Table 5.15). Over the years studied in Svarm, the susceptibility to penicillin and ampicillin has remained stable. Resistance to the other antibiotics tested has been rare from 1995 up to date (historical data not shown), except for trimethoprim-sulphametoxazole with gradually declining resistance rates and tetracycline with an unexplained peak of 7% resistance in 2010.

Streptococcus zooepidemicus have a low inherent susceptibility to fluoroquinolones (e.g. enrofloxacin) and aminoglycosides (e.g. gentamicin). The MICs of these antibiotics were high and above concentrations obtained during systemic therapy.

Staphylococcus aureus

Isolates of *Staphylococcus aureus* are from clinical sampling of skin, excluding wounds and abscesses. Table 5.16 presents the distribution of MICs and resistance in isolates from 2014. Levels of resistance for gentamicin, penicillin, streptomycin and trimethoprim-sulphametoxazole over the last eight years are shown in Figure 5.3. Resistance to penicillin due to beta-lactamase production dominates. After a peak in 2008-2009 (36%), the figures have stabilised around 20% for the last five years.

No MRSA was detected in this material. For more information on MRSA isolated from horses, see Notifiable diseases, MRSA in animals.

Dogs

Escherichia coli

Isolates of *Escherichia coli* are from clinical sampling of urine, submitted either as urine or cultures on dip-slides or other agar plates. As in previous years, resistance to ampicillin was the most common trait in 2014 (Table 5.17). Levels of resistance to ampicillin, enrofloxacin and trimethoprim-sulphametoxazole have been slightly declining since 2005 (Figure 5.4).

Multiresistance was detected in 2% (20/943) of the isolates. This is about the same figure as in 2013 (3%) and halved compared to 2011-2012. Fourteen of the twenty multiresistant isolates were resistant to three substances and six to four substances. Of the multiresistant isolates were 19 resistant to ampicillin, 15 to trimethoprim-sulphametoxazole, 12 to enrofloxacin and 11 to tetracycline. Furthermore four of those strains were resistant to one or more of cefotaxime, colistin, gentamicin and/or nitrofurantoin, but no specific phenotype stood out.

Six of seven *E. coli* isolates resistant to cefotaxime were further analysed for ESBL-production. Genes conferring transmissible ESBL or AmpC resistance were found in four of these isolates. For more information, see ESBL-producing Enterobacteriaceae in animals.

Staphylococcus pseudintermedius

Isolates of *Staphylococcus pseudintermedius* are from clinical sampling of skin, excluding wounds and abscesses. Occurrence of penicillin resistance due to beta-lactamase production was constantly high, 77% in 2014 and during the presented 15 years between 75 and 90% (Table 5.18 and Figure 5.5). Occurrence of resistance to clindamycin, erythromycin, fusidic acid and/or tetracycline fluctuate slightly between the years, but remains at approximately the same levels since 2004 (Figure 5.5).

Multiresistance is common in *S. pseudintermedius*, between 2009 and 2013 the figures have varied between 26 and 36%, and was in 2014, 34 % (173/513). Resistance to five or more antibiotics was observed in one fourth (44/173) of the multiresistant isolates (of all isolates 9%). The most common multiresistant phenotype was resistance to penicillin, clindamycin

FIGURE 5.4. Resistance (%) in clinical isolates of *Escherichia coli* from urine of dogs, 2005-2014. The number of isolates each year varies (n=304-943).

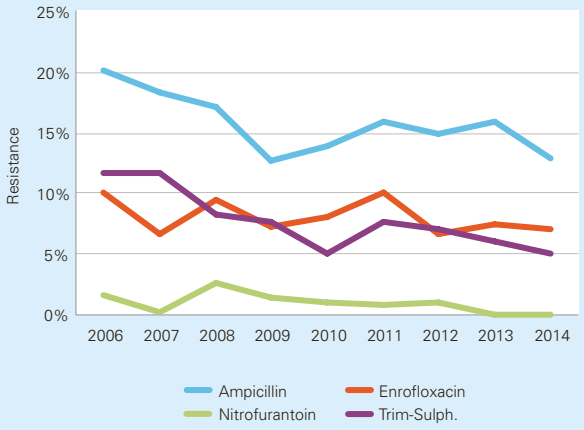


TABLE 5.17. Distribution of MICs and resistance (%) in *Escherichia coli* from dogs 2014. Clinical isolates from urine.

Antibiotic	Resistance (%) 2014 n=943 [b]	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	13					51.4	33..6	1.7	13.3		
Cefotaxime	<1			99.3	0.2	0.5					
Colistin	5				72.6	22.9	2.6	0.6	1.3		
Enrofloxacin	7	93.2	2.3	2.4	1.0	0.1		1.0			
Gentamicin	<1					98.7	1.0	0.1		0.2	
Nitrofurantoin	<1								97.6	1.7	0.7
Tetracycline	5					87.2	6.7	1.5	4.7		
Trim-Sulph.[a]	5			93.8	0.7	0.2		5.2			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphametoxazole); [b] n=943 for all substances, except colistin with 690 tested isolates.

TABLE 5.18. Distribution of MICs and resistance (%) in *Staphylococcus pseudintermedius* isolated from clinical submissions of skin samples in dogs 2014.

Antibiotic	Resistance (%) 2014 n=513	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Cephalothin	<1					99.8		0.2			
Clindamycin	22				78.2		0.2	21.6			
Enrofloxacin	2	68.4	27.1	5.2	1.2		0.4	0.8			
Erythromycin	23			77.2			0.2	22.6			
Fusidic acid	20					76.8	3.8	19.5			
Gentamicin	2					97.1	0.8	1.8	0.2	0.2	
Nitrofurantoin	0								99.6	0.4	
Oxacillin	<1			99.6	0.4						
Penicillin[a]	77										
Tetracycline	23				77.0				23.0		
Trim-Sulph.[b]	4			82.1	13.3	0.8	0.2	3.7			

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

and erythromycin in 15% (25/173) of all multiresistant isolates. This phenotype was present in 37% (65/173) of the isolates resistant also to four or more substances, most commonly combined with resistance to enrofloxacin, fusidic acid and/or tetracycline.

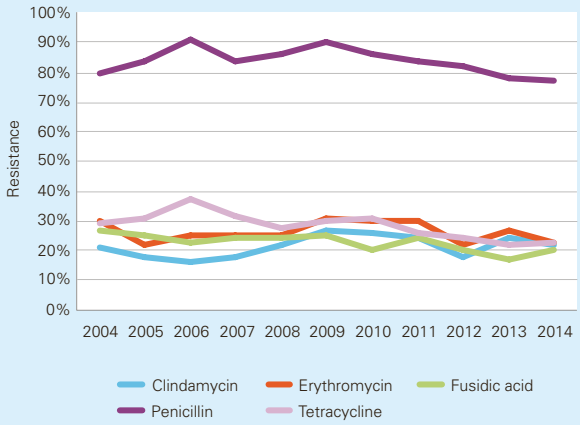
One MRSP isolate was found in this material. For more information on MRSP isolated from dogs, see Notifiable diseases, MRSP in animals.

Staphylococcus schleiferi

Isolates of *Staphylococcus schleiferi* are from clinical sampling of various locations, mainly external ear canal, skin or wound. The proportion of resistance in the presented isolates of *S. schleiferi* (Table 5.19) seems lower than in isolates of *S. pseudintermedius* from dogs (Table 5.18), but also lower compared to *S. aureus* in horses (Table 5.16) and *S. felis* in cats (Table 5.23). For example the occurrence of beta-lactamase production in the tested *S. schleiferi* isolates was only 4%, compared to 77% in *S. pseudintermedius*, and 18% in both *S. felis* and *S. aureus*. However, the occurence of resistance to one substance, enrofloxacin, is relatively high for the otherwise susceptible *S. schleiferi* (11%) compared to *S. pseudintermedius* (2%), *S. aureus* (3%) and *S. felis* (0%).

No further identification, to separate *S. schleiferi* in subspecies (subsp. *schleiferi* and subsp *coagulans*) was carried out.

FIGURE 5.5. Resistance (%) in clinical isolates of *Staphylococcus pseudintermedius* from skin of dogs 2004-2014. The number of isolates each year varies (n=89-566).



Pseudomonas aeruginosa

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

Pseudomonas aeruginosa is inherently resistant to trimethoprim-sulphonamides, tetracyclines and aminopenicillins (including combinations with clavulanic acid). Svarm data

TABLE 5.19. Distribution of MICs and resistance (%) in *Staphylococcus schleiferi* isolated from various locations in dogs 2014.

Antibiotic	Resistance (%) 2014 n=297	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Cephalothin	0					100					
Clindamycin	4				96.3			3.7			
Enrofloxacin	11	29.0	56.2	4.0	9.8	1.0					
Erythromycin	4			95.3	0.3	0.3		4.0			
Fusidic acid	3					95.3	1.3	3.4			
Gentamicin	0					98.7	1.3				
Nitrofurantoin	0								100		
Oxacillin	0			100							
Penicillin[a]	4										
Tetracycline	3				92.9	1.7	1.0	1.3	3.0		
Trim-Sulph.[b]	1			96.3	1.7	1.0	1.0				

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

TABLE 5.20. Distribution of MICs and resistance (%) in *Pseudomonas aeruginosa* from dogs 2014. Clinical isolates from the external ear canal.

Antibiotic	Resistance (%) 2014 n=389 [a]	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Enrofloxacin	12	0.8	1.3	16.5	48.3	20.8	6.2	6.2			
Colistin	1				65.6	28.5	5.0	0.3	0.7		
Gentamicin	1					88.7	8.0	2.3	0.8	0.3	

[a] Colistin, 302 isolate tested.

TABLE 5.21. Distribution of MICs and resistance (%) in *Pasteurella canis*. Clinical isolates from dogs 2014.

Antibiotic	Resistance (%) 2014 n=207	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0				100						
Enrofloxacin	1	98.6	1.0	0.5				0.4			
Gentamicin	0					100					
Penicillin	<1	97.6	1.9			0.5					
Tetracycline	<1				99.5				0.5		
Trim-Sulph.[a]	0			99.5	0.5	0.4					

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

prior to 2014 cover *P. aeruginosa* isolates of the described category tested with polymyxin B, and all tested isolates have been sensitive to the substance. In 2014 polymyxin B was replaced by colisitin as representative for polymyxines and three of 302 tested isolates (1%) were resistant to colistin. This may be true resistance or due to methodological errors, but the isolates were not available for further analyses. A trend of gradually declining resistance to enrofloxacin, from 25% in 2009 to 14% in 2013 and 12% in 2014 could be observed. The figures for gentamicin have also dropped from 5% in 2009 to 1% in 2013-2014 (Table 5.20).

Pasteurella

Isolates of *Pasteurella* spp. are from clinical sampling of various locations, but mainly from wound or skin, external ear canal and the respiratory tract. *Pasteurella canis* was the most commonly detected species of the included clincal isolates (n=207), while *P. multocida* was second most common (n=29). As shown in Table 5.21, resistance to antibiotics of the tested *P. canis* isolates are low. Furthermore, all *P. multocida* isolates (n=29) were susceptible to all the tested antibiotics (data not shown).

Cut-off values for resistance of *P. canis* isolates in Table 5.21 are the same as used for *P. multocida*.

Cats

Escherichia coli

Isolates are from clinical sampling of urine, submitted either as urine or cultures from dip-slides or other agar plates. In 2014 resistance to ampicillin was still the most common trait (Table 5.22 and Figure 5.6). Since 2007, the rate of resistance has differed somewhat between the years, but overall the figures seem rather stable (Figure 5.6).

Of the tested *E. coli* isolates in 2014, 3% (14/461) was multiresistant which is comparable to figures in 2010-2011 (3%) and 2012 (2%). Of the 14 multiresistant isolates were 12 resistant to three substances and 2 to 4 substances. All 14 of the multiresistant isolates were resistant to ampicillin, 8 to tetracycline and 7 to trimethoprim-sulphametoxazole.

Five *E. coli* isolates were resistant to cefotaxime. Genes conferring transmissible ESBL or AmpC resistance were found in one of these isolates. For more information see ESBL-producing Enterobacteriaceae in animals.

Staphylococcus felis

Isolates of *Staphylococcus felis* are from clinical sampling of various locations, but mainly external ear canal or other skin location, abscess or wound. *S.felis* is the only coagulase nega-

TABLE 5.22. Distribution of MICs and resistance (%) in *Escherichia coli* isolated from cats 2014. Clinical isolates from urine.

Antibiotic	Resistance (%) 2014 n=461 [b]	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	16					63.8	19.7	0.9	15.6		
Cefotaxime	1			98.9	0.2	0.9					
Colistin	3				74.6	21.9	2.5	0.6	0.3		
Enrofloxacin	7	93.5	3.3	2.0	0.7	0.2		0.4			
Gentamicin	0					99.1	0.9				
Nitrofurantoin	<1							25.8	71.1	2.4	0.7
Tetracycline	9				3.9	81.1	5.2	1.1	8.7		
Trim-Sulph.[a]	2			97.4	0.2			2.4			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphametoxazole); b Colisitin tested isolates n=319.

tive staphylococci in this material of clinical isolates from different animal species.

The proportions of resistance to the tested antibiotics in clinical isolates of *S. felis* (Table 5.23) seems comparable to those of *S. aureus* isolates from horses (Table 5.16) and lower compared to those of *S. pseudintermedius* in dogs (Table 5.18). For example resistance to penicillin due to beta-lactamase production was 18% in *S. felis* (cats) and *S. aureus* (horses), but 77% in *S. pseudintermedius* (dogs).

Pasteurella

Isolates of *Pasteurella* spp. are from clinical sampling of various locations, but mainly from wound or skin, external ear canal and the respiratory tract. *Pasteurella multocida* (approximately equal between subsp. *septica* and *multocida*) was the most commonly detected *Pasteurella* in the presented clincal material from cats (n=244), while *P. dagmatis* was second most common (n=20). As shown in Table 5.24 the proportion of resistance to antibiotics used in pets was low in the tested *P. multocida* isolates. All twenty isolates of *P. dagmatis* were susceptible to all the tested antibiotics (data not shown). Cut-off values for resistance of *P. dagmatis* isolates are the same as used for *P. multocida*.

FIGURE 5.6. Resistance (%) in clinical isolates of *Escherichia coli* from urine of cats, 2007-2014. The number of isolates each year varies (n=131-461).

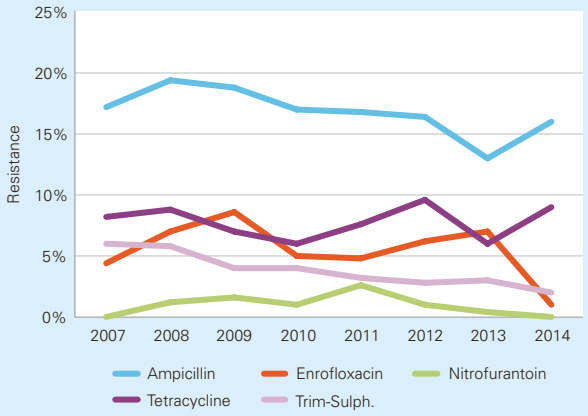


TABLE 5.23. Distribution of MICs and resistance (%) in *Staphylococcus felis* isolated from various locations in cats 2014.

Antibiotic	Resistance (%) 2014 n=244	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Cephalothin	<1					99.6	0.4				
Clindamycin	7				92.2		0.8	7.0			
Enrofloxacin	0	88.9	10.7	0.4							
Erythromycin	9			89.3	2.0	0.4		8.2			
Fusidic acid	3					95.5	2.0	2.5			
Gentamicin	0					99.6	0.4				
Nitrofurantoin	0								99.2	0.8	
Oxacillin	0			100							
Penicillin[a]	18										
Tetracycline	1				98.4	0.8			1.2		
Trim-Sulph.[b]	0			98.8	1.2						

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

TABLE 5.24. Distribution of MICs and resistance (%) in *Pasteurella multocida*. Clinical isolates from cats 2014.

Antibiotic	Resistance (%) 2014 n=244	Distribution (%) of MICs (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	0				100						
Enrofloxacin	2	96.3	1.6	0.4	0.4	0.4	0.4	0.4			
Gentamicin	2					46.3	47.5	4.1	0.8	1.2	
Penicillin	0	85.2	14.3	0.4							
Tetracycline	<1				98.7		0.4		0.8		
Trim-Sulph.[a]	3			94.7	2.0	0.4		2.9			

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

Indicator bacteria from animals

In programmes monitoring antibiotic 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 the presence of acquired resistance. The level of resistance in these so called indicator bacteria reflects the magnitude of the selective pressure from antibiotic use in an animal population. Moreover, although these bacteria are unlikely to cause disease they can be reservoirs for resistance genes that can spread to bacteria causing infections in animals or humans. Resistance in indicator bacteria contaminating meat indicates the potential exposure of humans to such reservoirs among farm animals through the food chain.

In 2014, indicator bacteria from broilers and turkeys were studied. Samples of intestinal contents were collected at slaughter and cultured for *E. coli* and samples from broilers were also cultured for enterococci. In addition, all samples were also screened for *E. coli* resistant to extended spectrum cephalosporins (ESC) by selective culture on media supplemented with cefotaxime. For details on methodology see Material and methods, resistance in bacteria from animals.

Escherichia coli

Broilers

Escherichia coli was isolated from 197 (99%) of 200 samples cultured. The majority of isolates (75%) was susceptible to all antibiotics tested, but one fourth of the isolates was resistant to one antibiotic or more (Table 6.1). Resistance to sulphonamides (13%), quinolones (nalidixic acid and ciprofloxacin) (11%), tetracycline (10%), ampicillin (9%) and trimethoprim (8%) were the most common traits. Sixteen isolates (8%) were multiresistant and all of these had resistance to sulphonamides and ampicillin in their phenotype. Twelve of these isolates were resistant also to trimethoprim and tetracycline.

Since the start of the monitoring in year 2000, resistance to single antibiotics has been below 15% and mostly stable. This favorable situation is likely due to the limited use of antibiotics in broiler production in Sweden (see Use of antibiotics in animals). Resistance to sulphonamides, tetracycline, ampicillin, trimethoprim and to quinolones has, however, gradually increased in recent years, although the levels this year are lower than in 2012 except for sulphonamides (Fig 6.1). The reasons for the increase are not known

TABLE 6.1. Resistance (%) and multiresistance (%) in indicator *Escherichia coli* from broilers and turkeys, 2014. Data on indicator *Escherichia coli* from previous Svarm-reports are given for comparison.

		Resistance (%)									
Antibiotic	**ECOFF (mg/L)**	**Broilers**	**Turkeys**	**Broiler meat**	**Calves**	**Laying hens**	**Pigs**	**Pig meat**	**Sheep**	**Horses**	**Dogs**
		2014 n=197	**2014** n=59	**2012** n=92	**2013** n=197	**2012** n=61	**2011** n=167	**2011** n=20	**2006-09** n=115	**2010-11** n=274	**2012** n=74
Ampicillin	>8	9	25	18	1	3	13	30	2	2	9
Cefotaxime	>0.25	0	2	0	0	2	<1	0	0	0	1
Ceftazidime	>0.5	0	2	-	0	-	-	-	-	-	-
Chloramphenicol	>16	0	3	0	0	0	4	0	0	<1	0
Ciprofloxacin	>0.06	11	3	4	1	5	2	10	<1	<1	3
Colistin	>2	0	0	1	0	0	0	0	-	<1	0
Gentamicin	>2	0	0	3	0	2	1	0	3	<1	0
Meropenem	>0,12	0	0	-	-	-	-	-	-	-	-
Nalidixic acid	>16	11	2	4	<1	5	2	0	0	<1	0
Sulphamethoxazole	>64	13	17	16	2	8	17	10	7	15	4
Tetracycline	>8	10	24	14	3	13	8	0	<1	2	8
Tigecycline	>1	0	0	-	-	-	-	-	-	-	-
Trimethoprim	>2	8	5	7	1	5	11	10	2	16	1
Multiresistance[a]											
Susceptible to all above		75	44	66	95	80	72	70	89	83	84
Resistant to 1		14	43	18	3	7	13	10	9	2	8
Resistant to 2		3	4	7	2	7	4	5	2	12	7
Resistant to 3		2	10	3	<1	7	5	15	<1	2	
Resistant to >3		6		5			6			<1	<1

[a] Ciprofloxacin and nalidixic acid as well as cefotaxime and ceftazidime considered as one antibiotic class.

FIGURE 6.1. Percent resistance in *Escherichia coli* from broilers 2000-2014. The number of isolates each year varies (n=194-307).

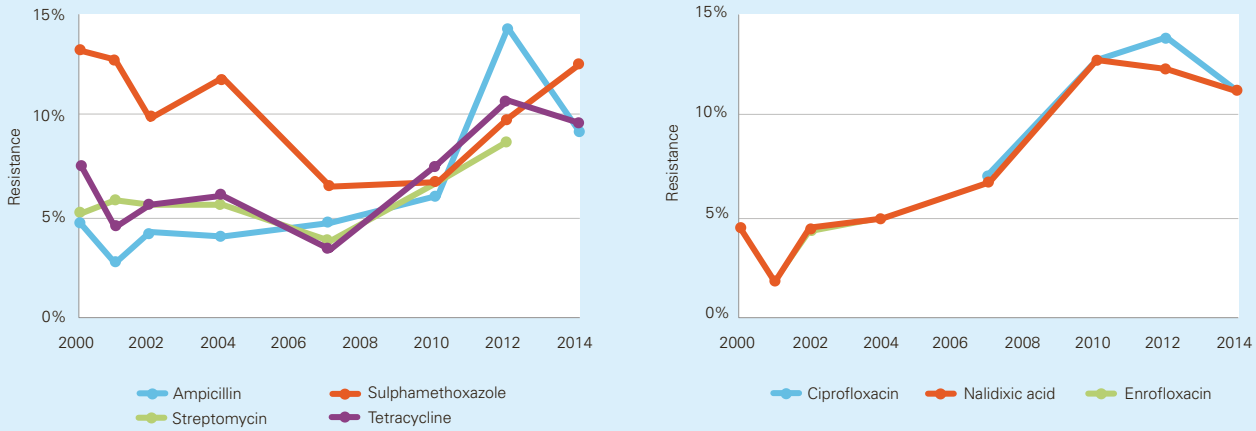


TABLE 6.2. Distribution of MICs and resistance (%) in *Escherichia coli* from intestinal content from broilers (n=197) and turkeys (n=59), 2014.

Antibiotic	Source	Resistance %	Distribution (%) of MICs (mg/L)																	
			≤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	Broilers	9							4.6	56.9	28.4	1.0				9.1				
	Turkeys	25							3.4	44.1	27.1					25.4				
Azithromycin	Broilers	NR[a]								3.6	54.8	40.1	1.5							
	Turkeys	NR[a]								6.8	37.3	55.9								
Cefotaxime	Broilers	0					100													
	Turkeys	2					98.3		1.7											
Ceftazidime	Broilers	0						100												
	Turkeys	2						98.3		1.7										
Chloramphenicol	Broilers	0										100								
	Turkeys	3										96.6				1.7	1.7			
Ciprofloxacin	Broilers	11	84.3	4.6		7.1	3.6	0.5												
	Turkeys	3	88.1	8.5		3.4														
Colistin	Broilers	0							99.5	0.5										
	Turkeys	0							100											
Gentamicin	Broilers	0						76.1	21.3	2.5										
	Turkeys	0						66.1	30.5	3.4										
Meropenem	Broilers	0		99.5	0.5															
	Turkeys	0		98.3	1.7															
Nalidixic acid	Broilers	11									88.3	0.5			9.1	1.5	0.5			
	Turkeys	2									96.6	1.7				1.7				
Sulphamethoxazole	Broilers	13										13.2	44.7	25.4	4.1					12.7
	Turkeys	17										5.1	23.7	42.4	11.9	5.1				11.9
Tetracycline	Broilers	10								89.8	0.5		0.5	0.5	5.1	3.6				
	Turkeys	24								74.6	1.7		1.7	5.1	8.5	8.5				
Tigecycline	Broilers	0					99.5	0.5												
	Turkeys	0					100													
Trimethoprim	Broilers	8					53.8	35.0	3.6						7.6					
	Turkeys	5					67.8	27.1							5.1					
			≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024

[a] Not relevant because no ECCOFF is available

but could be due to spread of multiresistant clones without a selective pressure from antibiotic use.

Using selective culture, ESC resistant *E. coli* was isolated from 72 (36%) of the 200 samples of intestinal content from broilers. One isolate had resistance genes of the CTX-M-1 group and 70 isolates genes of the CIT-group. In one isolate genes conferring transmissible ESBL or AmpC resistance were not detected. For details and comments see Notifiable diseases.

Turkeys

Escherichia coli was isolated from 59 of 60 samples cultured (98%). About half of the isolates (44%) was susceptible to all antibiotics tested but 33 isolates (56%) were resistant to at least one substance (Table 6.1). Resistance to ampicillin (25%), tetracycline (24%) and sulphonamides (17%) were the most common traits. Six isolates (10%) were multiresistant and of these, four isolates were resistant to both ampicillin and tetracycline in addition to other antibiotics. One isolate was resistant to cefotaxime and ceftazidime but genes conferring transmissible ESBL or AmpC resistance were not detected.

Resistance to single antibiotics is of the same magnitude as in 2013 when *E. coli* from turkeys were first studied in Svarm. The total number of isolates tested 2013-2014 is, however, small and the results should therefore be interpreted with caution. Resistance in *E. coli* from turkeys is about as prevalent as among isolates from broilers and involves the same antibiotics (Table 6.1). Quinolone resistance, however, seems to be more common in *E. coli* from broilers than in isolates from turkeys and the opposite applies for ampicillin, tetracycline and sulphonamide resistance.

Using selective culture, ESC resistant *E. coli* was isolated from 12 (20%) of the 60 samples cultured. Genes conferring transmissible ESBL or AmpC resistance were not found in any of these isolates. For details and comments see Notifiable diseases.

Enterococcus

Broilers

A total of 27 isolates of *Enterococcus faecalis* and 187 isolates of *Enterococcus faecium* were obtained from 200 samples cultured.

In *E. faecalis* the majority of isolates (70%) was resistant to at least one antibiotic but no isolate was multiresistant (Table 6.3). Resistance to narasin (41%) or tetracycline (37%) were the most common traits and resistance to erythromycin or bacitracin occurred at lower levels. The number of isolates tested is small and conclusions on occurrence of resistance must be made with caution. The findings are however in agreement with previous data from Svarm and the levels of resistance seem stable or slightly decreasing (Fig 6.2).

In *E. faecium* the majority of isolates (85%) was resistant to at least one antibiotic and six isolates (3%) were multiresistant (Table 6.4). Resistance to narasin was the most common trait (77%) and resistance to erythromycin, bacitracin, tetracycline, ampicillin, gentamicin, virginiamycin and vancomycin also occurred but at much lower levels. One isolate was phenotypically resistant to vancomycin (MIC 8 mg/L) but *vanA* or *vanB* genes were not detected in the isolate when tested by PCR. The findings are in agreement with previous data from Svarm and the levels of resistance seem stable or slightly decreasing (Fig 6.2).

Use of antibiotics in poultry is uncommon in Sweden (see Use of antibiotics in animals) and it is unlikely that the observed resistance to erythromycin, tetracycline and bacitracin is due to a direct selection pressure from use of antibiotics on poultry farms in Sweden. The high occurrence of resistance to the ionophore narasin in both *E. faecalis* and *E. faecium* are, however most likely a consequence of the common use of narasin as coccidiostat in broiler production (see Use of antibiotics in animals). Notably resistance to narasin in enterococci from other animals, where narasin is not used, is rarely found in Sweden (Table 6.3 and 6.4).

FIGURE 6.2. Percent resistance in *Enterococcus faecalis* and *Enterococcus faecium* from broilers, 2000-2014. The number of isolates each year varies; *E. faecalis* n=35-57 and *E. faecium* n=136-204

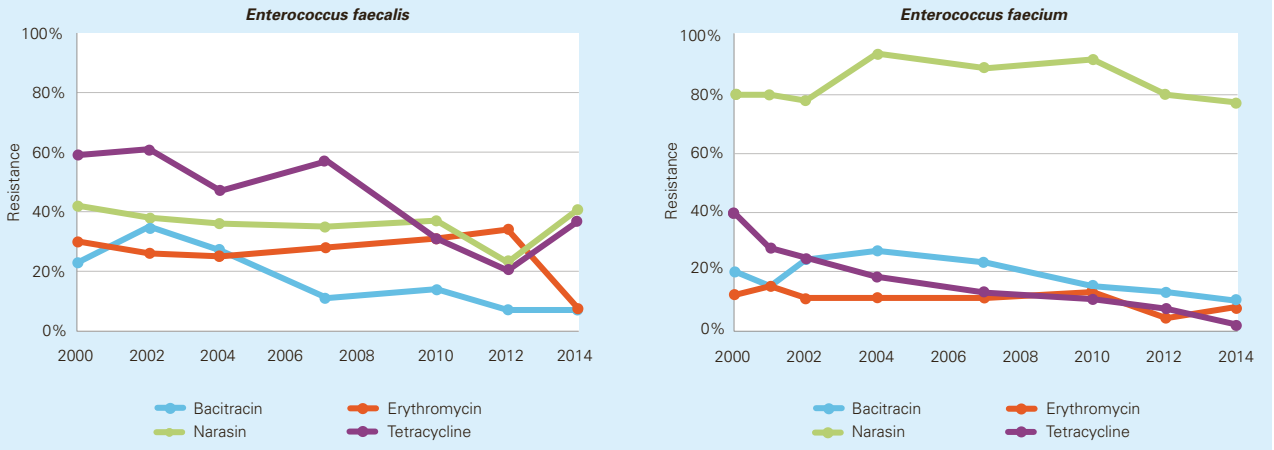


TABLE 6.3. Resistance (%) and multiresistance (%) in *Enterococcus faecalis* from broilers, 2014. Data on indicator *Enterococcus faecalis* from previous Svarm-reports are given for comparison.

		Resistance (%)								
Antibiotic	**ECOFF (mg/L)**	**Broilers**	**Calves**	**Broiler meat**	**Laying hens**	**Pigs**	**Pig meat**	**Horses**	**Sheep**	**Dogs**
		2014 n=27	**2013** n=11	**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]	7	0	23	10	0	0	0	0	1
Chloramphenicol	>32	0	0	5	0	0	0	18	0	7
Erythromycin	>4	7	0	13	10	43	0	21	0	14
Gentamicin	>32	4	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	41	0	37	0	0	0	0	0	1
Streptomycin	>512	0	0	5	0	17	3	9	4	9
Tetracycline	>4	37	0	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		30	100	27	45	17	90	56	92	25
Resistant to 1		44		37	45	35	10	24	4	38
Resistant to 2		26		29	10	43			4	27
Resistant to 3				1						2
Resistant to >3				5		4		21		7

[a] MIC in U/ml

TABLE 6.4. Resistance (%) and multiresistance (%) in *Enterococcus faecium* from broilers, 2014. Data on indicator *Enterococcus faecium* from previous Svarm-reports are given for comparison.

		Resistance (%)								
Antibiotic	**ECOFF (mg/L)**	**Broilers**	**Calves**	**Broiler meat**	**Laying hens**	**Pigs**	**Pig meat**	**Horses**	**Sheep**	**Dogs**
		2014 n=187	**2013** n=42	**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	2	0	0	0	0	0	15	0	0
Bacitracin	>32[a]	10	5	40	3	9	0	0	0	3
Chloramphenicol	>32	0	0	0	0	0	0	0	0	0
Erythromycin	>4	8	10	0	6	9	0	0	0	28
Gentamicin	>32	0	2	0	0	0	0	0	0	0
Kanamycin	>1024	0	2	0	0	9	0	0	0	0
Linezolid	>4	0	0	0	0	0	0	0	0	0
Narasin	>2	77	0	80	0	0	0	0	0	7
Streptomycin	>128	0	0	0	0	13	0	7	7	0
Tetracycline	>4	4	2	30	11	13	0	4	7	17
Vancomycin	>4	<1	0	0	0	0	0	0	0	0
Virginiamycin	>4	<1	0	10	8	4	100	4	0	0
Multiresistance (%)										
Susceptible to all above		15	15	83	78	74		74	87	62
Resistant to 1		71	63	12	17	13	100	22	13	30
Resistant to 2		11	21	5	6	4		4		6
Resistant to 3		2	1							
Resistant to >3		1				9				2

[a] MIC in U/ml

TABLE 6.5. Distribution of MICs and resistance (%) in *Enterococcus faecalis* (n=27) and *Enterococcus faecium* (n=187) from broilers, 2014.

Antibiotic	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			44.4	51.9	3.7											
	E. faecium	2		46.0	13.4	20.9	15.5	2.7	1.6									
Bacitracin[a]	*E. faecalis*	7				3.7			48.1	40.7			3.7	3.7				
	E. faecium	10				42.2	4.3	5.9	23.0	12.3	2.1	3.7	5.3	1.1				
Chloramphenicol	*E. faecalis*	0						70.4	29.6									
	E. faecium	0					16.6	75.9	7.5									
Erythromycin	*E. faecalis*	7			33.3	33.3	14.8	11.1					7.4					
	E. faecium	8			51.9	29.9	6.4	3.7	3.7	0.5	0.5	1.1	2.1					
Gentamicin	*E. faecalis*	4						3.7	85.2	7.4			3.7					
	E. faecium	0					13.9	56.7	26.7	2.7								
Kanamycin	*E. faecalis*	0									63.0	37.0						
	E. faecium	0								3.7	19.8	34.8	36.9	4.3	0.5			
Linezolid	*E. faecalis*	0			29.6	48.1	22.2											
	E. faecium	0			13.9	51.3	34.8											
Narasin	*E. faecalis*	41	7.4	18.5	3.7	3.7	25.9	40.7										
	E. faecium	77	1.6	2.1	3.2	1.6	14.4	66.3	10.7									
Streptomycin	*E. faecalis*	0										74.1	25.9					
	E. faecium	0							2.1	17.6	52.4	26.7	1.1					
Tetracycline	*E. faecalis*	37			25.9	33.3	3.7				18.5	14.8	3.7					
	E. faecium	4			81.3	12.3		2.1	1.1	0.5	1.1	1.6						
Vancomycin	*E. faecalis*	0				77.8	22.2											
	E. faecium	<1				98.4	1.1		0.5									
Virginiamycin	*E. faecalis*	0				3.7		14.8	66.7	14.8								
	E. faecium	<1			34.2	26.2	36.9	2.1	0.5									
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048

[a] MIC in U/ml

SafeOrganic – studies on antibiotic resistance in organic and conventional pig production in EU

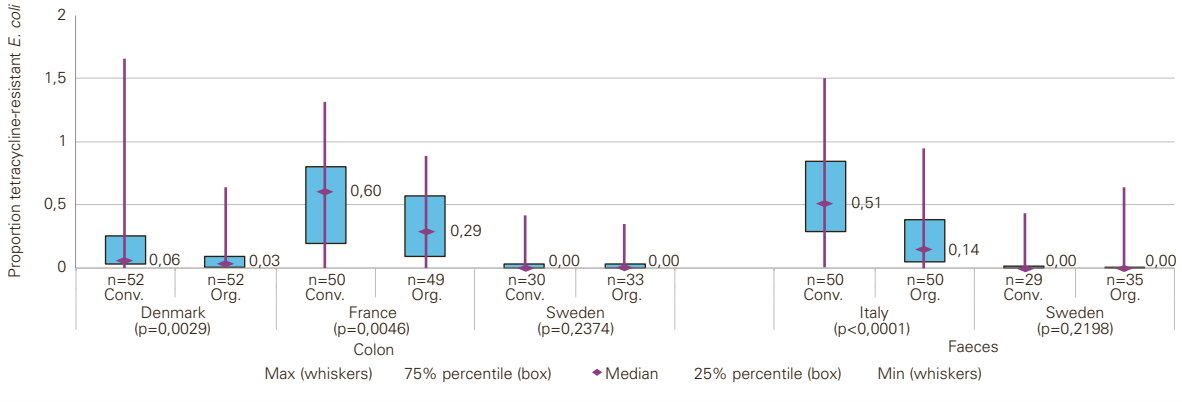
Valuable information on risk factors for antibiotic resistance could be gained by exploring and comparing resistance among farm animals raised in different production systems. In organic pig production the use of antibiotics is more restricted than in conventional production, but there are also other differences. Factors such as herd size, animal contacts, feeding regimes, outdoor access and space allowance per pig could hypothetically also influence the occurrence of resistant bacteria.

Several different aspects of antibiotic resistance in organic and conventional pig production were studied in the recently completed research project SafeOrganic funded by the CORE Organic II Funding Bodies, for further information see: www.coreorganic2.org. One of the studies in the project focused on differences in antibiotic resistance between organic and conventional pig production. Briefly, colon content and/or faeces from healthy pigs in Denmark, France, Italy and Sweden was collected. The goal was to include 25 herds of each production type from each country and two pigs from each herd. Samples were collected at abattoirs or on farms from pigs close to slaughter. Samples were cultured for *Escherichia coli* that were subsequently tested for antibiotic susceptibility by determining the minimum inhibitory concentration (MIC) of ten antibiotics using microdilution. MICs were interpreted by ECOFFs issued by EUCAST (www.eucast.org). In addition, as a quantitative measure of resistance in individual pigs the proportion of tetracycline resistant *E. coli* in colon contents or faeces was determined from the ratio of counts of colonies on culture plates with tetracycline and without tetracycline.

The results of the project are currently being prepared for publication but some preliminary data are presented here. In all four countries resistance to ampicillin, streptomycin, sulphonamides or trimethoprim was less common in *E. coli* from organic than from conventional pigs but there were also differences in resistance between countries within production type. In some countries also resistance to tetracycline, chloramphenicol, ciprofloxacin, nalidixic acid or gentamicin was less common in organic pigs. In three of the countries the median sample proportion of tetracycline resistant intestinal *E. coli* was lower in organic than in conventional pigs, except in Sweden where the resistance to tetracycline was generally low (Figure). Differences in the proportion of tetracycline-resistant *E. coli* between countries within production type were also observed with lower median proportions in Sweden and Denmark compared to France and Italy.

The results show that in each of the four countries resistance in intestinal *E. coli* is less common in organic than in conventional pigs and additionally that there are differences in resistance between countries within production type. This illustrates that country specific and production specific factors may interact, both contributing to occurrence of resistance. Thus, the findings suggest that not only a low consumption of antibiotics but also other factors may contribute to occurrence of resistance. If those factors could be identified, the information would be useful for designing measures to mitigate resistance and therefore future studies should be focused on identifying them.

FIGURE. The distribution of the proportion of tetracycline resistant *Escherichia coli* in samples of colon contents or faeces from 430 pigs in 110 conventional (Conv.) and 93 organic (Org.) herds in four European countries (median, 25% and 75% percentiles (box), maximum and minimum (whiskers)). n= number of samples; p= the significance level for the difference between distributions in conventional and organic herds for each country and sample type (Kruskal-Wallis test for non-normal distributions)



Partners of SafeOrganic: Technical University of Denmark, National Food Institute, Denmark (coordinator); Istituto Zooprofilattico Sperimentale delle Venezie, Italy; Agency for Food, Environment, and Occupational Health Safety, France; National Veterinary Institute, Sweden; University of Copenhagen, Denmark; Veterinary Research Institute, Czech Republic

Background data, material, metods and references

Demographics and denominator data

Human beings

TABLE 7.1. Population by county and age group. December 31st 2014.

	0-6 years	7-19 years	20-64 years	65-79 years	80 years-	All ages
Stockholm	202 618	314 385	1 309 052	251 770	85 217	2 163 042
Uppsala	28 966	49 684	205 011	46 544	15 276	345 481
Södermanland	22 363	41 534	153 272	44 984	15 416	277 569
Östergötland	35 599	63 294	251 874	63 345	23 736	437 848
Jönköping	28 352	51 707	191 540	49 641	19 995	341 235
Kronoberg	15 243	27 467	105 382	27 771	11 293	187 156
Kalmar	16 761	32 009	129 149	40 896	15 059	233 874
Gotland	4 017	7 710	32 129	9 937	3 368	57 161
Blekinge	11 457	21 535	84 353	25 957	9 455	152 757
Skåne	110 088	180 090	739 599	178 187	66 105	1 274 069
Halland	25 314	46 487	170 867	47 124	17 048	306 840
Västra Götaland	135 824	229 918	943 911	222 346	83 085	1 615 084
Värmland	19 821	37 496	153 705	45 227	17 566	273 815
Örebro	23 426	41 291	161 296	43 803	15 579	285 395
Västmanland	20 507	37 425	145 942	40 530	14 650	259 054
Dalarna	20 662	39 148	153 213	47 050	17 276	277 349
Gävleborg	20 389	39 106	154 663	47 159	16 653	277 970
Västernorrland	17 974	34 286	133 889	41 151	14 856	242 156
Jämtland	9 590	17 603	70 767	20 718	7 783	126 461
Västerbotten	20 510	36 499	151 526	38 544	14 033	261 112
Norrbotten	17 337	34 236	141 789	41 806	14 268	249 436
Sweden	**806 818**	**1 382 910**	**5 582 929**	**1 374 490**	**497 717**	**9 644 864**

TABLE 7.2. Population in Sweden 2000-2014 - Number represent the population by December 31st 2014.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Population	8882792	8909128	8940788	8975670	9011392	9047752	9113257	9182927	9256347	9340682	9415570	9482855	9555893	9644864

TABLE 7.3. Number of admissions and patient-days in somatic medical care in Sweden, 2009-2013

Year	Admissions	Patient-days
2010	1473835	6958834
2011	1496324	6979857
2012	1514608	6859956
2013	1385962	6144504

TABLE 7.4. Number of admisions and paitent-days in somatic medical care 2013. Data represent production by acute care hospitals in the counties.

County	Admissions	Patient-days
Blekinge	23906	119436
Dalarna	46829	197578
Gotland	9776	41628
Gävleborg	37348	161958
Halland	42884	186426
Jämtland	18719	87576
Jönköping	56083	240222
Kalmar	42855	160023
Kronoberg	26423	124862
Norrbotten	38793	184320
Skåne	193500	868293
Stockholm	235036	897561
Södermanland	36294	180197
Uppsala	56542	287668
Värmland	40654	191352
Västerbotten	50639	241877
Västernorrland	37843	171817
Västmanland	38094	176128
Västra Götaland	241812	1131076
Örebro	45003	216246
Östergötland	66929	278260
Sweden	**1488460**	**6776274**

TABLE 7.5. Denominator data from the microbiological laboratories 2014.

	Number of analyses 2014									Number of positive samples 2014	Number of positive cultures 2014				
Laboratory	**Blood (pair of bottles)**	**Cerebrospinal fluid (CFS)**	**Nasopharynx**	**Throat**	**General culture**	**Screen MRB**	**Urine**	**Faeces SSYC**	**Faeces *Clostridium difficile* (toxin)**	**Blood (pair of bottles)**	***Staphylococcus aureus***	***Streptococcus pneumoniae***	***Streptococcus pyogenes***	***Escherichia coli***	***Clostridium difficile* (toxinpositive)**
Aleris Medilab	965	0	10520	4212	10626	19054	43496	9280	1336	122	4645	663	876	10490	272
Borås	19605	189	4923	1859	6820	3267	23994	5085	1902	2521	4797	364	479	7220	145
Eskilstuna (Unilabs)	13611	148	5857	2900	7441	2469	28971	4790	1875	2303	4607	768	692	7654	271
Falun	19028	213	4443	1358	11377	4896	31001	3932	2019	1856	5491	542	567	9075	279
Gävle	13736	248	2712	969	12615	25249	24328	3119	2282	1978	5072	427	360	8629	386
Göteborg	43979	1525	1952	3447	19581	39446	66251	10561	4540	5550	11144	583	1136	16126	468
Halmstad	13570	136	2597	2211	8239	8542	26596	6038	2056	2030	4670	520	586	8600	323
Jönköping	22300	236	6100	2960	17100	23300	39500	7050	2920	3070	8020	500	501	11790	460
Kalmar	13301	146	4009	1667	8502	4444	28756	4446	1651	1811	4950	553	434	9605	267
Karlskrona/ Växjö	19500	193	6339	2054	11210	8376	35000	6067	3642	2363	4632	571	586	10300	482
Karlstad	19139*	262	3638	2358	13422	8054	36751	4096	2024	3735*	6260	459	627	9931	244
Karolinska Stockholm	88553	2801	30932	9075	79760	264327	158701	21354	11502	11606	30717	2646	3026	42474	1323
Linköping	24696	959	7194	2771	23505	9707	46676	5462	3487	2644	4776	427	699	9060	333
Lund/Malmö	71033	1912	17841	11222	30969	49947	161792	25717	10253	9390	22842	2204	2751	44779	1223
Skövde (Unilabs)	14064	137	3967	2629	14721	11009	55829	9325	2968	1415	7751	282	703	13715	333
S:t Göran (Unilabs)	12115	88	7121	2200	12243	52109	46630	8955	3419	1278	6196	658	865	11876	494
Sunderby Luleå	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sundsvall	14194	152	2129	1291	6704	5749	27328	3655	2107	2121	3824	406	389	8562	327
NÄL Trollhättan	20320	234	1936	1450	9089	17518	32439	3837	1906	2394	4999	258	469	9020	255
Umeå	16079	531	3673	1795	8217	7478	30847	3326	1843	1599	4990	508	630	9769	385
Uppsala	21196	957	7187	2616	16662	15143	35915	5148	3581	2366	6519	662	599	9410	562
Visby	4669	36	2109	382	3013	NP	6764	935	488	460	1560	208	144	2171	36
Västerås	14164	165	2713	1646	9883	4135	28771	4293	2230	2149	4171	320	347	9436	367
Örebro	17530	251	10437	1677	15380	8695	33882	5795	2936	2019	7049	1137	693	8727	380
Östersund	7612	110	2512	1158	6879	4734	18379	2539	1294	953	3216	333	NP	5994	242
Total	**524959**	**11629**	**152841**	**65907**	**363958**	**597648**	**1068597**	**164805**	**74261**	**67733**	**172898**	**15999**	**18159**	**294413**	**9857**

*not pair; 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) 1980-2014. From Yearbook of agricultural statistics for selected years, Statistical message JO 24 SM 1101 and the statistical database of the Board of Agriculture.

Animal Species	1980[a]	1985[a]	1990	1995	2000	2005	2010	2012	2013	2014
Cattle										
Dairy cows	656	646	576	482	428	393	348	348	346	344
Beef cows	71	59	75	157	167	177	197	193	193	186
Other cattle >1 year	614	570	544	596	589	527	513	479	499	490
Calves <1 year	595	563	524	542	500	509	479	481	468	472
Total, cattle	1 935	1 837	1 718	1 777	1 684	1 605	1 537	1 500	1 506	1 492
Sheep										
Ewes and rams	161	173	162	195	198	222	273	297	286	287
Lambs	231	252	244	266	234	249	292	314	297	301
Total, sheep	392	425	406	462	432	471	565	611	585	588
Pigs										
Boars and sows	290	260	230	245	206	188	156	142	150	145
Fattening pigs >20 kg[b]	1 254	1 127	1 025	1 300	1 146	1 085	937	851	851	857
Piglets <20kg[c]	1 170	1 113	1 009	769	566	539	427	370	397	376
Total, pigs	2 714	2 500	2 264	2 313	1 918	1 811	1 520	1 363	1 397	1 378
Laying hens										
Hens	5 937	6 548	6 392	6 100	5 670	5 065	6 061	6 735	6 874	6 549
Chickens reared for laying	2 636	2 159	2 176	1 812	1 654	1 697	1 647	1 551	1 708	1 713
Total, hens	8 573	8 708	8 568	7 912	7 324	6 762	7 707	8 286	8 582	8 262
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, 1980-2014. From the Yearbook of agricultural statistics for selected years and the statistical database of the Board of Agriculture.

Animal Species	1980	1985	1990	1995	2000	2005	2010	2012	2013	2014
Cattle										
Dairy cows	44 143	35 063	25 921	17 743	12 676	8 548	5 619	4 968	4 668	4 394
Beef cows	12 436	10 310	10 883	17 069	13 861	12 821	12 190	11 375	11 092	10 663
Other cattle >1 year	63 179	52 652	42 696	39 160	30 457	24 808	20 295	18 182	17 824	17 094
Calves <1 year	62 314	52 001	41 986	36 542	27 733	22 888	18 494	17 001	16 306	15 706
Total holdings with cattle	70 503	58 872	47 292	41 990	32 063	26 179	21 586	19 561	18 962	18 210
Sheep	10 238	10 595	9 749	10 037	8 089	7 653	8 657	9 263	8 869	8 912
Pigs	26 122	19 937	14 301	10 753	4 809	2 794	1 695	1 318	1 281	1 282
Laying hens	23 603	17 531	12 900	9 593	5 678	4 916	3 703	3 876	4 149	3 878
Chickens reared for laying	5 093	2 714	1 875	1 405	715	634	487	673	629	760
Broilers						234	181	217	242	260
Turkeys						383	102		126	
Horses						56 000[a]	78 000			

[a] Data from 2004.

TABLE 7.8. Number of animals slaughtered (in thousands) at slaughterhouses, 1980-2014. From the Yearbook of agricultural statistics for selected years and and the statistical database of the Board of Agriculture.

Animal Species	1980	1985	1990	1995	2000	2005	2010	2011	2012	2013	2014
Cattle											
Cattle >1 year	574	584	523	502	490	433	425	429	392	391	405
Calves < 1 year	130	152	70	30	39	33	27	27	29	27	26
Total, cattle	704	736	593	532	529	466	453	456	421	418	431
Sheep	302	328	280	189	202	206	255	262	260	281	258
Pigs	4 153	4 283	3 653	3 743	3 251	3 160	2 936	2 845	2 592	2 556	2 553
Broilers	40 466[a]	36 410[a]	38 577[a]	61 313	68 617	73 458	78 507	78 182	76 840	83 265	89 681
Turkeys							495	574	466	452	420

[a] Data supplied by the National Food Administration.

TABLE 7.9. Quantity of livestock slaughtered (in 1000 tonnes) at slaughterhouses, 1990-2014. From the Yearbook of Agricultural Statistics for selected years and and the statistical database of the Board of Agriculture.

Animal Species	1990	1995	2000	2005	2010	2012	2013	2014
Cattle								
Cattle >1 year	139.5	140.1	145.4	131.4	133.5	121.0	121.9	127.5
Calves < 1 year	6.8	3.2	4.4	4.5	4.3	4.5	4.2	4.1
Total, cattle	146.3	143.3	149.8	135.9	137.8	125.5	126.1	131.5
Sheep	5.0	3.5	3.9	4.1	5.0	5.0	3.9	4.1
Pigs	293.1	308.8	277.0	275.1	263.5	233.7	234.6	235.3
Broilers	44.0[a]	73.6[a]	89.9	96.2	112.0	109.7	116.8	128.7
Turkeys					3.2	3.0	2.9	3.3

[a] Data supplied by the National Food Administration.

Materials and methods, consumption of antibiotics

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, antibiotic 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 for self cost (no profit). In hospital care, both for human and animal, antibiotic drugs are bought on requisitions.

All pharmacies in Sweden are required to provide statistics on sales of all products on a daily basis to the Swedish eHealth Agency. This agency maintains a national database with sales 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 antibiotic products from a pharmacy. All quantities of antibiotic products used by feed mills are reported yearly to the SBA as part of the feed control. Mixing of antibiotics 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 1 000 inhabitants and day (DDD/1 000 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 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 sales statistics to the Swedish eHealth Authority. However, after the reregulation of the pharmacy market, counties can choose to manage drug supplies to hospital by them self. If so, the counties are not required to 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 sales statistic is available at this time. Efforts have been made to complement the data from the Swedish eHealth Agency with data from counties.

Definitions of DDD 2014

TABLE 7.10. DDD for all antibiotic substances (J01) sold in Sweden in 2014. 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	1.92
J01AA07 - tetracycline	1	J01FA01 - erythromycin	1
J01AA12 - tigecycline	0.1	J01FA01- 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		

Data sources and inclusion criteria

Data on sales of antibiotics 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.

Antibiotic consumption 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. The number of patient-days and admissions includes data on somatic medical care by each county (to be distinguished from consumption of the county's inhabitants).

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. Data for 2014 is not available until August 2015, denominator data from 2013 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) 2009-2013 is shown in Table 7.3. The National Board of Health and Welfare keeps a searchable database at the web, http://www.socialstyrelsen.se/statistik.

Antibiotic 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 products containing antibiotics 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 products with antibiotics as active substance 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. The term consumption is used for sales from pharmacies to private and professional animal care-takes as well as to veterinary clinics.

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 3.9.

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 consumption of veterinary medicinal products with a general marketing authorisation in Sweden is less complete than before 2010. SVA attempted to produce an estimate of the lack of completeness for the consumption of antibiotics in 2013 (see Swedres-Svarm 2013, Use of antimicrobials for animals). In brief, it was assumed that the lack of completeness primarily affects products that are typically sold from pharmacies to veterinarians on requisition. This is most common for products for parenteral administration. The ten injectable products with highest sales from pharmacies during 2013, in kg active substance, were selected. Information on sales to pharmacies for all marketed product-package types of these products was collected from Marketing authorisation holders. Number of packages sold and amount of active substance sold from wholesalers to pharmacies were compared to the sales from pharmacies to veterinarians and animal owners. The sales from wholesalers to pharmacies expressed as kg active substance were 11% higher than the sales from pharmacies.

A similar study was performed for the consumption of antibiotics in 2014. One of the products included for 2013 was not available on the market for most of the year, and was therefore excluded. The difference between sales to and from pharmacies of the remaining nine products, expressed as kg active substance was 8 and 14% for 2013 and 2014, respectively. The difference varied between classes (9 – 16% in 2014).

The above estimate was limited to products for injection with general marketing authorisation in Sweden. Other types of products are less likely to be affected by the observed lack of completeness. Based on this assumption, the overall difference in total sales as kg active substance to and from pharmacies in 2014 was calculated to 8%. The figure is uncertain as the difference varied between classes of antibiotics, and there may be some lack of completeness for certain other products.

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 still seems 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 microbiology laboratories in Sweden have a long tradition of using 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 Public Health Agency. 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 the Public Health Agency of Sweden. All resistant isolates are sent to the Public Health Agency of Sweden 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.

Gonorrhoea and invasive infections caused by *Neisseria meningitidis* are also notifiable. The descriptions of materials and methods for these pathogens are found under their respective result section.

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 26 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 microbiology 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. In 2014 *Acinetobacter* species was added to the programme.

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 laboratories in Sweden is coordinated through the Public Health Agency of Sweden, 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 seven laboratories in 2014 that are using the same laboratory information system (ADBakt). Their total catchment population is at present 4.7 million, thus representing 48% 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 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

Antibiotic 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 caecal content from broilers and turkeys, see below. Clinical isolates from cats, dogs, and horses 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.

Monitoring of MRSA in pigs was performed by sampling in all Swedish nucleus and multiplying herds (n=39). Weaned pigs 5-12 weeks old were sampled, 6 pigs per box, 15 boxes per herd. The 6 sampled pigs in one box were sampled by scrubbing the skin behind one ear with the same sterile compress.

Zoonotic pathogens

Salmonella

Salmonellosis in animals is a notifiable disease in Sweden and isolates from each notified incident are 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 caecal content from healthy broilers sampled at slaughter within the Swedish Campylobacter programme in which whole caeca are collected from each batch of broilers slaughtered. In 2014, 363 flocks were positive for *Campylobacter*. From these, 102 isolates of *Campylobacter jejuni*, each representing one flock was randomly selected for susceptibility testing. The isolates were stored in -70°C until tested.

Clinical isolates from animals

Clinical isolates included are from routine bacteriological examinations of clinical submissions or post-mortem examinations. Part of the isolates of *Actinobacillus pleuropneumoniae* from pigs, part of the isolates of *Pasteurella* spp. from calves and all isolates of *S. aureus* from dairy cows 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 or from milk samples. Isolates of *Pasteurella* spp. are from the respiratory tract.

In sheep, isolates of *M. haemolytica* and *Bibersteinia treahalosi* are from tissue samples from lungs taken post mortem.

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, *Staphylococcus schleiferi* from various organs (mainly external ear canal, skin or wound), and *Pseudomonas aeruginosa* from the external ear. In cats, isolates of *E. coli* are from urine samples and *Staphylococcus felis* from various organs (mainly external ear canal or other skin locations, abscess or wound).

In farmed fish, isolates of *Aeromonas salmonicida* subsp. *achromogenes*, *Flavobacterium columnare* and *Flavobacterium psychrophilum* are from post mortem examinations.

Indicator bacteria

Broilers

Indicator bacteria, i.e. *E. coli* and *Enterococcus faecalis* and *Eenterococcus faecium*, were isolated from caecal content of healthy broilers sampled at slaughter. Samples cultured were from the Swedish *Campylobacter* programme – see above. From these samples, 100 were selected by convenience in March-April and 100 in September-October. Each sample is from a unique flock but not always from a unique production site. Samples cultured were collected at six abattoirs that in 2014 accounted for approximately 98% of the total volume of broilers slaughtered. The number of samples from each abattoir was roughly proportional to the annual slaughter volume of the abattoir.

Turkeys

Indicator *E. coli* was isolated from caecal content of healthy turkeys sampled at slaughter. Sampling was performed at two abattoirs in Sweden, from January to December. Each sample is from a unique flock but not always from a unique production site.

Isolation and identification of bacteria

Antibiotic 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, both without and with prior enrichment in MacConkey broth with cefotaxime (1 mg/L).

Briefly, approximately 0.5 g of caecum content from broilers was diluted in 4.5 mL saline. After thorough mixing, 0.1 mL of this suspension was spread on MacConkey agar with cefotaxime (1 mg/L) and incubated overnight at 37°C.

Furthermore, 1 g of caecum content was diluted in 9 ml MacConkey broth with cefotaxime (1 mg/L) and incubated at 37°C overnight. From the MacConkey broth 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* growing on MacConkey agar with cefotaxime were sub-cultured on horse-blood agar (5% v/v) and further tested for ESBL detection.

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).

In the screening of pigs, each compress was incubated in 25 mL Mueller-Hinton broth with 6.5% NaCl overnight at 37°C. Then 1 mL was transferred to Tryptic Soy broth with 3.5 mg/L cefoxitin and 75 mg/L aztreonam and incubated overnight at 37°C. Thereafter 10 µL were streaked on selective agar plates (Brilliance, Oxoid) and on oxblood plates and incubated at 37°C for 24 and 48 h. Suspected MRSA colonies were tested by PCR for presence of *mecA* and *mecC* genes.

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 Public Health Agency of Sweden, Solna using the Colindale scheme. As from 2013 other serovars are not phagetyped.

Campylobacter

Campylobacter spp. from broilers were isolated and identified at the Dept. of Bacteriology, SVA. Samples were cultured according to ISO/DIS 10272-1:2014 for detection of thermophilic *Campylobacter* spp. by direct cultivation on mCCDA and incubation at 42°C. Identification was based on colony morphology, microscopic appearance including motility and the following phenotypic characteristics: production of oxidase, catalase and hippurate hydrolysis reaction. With these tests, 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, isolates of *M. haemolytica* and *B. trehalosi* from sheep 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 caecum content from broilers was diluted in 4.5 mL saline. After thorough mixing, 0.1 mL of this suspension was spread on MacConkey agar 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.

Enterococci

Caecum content from broilers 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 antibiotic susceptibility.

Susceptibility testing

Microdilution

At SVA, bacteria from animals are tested for antibiotic 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 Section of Substrate Production, SVA and Sensititre are produced at Trek diagnostics LTD. 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 antibiotic 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 antibiotics are dried in serial twofold 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 antibiotic susceptibility by broth microdilution adapted for aquatic bacteria according to CLSI (2014a).

Phenotypic confirmatory tests for production of extended spectrum beta-lactamases (ESBLs) in *E. coli* was performed with and without clavulanic acid in Sensititre EUVSEC2 microdilution panels and interpreted according to CLSI (CLSI, 2013b).

Genotyping

Suspected isolates of MRSA were confirmed by detection of the *nuc*, *mecA* and *mecC* genes applying 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, according to Harmsen et al. (2003) and the specific *spa*-type was determined using BioNumerics® (Applied Maths). MRSP *spa*-typing was performed according to Moodley et al. (2009) and MLST according to the MLST Scheme at http://pubmlst.org/spseudintermedius/.

PCR was performed for identification of $ESBL_M$ (Perez-Perez and Hanson 2002), $ESBL_A$ (Woodford et al. 2006), genes coding OXA-1 group, TEM-groups and SHV-groups (Fang et al. 2006) and $ESBL_{CARBA}$ (Poirel et al. 2011).

The specific gene variants were determined by sequencing using in-house primers and Big-Dye™ v1.1./3.1. or submitted to Macrogene Inc. (South Korea) for sequencing.

Quality assurance system

Laboratories performing antibiotic 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 antibiotic 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* CCUG 15915 (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 $B78^T$ ATCC 27164^T was used for quality control.

Dept. of Animal Health and Antimicrobial Strategies participates in two proficiency tests for antibiotic susceptibility testing. These are arranged by the European Union Reference Laboratory - Antimicrobial Resistance and as national ring trial. 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 databases at SVA. Data for indicator bacteria 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 program is used. This approach was used also for interpretation of narasin MICs for *E. faecium* because ECOFF (>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 2015) EUCAST epidemiological cut-off values (ECOFFs), blue underlined values deviate from ECOFFs, red underlined values are CLSI ECOFFs and for values in black, ECOFFs are not defined.

Antibiotic	*Actinobacillus pleuropneumonia*	*Aeromonas salmonicida*	*Brachyspira hyodysenteriae*	*Campylobacter jejuni*	*Campylobacter coli*	*Enterococcus faecalis*	*Enterococcus faecium*	*Escherichia coli* (indicator)	*Escherichia coli* (pathogen)	*Flavobacterium psycrophilum*	*Klebsiella pneumoniae*	*Pasteurella multocida*	*Pseudomonas aeruginosa*	*Salmonella enterica*	*Staphylococcus pseudintermedius, S. felis, S. schleiferi*	*Staphylococcus aureus*	*Streptococcus zooepidemicus*
Ampicillin	>1			>8	>8	>4	>4	>8	>8			>1		>8			>8
Bacitracin[a]						>32	>32										
Cefotaxime								>0.25	>0.5					>0.5			
Cefoxitin																>4	
Ceftazidime								>0.5									
Ceftiofur									>1		>1			>2		>2	
Cephalothin															>2	>1	
Chloram-phenicol	>2					>32	>32	>16	>16			>2		>16		>16	
Ciprofloxacin	>0.06			>0.5	>0.5			>0.06				>0.06		>0.06		>1	
Clindamycin															>4	>0.25	
Colistin								>2	>2				>4				
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	>4	>4							>16	>2	>16	>4		>16		>8	>8
Fusidic acid															>4	>0.5	
Gentamicin	>8			>1	>2	>32	>32	>2	>4		>4	>8	>8	>2	>4	>2	
Kanamycin						>1024	>1024							>16		>8	
Linezolid						>4	>4										
Nalidixic acid	>16			>16	>16			>16				>16		>16			
Narasin						>2	>2										
Neomycin									>8		>8			>4			
Nitrofuran-toin									>32						>32		
Oxacillin															>0.5	>1	
Oxolinic acid										>0.25							
Penicillin	>0.5											>0.5			[c]	[c]	>1
Polymyxin B													>4				
Spiramycin																>16	>16
Streptomycin				>2	>4	>512	>128		>16		>16			>16		>16	
Sulphame-toxazole								>64						>256			
Tetracycline	>1	>1		>1	>2	>4	>4	>8	>8	>0.12	>8	>2		>8	>8	>1	>8
Tiamulin			>0.25														
Tigecycline								>1									
Trimethoprim	>4							>2						>2		>2	
Trim & sulpha[b]									>1	>0.25	>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 sulphametoxazole in concentration ratio 1/20; [c] beta-lactamase production.

SVARM 2000-2014

The number of isolates of different matrices reported in Svarm since 2000 is presented below.

TABLE 7.12. *Salmonella enterica,* number of isolates 2000-2014.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Warm-blooded animals	67	52	49	101	68	105	101	112	122	117	82	71	71	86	77
Cold-blooded animals										17					

TABLE 7.13. *Campylobacter* spp., number of isolates 2000-2014.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Cattle		67					68							109	
Pigs		98		105		100	46		97			83			
Broilers		50	100		100				38		100		100		102
Broiler meat														111	
Meat (different sources)		74													
Water		19													

TABLE 7.14. Indicator *Escherichia coli,* number of isolates 2000-2014.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
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		197
Broiler meat											77		92		
Laying hens													61		
Turkeys														55	59
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 2000-2014 *(E. faecalis/E. faecium).*

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
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		27/187
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 2000-2014.

Animal species & bacterial species	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Cattle															
Escherichia coli (enteric)			220		87	39	24			40	15	15	58	30	29
Escherichia coli (uterine)														60	
Escherichia coli (udder)				169										142	95
Klebsiella spp. (udder)				44			24							41	39
Pasteurella spp.	254			100				27	32	14	27	80	37	39	39
Staphylococcus aureus (udder)		100	100			96			87						74
Streptococcus dysgalactiae (udder)			100												
Streptococcus uberis (udder)			100												
Fusobacterium necrophorum										41					
Pigs															
Actinobacillus pleuropneumoniae	18							84	39	24	39	57	33	36	37
Brachyspira hyodysenteriae	50	75	109	100		31	26	23	15	24	9	7	7	8	7
Brachyspira pilosicoli				93		57	72	44	31	24	13	16	17	12	13
Escherichia coli (enteric)	399	82	340	340	386	325	298	93	83	102	94	91	74	142	118
Pasteurella spp.		75						38	25	24	10	17	24	95	19
Staphylococcus hyicus					20										
Streptococcus equisimilis												82			
Poultry (laying hens)															
Escherichia coli (infection)								70							
Sheep															
Staphylococcus aureus (udder)								25							
Fusobacterium necrophorum										24					
Mannheimia haemolytica and *Bibersteinia trehalosi*															44
Fish															
Aeromonas salmonicida subsp. *achrom.*								67	20	23	8	14	5	10	9
Flavobacterium columnare								30	16	10	5	8	3	5	9
Flavobacterium psychrophilum								42	27	24	21	27	31	23	61
Horses															
Actinobacillus spp.		40													
Escherichia coli (genital)	323	103	166	188	188	161	124	273	174	210	236	174	196	140	229
Rhodococcus equi	73	20			187										
Streptococcus zooepidemicus	301	174	163	150	185	175	174	180	159	152	43	311	140	123	129
Staphylococcus aureus										308	131	135	145	139	132
Dogs															
Escherichia coli (urinary)	185	183	204	234	247	304	366	425	503	599	803	666	407	840	943
Pasteurella canis															207
Pasteurella multocida					231										
Pseudomonas aeruginosa				234						261	313	353	178	309	389
Staphylococcus pseudintermedius	145	156	133	102	159	126	89	220	258	381	444	388	229	566	513
Staphylococcus schleiferi															297
Cats															
Escherichia coli (urinary)			46	52	55	74	95	131	170	245	236	274	310	404	461
Beta-hemolytic streptococci												184			
Pasteurella multocida															244
Staphylococcus felis															244

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SWEDRES|SVARM 2014

The 2014 Swedish report from the monitoring of antibiotic resistance and antibiotic usage in human and veterinary medicine, Swedres-Svarm, is an integrated report from the Public Health Agency of Sweden and the National Veterinary Institute that includes data from humans, animals, and food of animal origin.

The situation in Sweden regarding antibiotic resistance in bacteria from humans and animals is favourable when seen in an international perspective. This confirms that the Swedish strategies to promote rational use and to contain antibiotic resistance have been effective. The total consumption of antibiotics in humans has continued to decrease and positive trends regarding choices of antibiotics have also continued in 2014. Downward trends are also noted for consumption of antimicrobials in animals.

Still, this year's report also reports some unfavourable trends, for example, a large hospital in Sweden has been hit with VRE (vancomycin resistant enterococci) and there have been domestic human cases of Enterobacteriaceae with $ESBL_{CARBA}$ (extended spectrum beta-lactamase with activity against carbapenems) where the sources of infection are unknown. This highlights once again that efforts to optimize antibiotic use, prevent infections, and minimize dissemination of antibiotic resistance must be ongoing and continually improved activities.

Focus areas:
- ESBL-producing *Escherichia coli* with food as a potential dissemination route to humans
- National campaign for improved patient safety
- A national IT tool for surveillance of healthcare-associated infections and antibiotic use
- MRSA in pigs in Sweden
- Risk factors for antibiotic-resistant *Escherichia coli* in the faeces of preweaned dairy calves
- SafeOrganic – antibiotic resistance in organic and conventional pig production in the EU
- Svarmpat – monitoring resistance in pathogens from farm animals

The Public Health Agency of Sweden has a national responsibility for public health issues. The agency promotes good public health by building and disseminating knowledge to professionals involved in the area of public health, including infectious disease prevention.

The National Veterinary Institute (SVA) is an expert authority within the field of risk assessment, diagnostics, and the prevention and control of infectious animal diseases. The Institute strives for good animal and human health through research, contingency planning, and communication of knowledge.