2012

SWEDRES | SVARM

Swedish Antibiotic Utilisation and Resistance in Human Medicine
Swedish Veterinary Antimicrobial Resistance Monitoring

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SMITTSKYDDSINSTITUTET
Swedish Institute for Communicable Disease Control

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

Published by:
Swedish Institute for Communicable Disease Control and National Veterinary Institute

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Article number 2013-101-1

ISSN 1650-6332

This title and previous SWEDRES and SVARM reports are available for downloading at
www.smi.se/publikationer or www.sva.se

This title can be ordered from:
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Suggested citation:
SWEDRES-SVARM 2012. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala ISSN 1650-6332

Print & Layout: DanagårdLiTHO AB

Omslag: Ingvar Westerdahl/Thomas Isaksson

Content

1. Preface

The 2012 Swedish report from the monitoring of antimicrobial resistance and antimicrobial usage in human and veterinary medicine, SWEDRES-SVARM, is the first fully integrated report from the Swedish Institute for Communicable Disease Control (SMI) and the National Veterinary Institute (SVA) on antimicrobial resistance and use of antimicrobials, with data from humans, animals and food where applicable; efforts have been made to discuss zoonotic aspects.

Antibiotic resistance is one of the 21st century's greatest challenges to human and animal health. Use and misuse of antimicrobials for humans and animals have undermined the usefulness of antibiotics by selecting for antimicrobial resistance. Globally the situation is alarming with reports of high resistance levels with therapeutic failures as a consequence. This affects not only the most vulnerable population such as the immunocompromised, the elderly and the premature children but also the generally healthy population for which common bacterial infections have been treatable since the introduction of antibiotics in the 1940s. We are beginning to see the same consequences in Sweden, although at a yet much lower level compared to many countries around the world.

With increased globalization, including travel and worldwide food and animal trade, the challenge grows. As can be seen in this year's report both MRSA and Enterobacteriaceae producing ESBLs are increasing in human infections. There are no indications that the observed increase is linked to Swedish animals, but there is a risk for direct transmission of bacteria of these particular types of resistance between humans and animals and through the food chain. Consequently, intersectorial collaboration between human and veterinary medicine is one of the important measures needed when trying to counteract the problem in humans and animals. Based on the long experience of surveying antibiotic resistance and use both in humans and in animals, Sweden has a unique possibility to assess the impact of the strategies that have been applied. Compared to the majority of the countries in the world, the situation in Sweden is favorable, but we are far from spared from the problem with antibiotic resistance. Further efforts are needed to counter the selection and spread of resistance, and one key component in that work is high quality information about the current situation.

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Acknowledgements

SMIs external group for analysis of antibiotic sales data: Ingrid Brännström, Jonatan Dahlqvist, Mats Erntell, Annika Hahlin, Mikael Hoffman and Pinelopi Lundquist

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

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

Data on antibiotic use in relation to number of admissions and number of patient days in somatic hospital care during 2006-2011 were kindly provided by pharmacists in local Strama-groups.

The SMI Strama advisory board against antibiotic resistance (Stramarådet) for supporting the work with SWEDRES.

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

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

3. Sammanfattning/Summary

Sammanfattning

Detta är den första helt integrerade rapporten från övervakningsprogrammen SWEDRES och SVARM. Rapporten visar att situationen avseende antibiotikaresistens hos bakterier från såväl människor som djur är gynnsam i ett internationellt perspektiv. Detta bekräftar att den svenska strategin att verka för ansvarsfull användning av antibiotika och att begränsa spridning av resistens är effektiv. Årets rapport visar trots det också på några oönskade trender.

Förbrukning av antibiotika

Antibiotikaförbrukning inom humanmedicin

Den totala antibiotikaförsäljningen minskade med 1 procent (från 14,5 till 14,2 DDD per 1000 invånare och dag) under 2012 jämfört med 2011. I öppenvården minskade antibiotikaförsäljningen med 3 procent, från 385 till 374 recept per 1000 invånare och år. Minskningen sågs i alla åldersgrupper utom i åldersgruppen barn 0-6 år, där förbrukningen ökade något (1 procent). Den ökade antibiotikaförbrukningen bland barn var till stor del orsakad av en relativt stor ökad användning av smalspektrum penicillin (J01CE) och linkosamider (J01FF). Antibiotikaförbrukningen minskade i nästan alla län (19 av 21) under 2012. Skillnaderna mellan länen är fortfarande stor och varierade från 410 i Stockholms län till 290 i Västerbottens län, mätt i recept per 1000 invånare och år. Minskningen omfattade nästan alla antibiotikagrupper utom nitrofurantoin (J01XE) och makrolider (J01FA) som ökade.

Betalaktamas-känsliga penicilliner tillsammans med tetracykliner var de antibiotika som förskrevs mest på recept under 2012. Antibiotika som ofta används mot luftvägsinfektioner (LVI) är den grupp av antibiotika som används mest och under 2012 minskade förbrukningen av dessa substanser med 3 procent. Minskningen är främst relaterad till en stor nedgång i förbrukning av doxycyklin (28 procent) och makrolider (28 procent) under sista kvartalet 2012 jämfört med samma period 2011. Användningen av dessa två antibiotikagrupper var ovanligt hög under 2011, troligen relaterat till det ökade antalet *Mycoplasma pneumoniae* som sågs under 2011.

Behandling av nedre urinvägsinfektion (UVI) hos kvinnor ser ut att följa nationella rekommendationer. Användning av de två rekommenderade förstahandspreparaten, pivmecillinam och nitrofurantoin, har successivt ökat och utgjorde 2012 77 procent av den totala försäljningen av antibiotika som ofta används mot UVI i denna patientgrupp under 2012. Totalt sätt har förskrivning av antibiotika som ofta används mot UVI hos kvinnor 18-79 år minskat blygsamt (2 procent) sedan 2000, mätt i recept per 1000 kvinnor och år. Mätt i DDD per 1000 kvinnor och år har användningen däremot minskat betydligt mer (13 procent). Detta indikerar bland annat på kortare behandlingstid vid behandling av UVI. I slutenvård ökade den totala antibiotikaförsäljningen med 3 procent under 2012, från 1,59 DDD/1000 invånare och dag 2011 till 1,63 DDD/1000 invånare och dag. Minskningen i användningen av cefalosporiner som setts de senaste åren fortsätter och från 2006 till 2012 har användningen cefalosporiner minskat med 46 procent. Inom slutenvård finns det också en förskjutning från andra generationens till tredje generationens cefalosporiner. Bredspektrumantibiotika som karbapenemer och piperacillin med tazobaktam används allt oftare och det finns en möjlig koppling till flera ökande antal infektioner orsakade av bakterier med ESBL.

Försäljning av antimykotika

För första gången sedan 2002 ses en minskning av den totala konsumtionen av antimykotika på svenska sjukhus. Efter att ha ökat stadigt sedan 2000 (40 DDD/miljon invånare och dag) med en topp 2011 på 64 kunde man 2012 räkna fram ett nationellt genomsnitt på 60. Det är för tidigt att uttala sig om detta är ett trendbrott. Någon kampanj för att minska förbrukningen av antimykotika har inte skett på samma vis som för antibiotika.

Flukonazol är det mest förskrivna preparatet och utgör cirka 70 procent av all sjukhusanvändning. Posakonazol har ökad sin andel och har passerat vorikonazol som den mest förskrivna bredspektrumazolen. Echinokandinerna som grupp har ökat trots att den totala förbrukningen av svampläkemedel har minskat något, och de används nu mer än amphotericin B. Caspofungin har minskat något till fördel för anidulafungin som nu utgör nästan 20 procent av echinocandinerna. Användningen av micafungin har ökat något och utgör 4 procent av den totala echinocandinanvändningen 2012.

Antibiotikaförbrukning inom veterinärmedicin

Försäljningen av antibiotika för djur under 2012 var totalt 11 745 kg. Uttryckt som mg aktiv substans per skattad kilo levandevikt av livsmedelsproducerande djur var försäljningen 15,6 mg/kg vilket är 26 procent lägre än 2008. En minskad försäljning noterades för alla antibiotikaklasser.

Jämförelse mellan human- och veterinärmedicin

En jämförelse av försäljningen av antibiotika för systemiskt bruk och som medel vid tarminfektioner visade att 64,9 och 11,6 ton sålts för användning inom humanmedicin respektive veterinärmedicin. Användning inom humanvården dominerade alla antibiotikaklasser utom trimetoprim-sulfa och aminoglykosider.

Resistens som anmälningspliktig sjukdom

ESBL-producerande Enterobacteriaceae

Totalt rapporterades 7225 fall av ESBL-bildande bakterier bland människor under 2012 vilket var en ökning med 28 procent. Ökningen skedde i samtliga län, och liksom tidigare år var *Escherichia coli* den helt dominerande bakteriearten som förekom hos 88 procent av fallen. På andra plats kom *Klebsiella pneumoniae* som fanns hos 7 procent av fallen. Bakteriefynden gjordes framför allt i urinprov, och den pågående ökningen i förekomst av resistenta bakterier kan på sikt komplicera behandlingen av dessa förhållandevis enkla infektioner.

En viss typ av ESBL, så kallad $ESBL_{CARBA}$, utgör en mer elakartad resistensmekanism, och bakterier med sådan resistens blev under 2012 anmälningspliktiga både av den behandlande läkaren och av laboratoriet som gjort fyndet. Totalt 23 fall upptäcktes 2012, och de två vanligaste enzymtyperna var NDM och OXA-48. Trots den ringa förekomsten hittills så är en ökad vaksamhet mot dessa extremt resistenta bakterier nödvändig för att vi tidigt ska upptäcka dem och också kunna förhindra spridningen av dem inom vården, eftersom behandlingsalternativen vid en eventuell infektion är få eller inga.

Tillgänglig information visar att ESBL-bildande bakterier är ovanliga hos svenska djur undantaget fjäderfä där en stor andel av djuren bär *E. coli* som bildar CMY-2 ($ESBL_{M}$). En jämförelse av plasmider hos isolat från kyckling och människa har visat att överlappet är begränsat, vilket indikerar att överföring mellan djur och människa inte är vanligt.

MRSA

Totalt anmäldes 2097 nya fall av MRSA bland människor under 2012, vilket var en ökning med 11 procent. Det var nästan lika vanligt med smitta i Sverige (43 procent) som smitta utomlands (39 procent). Samhällsförvärvad smitta var vanligare bland de inhemskt smittade fallen (68 procent) än bland de utomlands smittade (44 procent). Sjukhusförvärvad smitta var däremot vanligare bland importerade fall (34 procent) än bland inhemska (8 procent). Epidemiologisk typning av alla MRSA-isolat med *spa*-typning visade att de fem vanligaste *spa*-typerna fortfarande var t008, t002, t044, t019 och t223. Andelen PVL-positiva MRSA hade minskat något till 34 procent.

Under 2012 isolerades MRSA från två hästar, två katter och från djur i en mjölkkobesättning. I det senare fallet är det troligt att det är djurägaren som smittat sina djur. Förekomsten av MRSA hos djur är fortfarande låg vilket begränsar risken för spridning från djur till människa.

MRSP

Sedan 2009 noteras en numerär minskning av antalet fall av MRSP och 2012 anmäldes 53 fall hos hund och katt. En undersökning av ett slumpmässigt urval av isolat visar på en hög grad av släktskap mellan isolat från olika år. Inom humanmedicinen är MRSP inte generellt anmälningspliktig och inga fall har under året rapporterats till nationella myndigheter.

PNSP

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

VRE

Totalt anmäldes 152 nya fall av VRE bland människor under 2012, vilket var en ökning med 24 procent. Merparten av isolaten var *Enterococcus faecium*, men anmärkningsvärt är att antalet isolat med resistensgenen *vanA* nu kraftigt överstiger antalet med *vanB*. Sjukvårdsrelaterade utbrott förekom under året i Stockholms, Jönköpings och Hallands län. Kraftfulla åtgärder i respektive län ledde till att utbrotten kunde stoppas.

Tidigare data från SVARM visar att *E. faecium* som bär *vanA*-genen förekommer hos svensk kyckling. Majoriteten av VRE-fallen med *vanA* inom humanmedicinen var dock associerade med sjukhusvård i andra länder, och epidemiologisk typning av isolat från alla nya VRE-fall visade också att smittan inte i något fall kunde hänföras till svenska kycklingar.

Resistens hos zoonotiska smittämnen

Salmonella är ovanligt hos djur i Sverige och de fall som påvisas orsakas oftast av stammar som är känsliga för de antibiotika som används för att behandla infektioner hos människa. Resistens mot tredje generationens cefalosporiner har exempelvis inte påvisats hos *Salmonella* från svenska djur och resistens mot antibiotikagruppen fluorokinoloner är mycket ovanligt. Det gynnsamma läget innebär att djur i Sverige är en osannolik källa till antibiotikaresistent *Salmonella* hos människor. Av tillgängliga data hos människa där *Salmonella*-bakterier påträffats i blodet framgår att smittan i mer än två tredjedelar av fallen sannolikt inträffat utomlands.

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

Resistens hos kliniska isolat från människor

Isolat från blododlingar av sju definierade bakteriearter ingår i det europeiska nätverket för resistensövervakning, EARS-Net. Från Sverige medverkar 20 laboratorier, vilket ger en täckning av ca 80 procent av befolkningen, och följande fynd gjordes 2012. *E. coli* förekom i cirka 20 procent av de positiva blododlingarna och *S. aureus* i cirka 10 procent. De övriga fem bakteriearterna som ingår i övervakningen är viktiga

men utgjorde ändå en avsevärt mindre andel av de positiva odlingarna. Hos *E. coli* och *K. pneumoniae* har andelen cefalosporinresistenta och ESBL-producerande isolat ökat varje år och uppgick till 4,4 respektive 2,6 procent 2012. Andelen MRSA av drygt 3000 rapporterade *S. aureus* var fortfarande mindre än 1 procent, vilket ur ett europeiskt perspektiv är en anmärkningsvärt låg siffra. VRE påvisades inte alls, och andelen PNSP av de knappt 1000 *S. pneumoniae* var 5 procent.

I den andra delen av den nationella resistensövervakningen, tillgänglig i applikationen ResNet, undersöks samma bakteriearter som de som ingår i EARS-Net. Alla kliniska laboratorier ombeds testa isolat från urinvägs-, sår- eller luftvägsinfektioner, och avsikten är att bättre kunna spegla situationen i öppenvården. Andelen resistenta bakterieisolat i de båda övervakningssystemen är dock förvånansvärt lika. Det kan tolkas som att bakterier i blodet normalt inte utgörs av mer resistenta bakterier, utan att det är de bakterier som människan bär i sin normalflora som vid ogynnsamma omständigheter orsakar sjukdom av mildare eller svårare slag.

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

Resistens hos kliniska isolat från djur

Bakterier som orsakar sjukdom hos djur är oftast känsliga för de antibiotika som används vid behandling. Så är exempelvis bakterier som orsakar luftvägsinfektioner hos lantbrukets djur och hos hästar generellt känsliga för bensylpenicillin. Resistens förekommer dock hos *Escherichia coli* från flera djurslag och för att kunna välja rätt antibiotika vid behandling är resistensundersökning motiverad.

Resistens hos indikatorbakterier från friska djur

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

Summary

This is the first fully integrated report from SWEDRES and SVARM. The report shows that the Swedish situation regarding antimicrobial resistance in bacteria from humans and animals is still favorable when seen in an international perspective. This confirms that the Swedish strategies to promote rational use and to contain antimicrobial resistance in bacteria from animals and humans are effective. Still, this year's report also describes unfavorable trends.

Use of antimicrobials

Antibiotic use in humans

The total sale of antibiotics decreased by 1 percent in 2012 as compared with 2011 (from 14.5 to 14.2 DDD per 1000 inhabitants and day). In outpatient care, the antibiotic sale decreased by 3 percent, from 385 to 374 prescriptions per 1000 inhabitants and year. The decrease was seen in all age groups except children aged 0-6 years, where the use slightly increased (1 percent). The increased sale of antibiotics to children was mostly related to a great increase in sale of narrow spectrum penicillin (J01CE) and lincosamides (J01FF).

The antibiotic sale decreased in 19 out of 21 counties in 2012. The differences between counties are still large and ranged from 410 in the county of Stockholm to 290 in the county of Västerbotten, measured as prescriptions per 1000 inhabitants and year. The decrease encompassed almost all antibiotic groups except nitrofurantoin (J01XE) and macrolides (J01FA) which increased. Beta-lactamase sensitive penicillins together with tetracyclines were the most commonly used antibiotics in outpatient care.

Antibiotics commonly used to treat respiratory tract infections are the most frequently prescribed group of antibiotics and in 2012 the sale decreased with 3 percent. The decrease is mainly related to a great drop in sale of doxycycline (28 percent) and macrolides (28 percent) during the last quarter in 2012 compared with the same period in 2011. The use of these two antibiotic groups was higher than usual during 2011, probably related to the increased number of *Mycoplasma penumoniae* infections in 2011.

Treatment of lower urinary tract infections (UTI) in women appears to follow national recommendations. Usage of the two first line recommended substances, pivmecillinam and nitrofurantoin, has gradually increased and in 2012 these substances represented 77 percent of the total sale of antibiotics commonly used to treat UTI in this population. In total, the sale of antibiotics commonly used to treat UTI in women 18-79 years has only declined slightly (2 percent) since 2000, measured by prescriptions per 1000 women and year. Measured by DDD per 1000 women and year, the sale has, however, decreased significantly more (13 percent). This indicates shorter treatment duration for the treatment of UTI according to treatment recommendations.

The total sales of antibiotics in hospital care increased by 3 percent during 2012, from 1.59 DDD/1000 inhabitants and day in 2011 to 1.63 DDD/1000 inhabitants and day in 2012. The decrease in the use of cephalosporins the latest years continued, from 2006 to 2012 the sales decreased by 46 percent, and there is also a shift from second generation to third generation cephalosporins. Broad spectrum antibiotics such as carbapenems and piperacillin with tazobactam are used more often and there is a possible connection to an increased number of infections caused by bacteria with ESBL.

Sales of antifungals

For the first time since 2002 there has been a decrease in the total use of antifungal drugs for systemic use. Compared to 2011 the total consumption in 2012 decreased by 7 percent, yielding a national average of 60 DDD/one million inhabitants and day. Since the total use is very low, it is difficult to interpret whether this decrease represents a new trend in the use of antifungals in Sweden. Nevertheless there has previously been a small but steady increase in the use of antifungals for systemic use in Sweden for the past 12 years. In 2000 the total use was 40 DDD/one million inhabitants and day, and this volume has increased almost every year, reaching the highest level in 2011 with 64.

Fluconazole still constitutes the absolute majority of the antifungals used, 70 percent or 42 DDD/one million inhabitants and day. Amphotericin B and caspofungin are the two secondly most used compounds representing 8 and 7 percent, respectively. Among the broadspectrum antifungals the use of posaconazole has increased and it has bypassed voriconazole as the most commonly used broadspectrumazole used in hospitals. The echinocandins as a group has increased its share and now constitutes 10 percent of all antifungals in hospitals. The use of caspofungin has decreased by 10 percent, the use anidulafungin has increased proportionally and micafungin has appeared in the statistics for the first time.

Antibiotic use in veterinary medicine

In veterinary medicine, the total amount of antimicrobials was 11 745 kg. Expressed as mg per 'population correction unit' (PCU), the sales in 2012 were 15.6 mg/PCU. This is 26 percent lower than five years ago. Decreases are noted for all antimicrobial classes and for all animal species.

Comparison between use in human and veterinary medicine

When antimicrobials sold for systemic use and as intestinal anti-infectives were compared, a total of 64.9 and 11.6 tonnes were used in human and veterinary medicine, respectively. Human use by far outweighs animal use for most classes, except for trimethoprim-sulphonamides and aminoglycosides.

Resistance as notifiable disease

ESBL-producing Enterobacteriaceae

A total of 7225 cases were notified among humans in 2012, corresponding to an incidence of 76 cases per 100 000 inhabitants. The increase was 28 percent compared to 2011, and it was seen in all counties. The most commonly reported species was *Escherichia coli* with 88 percent of all cases, followed by

Klebsiella pneumoniae with 7 percent. Most ESBL-producing bacteria were found in urine samples (60 percent), and the increasing prevalence will soon complicate the empiric treatment of these relatively harmless infections.

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

The available data indicate that ESBL-producing bacteria are rare in animals in Sweden with the exception of poultry where *E. coli* producing CMY-2 ($ESBL_M$) are found in a large proportion of birds. A comparison of plasmids from isolates of chickens and humans concluded that the overlap was limited, indicating that transmission is uncommon.

MRSA

The total number of human cases of MRSA was 2097 in 2012, an increase by 11 percent compared to 2011. According to the systematically reviewed notification reports, the infection was acquired in Sweden (43 percent) only slightly more often than abroad (39 percent), but in many cases the country of acquisition could not be defined. Community-acquired infections dominated among domestic cases (68 percent) but were less frequent among imported cases (44 percent). Hospital-acquired infections were comparatively more common in imported cases (34 percent) than among domestic cases (8 percent), indicating continued good compliance to basal hygiene principles among healthcare staff. Only 23 new invasive isolates of MRSA were found in 2012. Epidemiological typing of all MRSA isolates by *spa*-typing showed that the five most commonly encountered *spa*-types in 2012 were t008, t002, t044, t019 and t223. The prevalence of MRSA with PVL toxin had decreased to 34 percent.

During 2012, MRSA was isolated from two horses, two cats and in one dairy herd. In the latter case, it is likely that transmission from the farmer to the cows had occurred. The prevalence of MRSA in animals is still low which limits spread from animals to humans.

MRSP

Since 2009, an apparent decline in notified cases of MRSP is noted and in 2012, 53 cases of MRSP in dogs and cats were reported. Analysis of a random selection of isolates showed a high relatedness between isolates over the years. In human medicine, MRSP is not generally notifiable and no cases have been reported to the national authorities.

PNSP

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

VRE

In 2012 a total of 152 new cases of VRE in humans were reported, an increase with 24 percent compared to 2011. The majority of isolates were *Enterococcus faecium*, and for the first time isolates with resistance gene *vanA* outnumbered those with *vanB* gene. Healthcare related outbreaks were reported from Stockholm, Jönköping and Halland Counties. Rapid and effective infection control measures were taken and the outbreaks were ended.

Previous data from SVARM has shown that *E. faecium* with *vanA* gene was present among Swedish broilers. The majority of the cases of VRE with the *vanA* gene in humans were associated with healthcare in other countries, and transfer from Swedish broilers therefore seems unlikely.

Resistance in zoonotic pathogens

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

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

Resistance in human clinical isolates

EARS-Net surveillance

Invasive isolates of seven defined bacterial species have been reported to EARSS/EARS-Net since 2000. *Escherichia coli* was the most frequently found pathogen in blood cultures and constituted approximately 20 percent, followed by *Staphylococcus aureus* at 10 percent. The five other pathogens in the EARS-Net system were all much less frequently found. In *E. coli* and *K. pneumoniae* the levels of resistance to third generation cephalosporins had increased to 4.4 and 2.6 percent, respectively. MRSA isolates accounted for 0.8 percent of all invasive *S. aureus*, which is extremely low in the European perspective. The rate of non-susceptibility to penicillins in *Streptococcus pneumoniae* (referred to as PNSP) was higher than in previous years, now 5 percent. There were no VRE reported among invasive isolates of *Enterococcus faecalis* and *E. faecium*, but high-level resistance to aminoglycosides (HLAR) was common with 14 and 18 percent, respectively.

National surveillance and quality assurance programme, displayed in ResNet

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

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

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

Resistance in animal clinical isolates

Bacteria causing clinical disease in animals are mostly susceptible to relevant antimicrobials. Particularly, bacteria causing respiratory infections in farm animals and horses are usually susceptible to bensylpenicillin. Resistance is however not uncommon in *E. coli* from all animals and susceptibility testing to guide the choice of antimicrobial for therapy is therefore warranted.

Resistance in indicator bacteria from healthy animals

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

4. Guidance for readers

The present SWEDRES-SVARM report is the result of a close cooperation between SMI and SVA to present data relating to both humans and animals on the use of antimicrobials and on the notifiable diseases caused by resistant bacteria. Moreover, data on resistance in zoonotic bacteria, in bacteria from clinical submissions and in so called indicator bacteria from healthy animals are presented. The methods used for antimicrobial susceptibility testing in SWEDRES, whether it is 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 tables with yearly updated interpretative critera (clinical breakpoints for human use). But not all antimicrobials have been given clinical breakpoints because there is not enough data from clinical trials to support a clinical breakpoint. However, many antimicrobials have been given epidemiological cut-off values (ECOFF), which ”separates microorganisms without (wild type) and with acquired resistance mechanisms (non-wild type) to the agent in question” (citation from EUCAST website).

In SVARM, susceptibility testing is performed following the standards for microdilution of the Clinical and Laboratory Standards Institute (CLSI, 2008).

Use of ECOFFs in SWEDRES

Most of the data in SWEDRES is based on routine susceptibility testing in clinical laboratories. The results have been compiled and are most often presented as percent resistance in tables or graphs. Only in the case of *Clostridium difficile* were the MIC results interpreted based on ECOFFs from EUCAST.

Use of ECOFFs in SVARM

In SVARM, isolates of indicator bacteria and zoonotic bacteria are classified as susceptible or resistant by ECOFFs. Also, animal pathogens are classified by ECOFFs when such values are available and suitable for the concentration range tested. Cut-off values used are given in Appendix 4.

ECOFFs classify isolates with acquired reduced susceptibility as non-wild type, in SVARM called “resistant”. This classification is relevant for monitoring purposes, but it should be understood that “resistance” does not always imply clinical resistance.

Since the first report from SVARM, some cut-off values for resistance have been changed. To facilitate comparisons when retrospect data are presented in SVARM 2012, levels of resistance have been recalculated using current cut-off values if not otherwise stated.

Indicator bacteria

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

Presentation of MIC distributions

When susceptibility testing was performed by MIC determination the data is 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 substance and vertical bold lines indicate cut-off values used to define resistance.

The percentage of isolates with a certain MIC of an antimicrobial is given in the corresponding white field. For MICs above the range tested of an antimicrobial (>X mg/L) the percentage is given in the field closest to the range, *i.e.* in the first shaded field to the right of the tested range. For MICs equal to or lower than the lowest concentration tested for an antimicrobial (≤Y mg/L) the percentage is given as the lowest tested concentration, *i.e.* in the first white field of the tested range.

Multidrug resistance

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

Example of a table with distributions of MICs

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

Abbreviations of generic antimicrobial names

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

Amp	Ampicillin
Bac	Bacitracin
Caz	Ceftazidim
Cdr	Cefadroxil
Cer	Ceftiofur
Cet	Cephalothin
Chl	Chloramphenicol
Cip	Ciprofloxacin
Cli	Clindamycin
Col	Colistin
Ctx	Cefotaxim
Enr	Enrofloxacin

Ery	Erythromycin
Flf	Florfenicol
Fox	Cefoxitin
Fus	Fusidic acid
Gen	Gentamicin
Imp	Imipenem
Kan	Kanamycin
Lin	Linezolid
Mec	Mecillinam
Mer	Meropenem
Nal	Nalidixic acid
Nar	Narasin

Oxa	Oxacillin
Pen	Penicillin G
Rif	Rifampicin
Str	Streptomycin
Sul	Sulphonamide
Tet	Tetracycline
Tmp	Trimethoprim
Tsu	Trimethoprim-sulfonamide
Tob	Tobramycin
Van	Vancomycin
Vir	Virginiamycin

Interpretation of data on antibiotic use

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

Comparison of sales 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 and parts of nursing homes). Since national data on sales of antibiotics to hospitals in Sweden is aggregated with sales to some nursing homes, this is not suitable for evaluation of antibiotic use in hospital care. Therefore, data on sales exclusively to hospitals has been provided by pharmacists in local Strama groups in all counties (in the report stated as data in Swedish hospitals).

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

Abbreviations

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

5. Use of antimicrobials

Use of antimicrobials in humans

Total sales of antibiotics

In 2012, the total sale of antibiotics (J01 excl. methenamine) in Sweden (outpatient care and hospital care) decreased 1% compared with 2011 (from 14.5 to 14.2 DDD per 1000 inhabitants and day), Table 5.1. Eighty-nine percent of all antibiotics sales in Sweden 2012 were sold in outpatient care, Figure 5.1. Even though the majority of all antibiotics is prescribed in outpatient care, studies have shown that the antibiotic pressure in Swedish hospitals is high. One of three inpatients are treated with antibiotics.

The overall consumption has followed a wavy pattern over the years. In total, the sale of antibiotics has decreased with 2% since 2000, from 14.5 to 14.2 DDD per 1000 inhabitants and day, Figure 5.1. During 2005-2007, the total sale of antibiotic increased in Sweden and in 2007 the consumption was the highest since the beginning of 21st century.

Beta-lactamase sensistive penicillins and tetracyclines are the two antibiotics that were used in greatest amount in Sweden in 2012, Figure 5.2.

TABLE 5.1 Sales of antibiotics in outpatient and hospital care 2000-2012, DDD/1000 inhabitants and day.

		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
J01 exclusive J01XX05	Outpatient care	13.3	13.5	13.2	13.1	12.8	13.2	13.5	13.9	13.7	12.9	12.8	12.9	12.6
	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
	Total care	14.5	14.7	14.4	14.4	14.1	14.6	15.0	15.4	15.2	14.4	14.3	14.5	14.2
J01	Outpatient care	14.84	15.0	14.8	14.7	14.6	15.0	15.3	15.6	15.3	14.3	14.1	14.1	13.9
	Hospital care	1.21	1.25	1.27	1.37	1.43	1.5	1.56	1.62	1.57	1.52	1.55	1.61	1.65
	Total care	16.1	16.3	16.1	16.1	16.0	16.5	16.9	17.3	16.8	15.8	15.7	15.7	15.5
J01XX05	Outpatient care	1.5	1.5	1.6	1.7	1.8	1.8	1.8	1.7	1.6	1.4	1.3	1.3	1.3
	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
	Total care	1.6	1.6	1.6	1.7	1.9	1.9	1.9	1.8	1.6	1.4	1.3	1.3	1.3

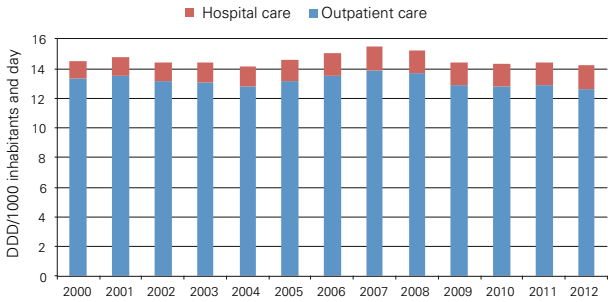


FIGURE 5.1. Sales of antibiotics in outpatient and hospital care 2000-2012, DDD/1000 inhabitants and day.

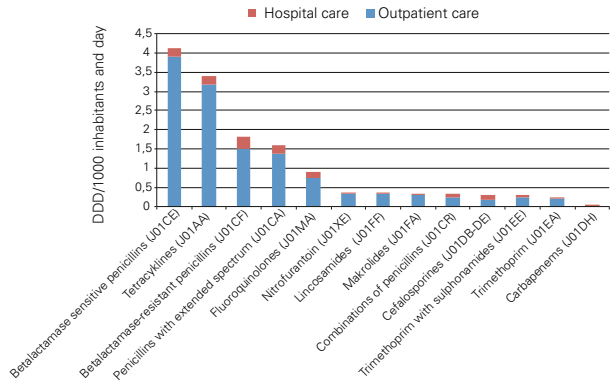


FIGURE 5.2 Antibiotics (ATC-5) in outpatient and hospital care 2012, DDD/1000 inhabitants and day.

Antibiotics in outpatient care

Sales of antibiotics in outpatient care continued to decrease (3%) in 2012, from 385 to 374 prescriptions per 1000 inhabitants and year, Figure 5.3.

The decrease in 2012 was seen in all age groups except the children aged 0-4 years. In this age group the number of prescriptions slightly increased, from 482 to 484 prescriptions per 1000 inhabitants and year. This should be seen in the light of the great decrease that has been seen among

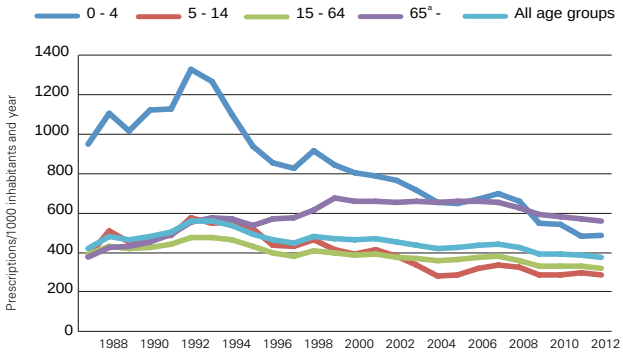


FIGURE 5.3. The sales of antibacterial drug for systemic use in outpatient care 1987- 2012, prescriptions/1000 inhabitants and year, both sexes, different age groups. [a]1987-1999 includes antibiotic sale to people aged 65-99 years and from 2000 the statistic also includes data for people aged over 100 years.

children since 1992, where the antibiotic sale has decreased with 64% measured as prescriptions per 1000 inhabitants and year. The greatest decrease in antibiotic use in 2012 was in the age group 15-64 years where the antibiotic sale decreased from 331 to 318 prescriptions per 1000 inhabitants and year (4%). Since 2009, the age group 65 year and older has the highest use of antibiotics in Sweden measured as prescriptions per 1000 inhabitants and year, Figure 5.3. As mentioned earlier in the chapter Guidance for readers, some of the antibiotic sales to elderly people is not included in the statistics and possible under-reporting must be taken into account. Although, a steady decrease in antibiotic sale to the oldest age group (80 years and older) has been seen during the 21st century, from 928 to 673 prescriptions per 1000 inhabitants and year.

The decrease in antibiotic prescriptions during 2012 encompasses a majority of all antibiotic groups except nitrofurantoin (J01XE) and macrolides (J01FA) which increased, Figure 5.4.

As shown in figure 5.4, narrow spectrum penicillins (J01CE) and tetracyclines (J01AA) were the most commonly prescribed antibiotics in outpatient care in 2012, Figure 5.4 and Table 5.2. The sale of beta-lactamase sensitive penicillins (J01CE) decreased with 2%, from 118 to 116 prescriptions per 1000 inhabitants in 2012 compared with 2011. Doxycycline (J01AA02) is the most frequently used tetracycline and represents 76% of the sales in this group of substances measured as prescriptions per 1000 inhabitants and year.

Trimethoprim (J01EA), cephalosporines (J01DB-DE) and penicillins with extended spectrum (J01CA) excl. pivmecillinam (J01CA08) are the antibiotic groups with the greatest decrease during 2012 compared with 2011 expressed in percentage (14%, 10% and 7% respectively), Figure 5.4. The reduction of these substances is seen in all age groups but in varying magnitude, Table 5.2.

The sale of tetracyclines (J01AA) has also decreased in a great amount during 2012 compared with 2011, from 55 to 52 prescriptions per 1000 inhabitants (5%). During 2011 an increased frequense of *Mycoplasma pneumoniae* was seen in Sweden which probably caused the increased use of tetracylines and macrolides during 2011 (Linde A *et al*., 2012). In 2012, the frequency of *Mycoplasma pneumoniae* has decreased and so the use of tetracylines, Figure 5.4.

Gender differences

Of all antibiotics prescribed in Sweden 2012, 60% were sold to females and 40% to males. This proportion has almost been constant over time and the decrease in antibiotic use that has been seen during the last years has included both genders. Read more about gender differences in antibiotic use in Swedres 2011.

Antibiotic commonly used to treat respiratory tract infections, urinary tract infections and skin and soft tissue infections in different age groups

Figure 5.5 and 5.6 clearly illustrate the consumption of different antibiotics in different age groups measured as prescriptions. Even though the antibiotic use is high among children and the oldest, other age groups represent a great share of the total antibiotic consumption. If measuring the antibiotic sale during 2012 as DDD, the sale is greatest in the

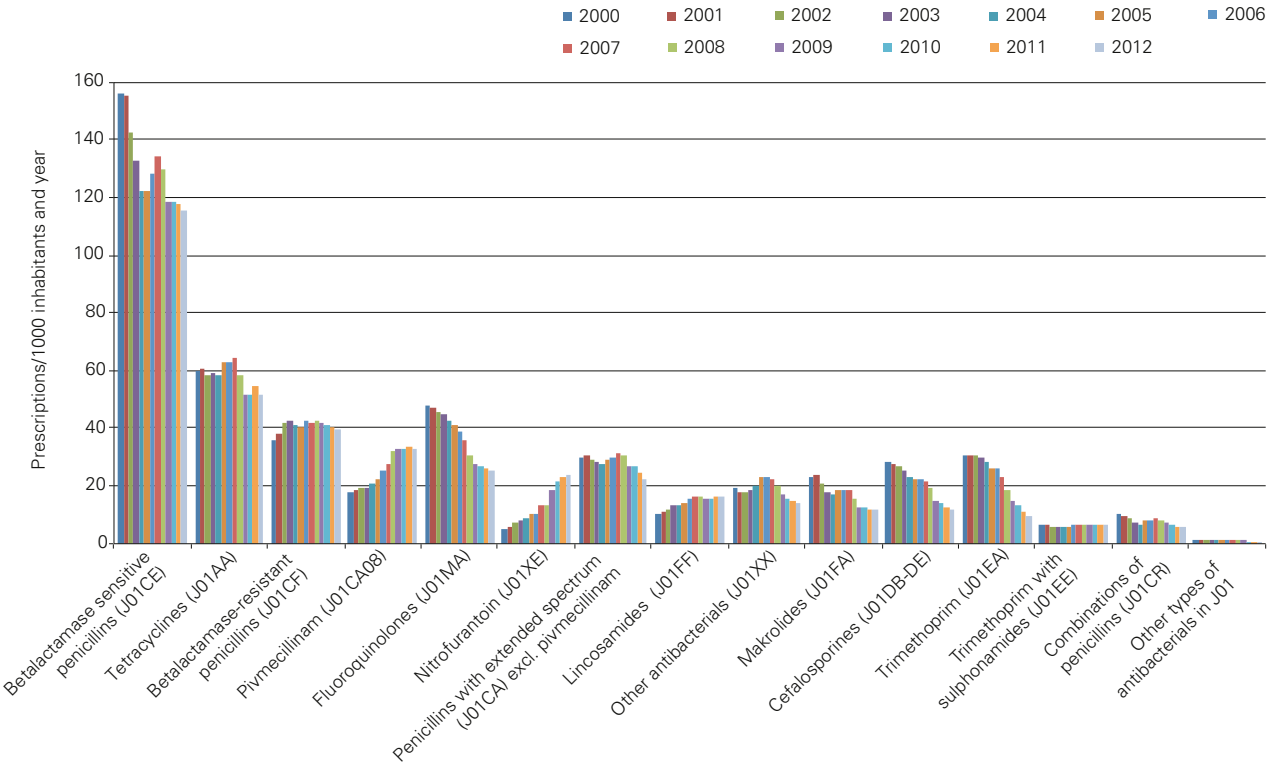


FIGURE 5.4. Antibiotics in outpatient care 2000-2012, prescriptions/1000 inhabitants and year, both sexes, all ages. The data are sorted according to the use in 2012.

TABLE 5.2. Antibiotics in outpatient care, classes of antibiotics and age groups. DDD/1000 inhabitants and day, prescriptions/1000 inhabitants and year and users/1000 inhabitants and year.

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

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

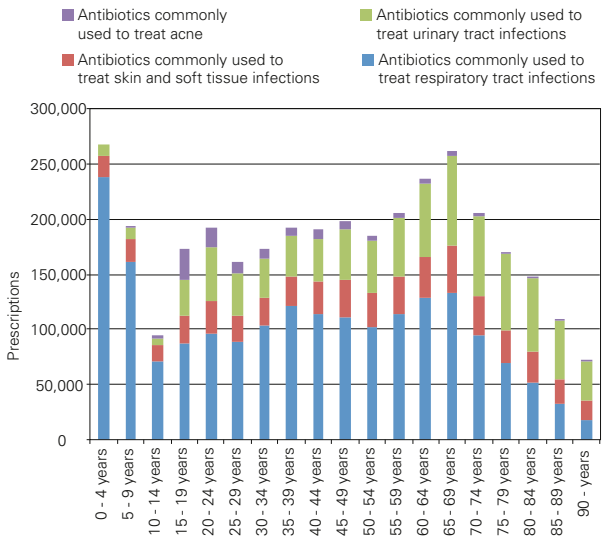


FIGURE 5.5. Antibiotics commonly used to treat: respiratory tract infections (J01AA02, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infections (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), skin and soft tissue infections (J01FF01 and J01CF05), acne (J01AA04, J01AA06 and J01AA07), both sexes, different age groups, prescriptions in 2012.

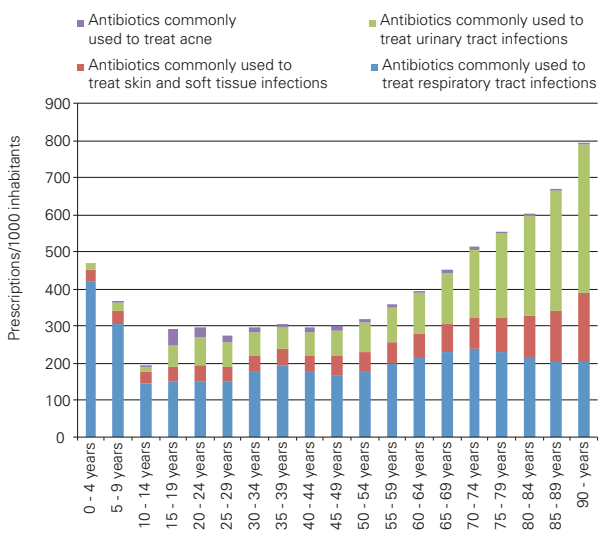


FIGURE 5.6. Antibiotics commonly used to treat: respiratory tract infections (J01AA02, J01CE02, J01CA04, J01CR02, J01DB-DE and J01FA), urinary tract infections (J01CA08, J01EA01, J01MA02, J01MA06 and J01XE01), skin and soft tissue infections (J01FF01 and J01CF05), acne (J01AA04, J01AA06 and J01AA07), both sexes, different age groups, prescriptions/1000 inhabitants in 2011.

age groups 15-19, 60-64 and 65-69 years. In the age group 60-64 and 65-69 antibiotics commonly used to treat respiratory tract infections is most commonly used. Differently, in the age group 15-19 years, antibiotics commonly used to treat acne represent the largest proportion of all antibiotics and the prescribing of these antibiotics has increased over the recent years.

Antibiotics commonly used to treat respiratory tract infections

Antibiotics commonly used to treat respiratory tract infections (RTI) are the most frequently prescribed antibiotics in Sweden. Among these substances we also find the greatest decrease over time in terms of number of prescriptions per 1000 inhabitants and year, from 294 in 2000 to 208 in 2012. Narrow spectrum penicillin, penicillin V, is the recommended first line antibiotic for treatment of common community acquired RTI in Sweden and is the most prescribed antibiotic in outpatient care, (Medical Products Agency & STRAMA, 2008), Figure 5.7. In all age groups, except children 0-6 years and the age group 80 years and older, the use of penicillin V (J01CE02) decreased in 2012, Table 5.2. Doxycycline is the second most prescribed antibiotic substance in outpatient care.

In total, antibiotics commonly used to treat RTI decreased in 2012 compared with 2011, from 215 to 208 prescriptions per 1000 inhabitants and year (3%). The decrease is mainly related to a great reduction in use during the last quarter in

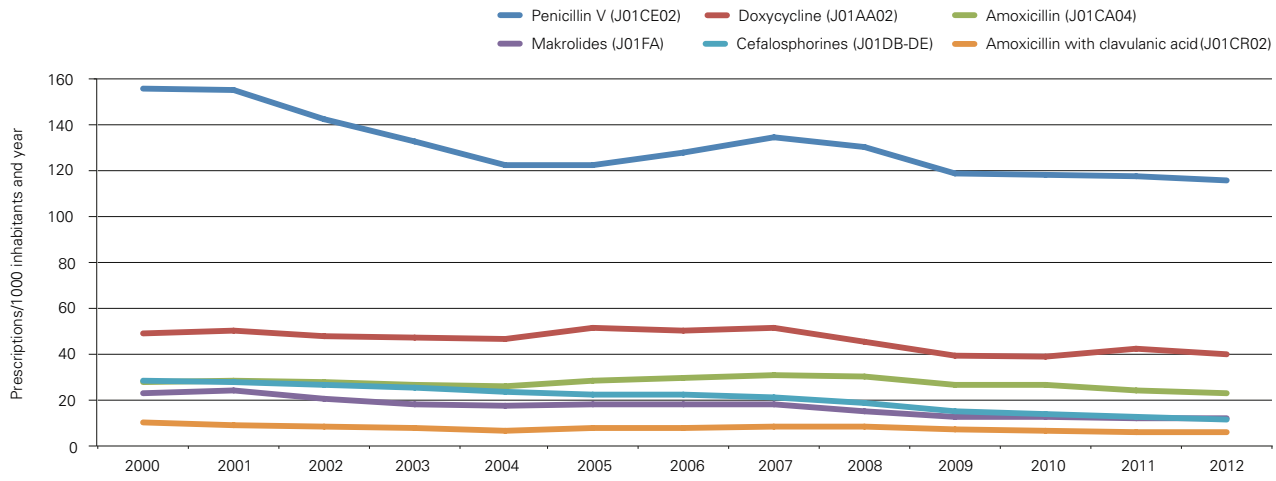


FIGURE 5.7. Antibiotics commonly used to treat respiratory tract infections in outpatient care, 2000-2012, prescriptions/1000 inhabitants and years, both sexes, all ages.

2012 (15%) compared with the same period in 2011. During this period, the greatest decrease was seen among doxycycline (28%) and macrolides (28%). The use of doxycycline and macrolides was higher than usual during 2011, which probably was related to an increased number of *Mycoplasma pneumonia* that was seen in Sweden during the influenza season 2011. However, the sale of doxycycline in 2012 is still greater than in 2010.

In 2012, the Swedish Institute for Communicable Disease Control and the Swedish Medical Products Agency issued a new recommendation for treatment of pharyngotonsillitis (acute sore throat). According to the recommendation, antibiotic treatment should in most cases be preceded by a positive Strep A test for detection of group A streptococci (GAS) in the throat. Any decision on a Strep A test should be preceded by the fulfillment of at least three Centor criteria as assessed during clinical examination by a physician. Narrow spectrum pencillin V (J01CE) is first line antibiotic for pharyngotonsillitis caused by GAS. In relapsing infection clindamycin or a cephalosporin is recommended (Medical Products Agency & Swedish Institute for Communicable Disease Control, 2012).

Antibiotics commonly used to treat urinary tract infections in women

Recommendations for the treatment of lower urinary tract infections in women over 18 years, launched by Strama and the Swedish Medical Products Agency in 2007 (Medical Products Agency & STRAMA, 2007), recommend pivmecillinam and nitrofurantoin over trimethoprim, and prescribers are also encouraged to minimize the use of fluoroquinolones because of the resistance situation. The use of the two first-line drugs has increased every year and pivmecillinam and nitrofurantoin account for 77% of antibiotics commonly used to treat this condition in women in 2012. This is a greater proportion than in 2011. Taken together, a clear shift from a high use of fluoroquinolones to a use of pivmecillinam and nitrofurantoin is seen, figure 5.8, which is according to recommendations.

In 2012, the sale of these antibiotics to women 18-79 years decreased with 2% compared with 2011. The decrease in 2012 is mostly related to a decreased use of trimethoprim and fluoroquinolones, Figure 5.8. However, the total sale of antibiotics commonly used to treat UTI in women aged 18-79 years has decreased slightly over the years, 2% since 2000, measured as prescriptions per 1000 women and year. When measured the sale in DDD per 1000 women and day, the sale has decreased more, with 13% since 2007 and with 2% in 2012, Figure 5.9. The greater decrease when measured in DDD is partly related to the shift in more use of pivmecillinam and nitrofurantoin and it indicates shorter treatment duration for treatment of UTI in women.

In 2006-2008 national Strama, now a part of the Swedish Institute for Communicable Diseases and Control, conducted an independent clinical trial comparing 7 and 14 days of treatment with ciprofloxacin (J01MA02) for treating acute pyelonephritis in women. The study showed that 7 days of treatment had the same effect on symptoms as a course of

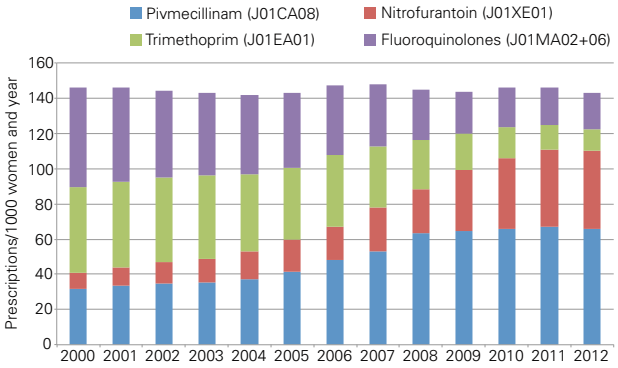


FIGURE 5.8. Antibiotics commonly used to treat lower urinary tract infections in women, 18-79 years, 2000-2012, prescriptions/1000 women and year.

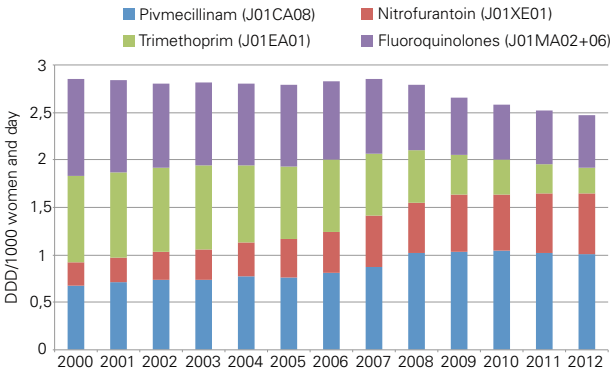


FIGURE 5.9. Antibiotics commonly used to treat lower urinary tract infections in women, 18-79 years, 2000-2012, DDD/1000 women and day.

14 days (Sandberg T *et al.*, 2012). Ciprofloxacin belongs to the antibiotic group fluoroquinolones, which is a broad spectrum antibiotic that is active against a variety of bacteria and also drives the development of resistance to other antibiotics. A rational use and being able to shorten the treatment to 7 days is important to minimize the selection and spread of resistant bacteria. Several bacteria that commonly causes UTI are already showing an increased resistance to quinolones. Moreover, shorter treatment duration also likely lower the risk of side effects to the drug.

Antibiotics commonly used to treat urinary tract infections in men

Ciprofloxacin and trimethoprim are the most commonly used antibiotics to treat UTI in men in Sweden. Prostatic involvement is often seen in febrile UTIs in men why quinolones and trimethoprim, with good concentrations in prostate, are appropriate. It is unknown how often the prostate is infected in symptomatic UTI without fever and because of increasing resistance in gram-negative bacteria, nitrofurantoin and pivmecillinam may be considered as first line antibiotics. In a newly published document from SMI, experts are recommending nitrofurantoin or pivmecillinam as first line antibiotics for treatment of symptomatic UTI without fever in

men, (Swedish Institute for Communicable Disease Control, 2013).

The sale of fluroroquinolones to men has decreased with 21% from 2000 to 2012, measured as prescriptions per 1000 men and year. The decrease in use of fluoroquinolones continued in 2012 where the sale decreased with 5% compared with 2011. The last years, the use of the narrower spectrum pivmecillinam and nitrofurantoin has increased. In 2012, the sale of pivmecillinam increased with 10% and nitrofurantoin with 8%, measured as prescriptions per 1000 men and year, compared with 2011. In total, the sale of antibiotics commonly used to treat UTI in men has decreased with 16% since 2000, Figure 5.10.

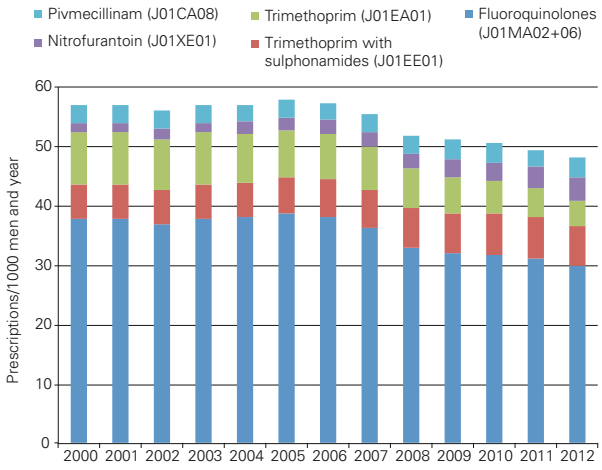


FIGURE 5.10. Antibiotics commonly used to treat urinary tract infections in men, 2000-2012, prescriptions/1000 men and year.

Antibiotic consumption in children

Antibiotic prescribing to children aged 0-6 years increased by 1% in 2012, from 468 to 472 prescriptions per 1000 children. The increased sale in this age group during 2012 compared with 2011 was related to a great increase in uses of narrow spectrum penicillin (J01CE) and lincosamides (J01FF), Table 5.2. Narrow spectrum penicillins (J01CE) accounts for the greatest increase measured as prescriptions per 1000 inhabitants and year, from 271 in 2011 to 286 in 2012, Table 5.2.

Even though the total antibiotic use in children increased in 2012 compared with 2011, the sale of most antibiotic substances actually decreased. The greatest decrease was seen in the sale of macrolides (J01FA), cephalosporins (J01DB-DE) and amoxicillin (J01CA04) (19%, 8% and 7% respectively), Figure 5.11 and Table 5.2. New recommendations for treatment of acute otitis media were launched by Strama and the Swedish Medical Products Agency in 2010 (Medical Products Agency & STRAMA, 2010). The new recommendations have been attracting attention from professionals and the public which may have influenced the antibiotic use to young children.

Over the years, antibiotic sale to this age group has decreased dramatically, with 37% since 2000.

Different kinds of penicillins are the most commonly prescribed antibiotics to this age group and penicillin V (J01CE02), amoxicillin (J01CA04) and flukloxacillin (J01CF05) represents 78%, Figure 5.11 and Table 5.2.
Data from the Swedish Prescribed Drug Register (Appendix 2) shows that the share of children treated with at least one

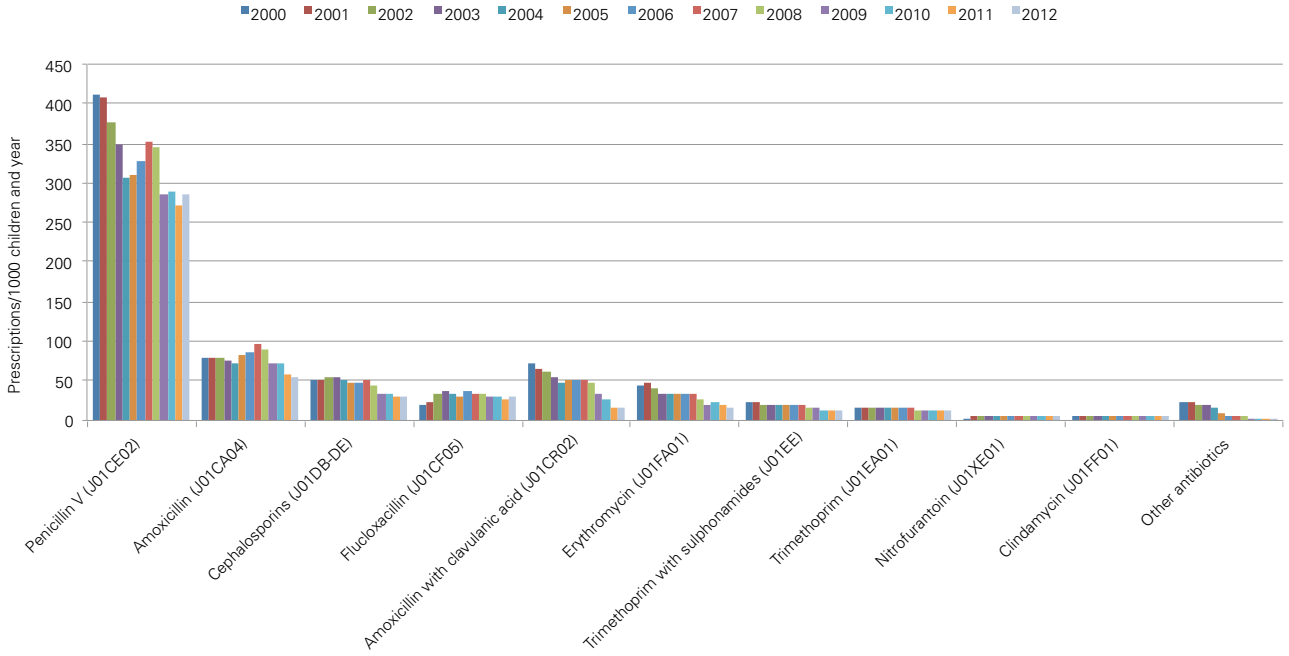


FIGURE 5.11. Antibiotics groups, children aged 0-6 years, 2000-2012, prescriptions per 1000 children and year.

course of any kind of antibiotic decreased in eleven out of 21 counties in 2012. The share ranges within the country from 309.1 users per 1000 children in Stockholm County to 155.5 users per 1000 children in Jämtland County, Figure 5.12. Taken together, in Sweden the share of children treated with at least one course of antibiotics was 274.4 users per 1000 children, which is 0.4 % higher than in 2011, Table 5.2.

Antibiotic use in children has been in focus of both local and national information activities the last years. The great reduction in sales of antibiotics to children the last years may have several explanations; information about hand hygiene being one and new treatment recommendations for acute otitis media being another.

County data

The share of people treated with at least one course of any kind of antibiotic was 218.7 users per 1000 inhabitants, which is 3.4 % less than in 2011 (226.3 user per 1000 inhabitants), Table 5.2. However, the share of people treated with antibiotics varies within Sweden, from 240.5 users per 1000 inhabitants in Stockholm County to 168.1 users per 1000 inhabitants in Västerbotten County. The antibiotic use is greatest in big cities and their surroundings. In total, the share decreased in 20 out of 21 counties, in 2012, Figure 5.13.

In 2012 the average sale of antibiotics in outpatient care measured as prescriptions per 1000 inhabitants in Sweden was 374, Figure 5.14. To reach the Swedish long term target of at most 250 prescriptions per 1000 inhabitants and year the antibiotic use in Sweden must decrease with 33%. Read more about the Swedish target for antibiotic use in chapter *Agreement concerning improved patient safety*. In 2012, a decreased number of prescriptions per 1000 inhabitants is seen in 19 out of 21 counties. There are great regional differences within the country and prescriptions per 1000 inhabitants range from 410 in Stockholm County to 290 in Västerbotten County, Figure 5.14. Note that this is the first year any county used less than 300 antibiotic prescriptions per 1000 inhabitants and year in Sweden since 2000.

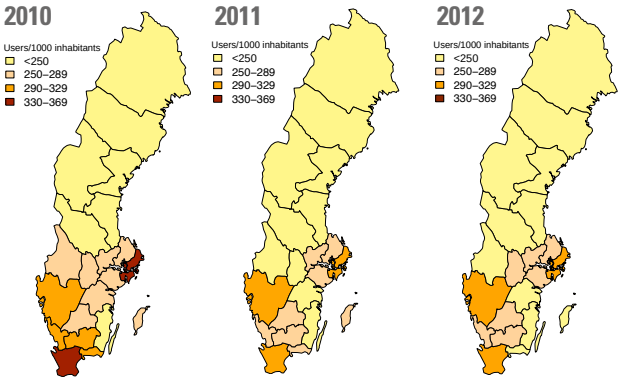


FIGURE 5.12. Share of children age 0-6 years treated with at least one course of antibiotics (J01 excl. methenamine) in 2010 to 2012 (users/1000 children and year).

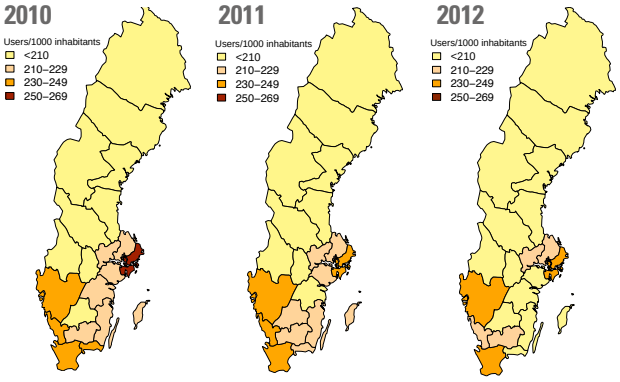


FIGURE 5.13. Share of people treated with at least one course of antibiotics (J01 excl. methenamine) in 2010 to 2012 (users/1000 inhabitants and year).

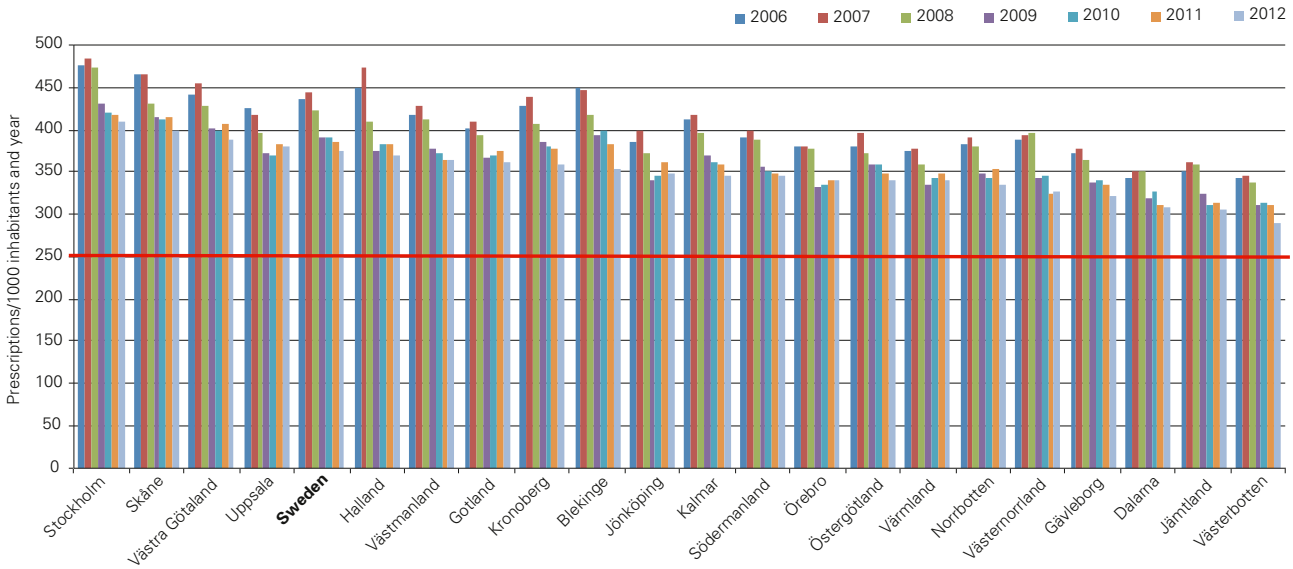


FIGURE 5.14. Sales of antibiotics in outpatient care 2006-2012, prescriptions/1000 inhabitants and year. The red line indicates the Swedish long term target of at most 250 prescriptions / 1000 inhabitants and year. The data are sorted according to the use in 2012.

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

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

In 2012 the proportion of penicillin V of antibiotics commonly used to treat respiratory tract infections in children aged 0-6 years was 71% on the national level and the proportion of penicillin V increased in the majority of all counties.

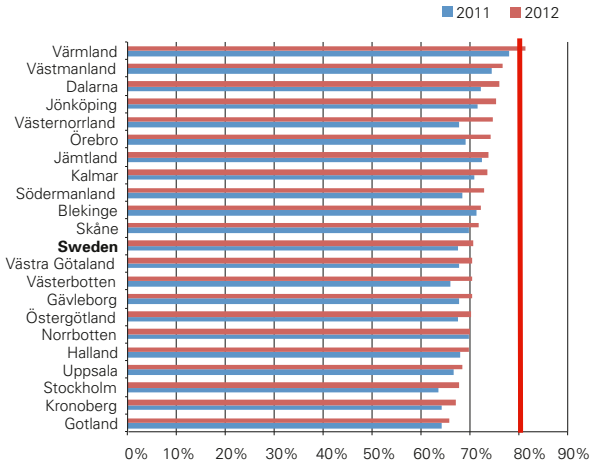


Figure 5.15. Proportion penicillin V of antibiotics commonly used to treat respiratory tract infections in children 0-6 years, per county. The red line indicates Strama´s goal at minimum 80% penicillin V.

[a] *Amoxicillin (J01CA04), penicillin V (J01CE02), amoxicillin-clavulate (J01CR02), macrolides (J01FA) and cephalosporins (J01DB-DE). The data are sorted according to the use in 2012.*

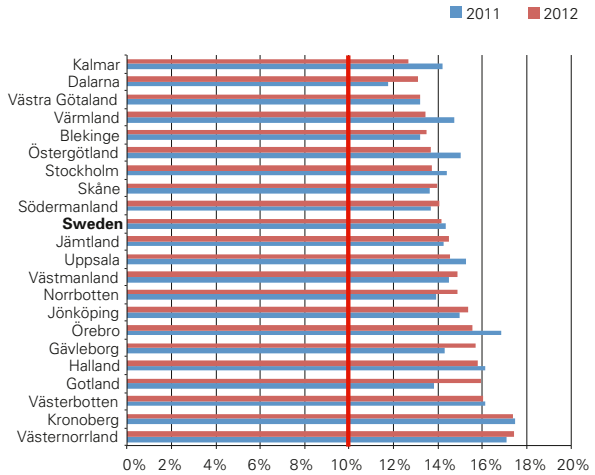


Figure 5.16. Proportion of fluoroquinolones of commonly used antibiotics in treatment of urinary tract infectionsa in women 18-79 years, per county. The red line indicates Strama´s goal of maximum 10% fluoroquinolones.

[a] *Fluoroquinolones (J01MA02+06), pivmecillinam (J01CA08), nitrofurantoin (J01XE01), trimetboprim (J01EA01). The data are sorted according to the use in 2012.*

Värmland County had the greatest proportion, 81%, and Gotland County the lowest, 66%, Figure 5.15. The increased share of penicillin V to children in 2012 is mostly related to a great increase in sale of penicillin V to children during the year. The total sale of antibiotics commonly used to treat RTI to children increased during 2012.

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

In Sweden the average proportion of fluoroquinolones prescribed to women aged 18-79 was 14% in 2012. Västernorrland and Kronoberg were the counties with the highest proportion (17%) and Kalmar was the county with lowest proportion (13%), Figure 5.16.

Agreement concerning improved patient safety

The Government and the Swedish Association of Local Authorities and Regions (SKL) agreed in late 2010 on a performance-based reimbursement for the patient safety efforts in the county councils. SEK 100 million was allocated for the period October 1 2010 - September 31 2011 to improvements of rational use of antibiotics. A prerequisite for receiving compensation was that the county councils must have met a number of basic requirements. One important requirement, based on the work with antibiotic use, was the establishment of a local strategic program against antibiotic resistance (Strama) with a clear mission and adequate financing. All the county councils met this requirement. Those county councils who also worked for an increased compliance to local treatment recommendations concerning common infections in outpatient care, and also decreased the number of antibiotic prescriptions by ten percent of the difference between the number of prescriptions per 1000 inhabitants per year for the period October 1 2009 – September 31 2010, and the long term target of at most 250 prescriptions per 1000 inhabitants and year were entitled to the compensation. An assessment from The Swedish Institute for Communicable Disease Control showed that all the county councils met the requirement regarding compliance to local treatment guidelines. Five counties decreased the antibiotic prescriptions, including Stockholm, the largest county in Sweden. The county councils of Dalarna, Västernorrland and Jämtland furthermore reached the target regarding antibiotic prescriptions and shared SEK 75 million. In 2012 another SEK 100 million was allocated to improvements of rational use of antibiotics. Nine counties decreased the antibiotic prescriptions during the measured period (October 1 2011- September 31 2012 compared with October 1 2010- September 3 2011) and the county councils of Blekinge, Gotland, Gävleborg and Västerbotten reached the target and shared SEK 75 million. A closer look shows some disadvantages of the chosen method. The most striking example is the small county of Gotland which reached

the target 2012 mainly because of the large increase of the prescription rate in the county the preceding year, which became the baseline period in the following year (Swedish Institute for Communicable Disease Control, 2012).

The patient safety drive will continue in 2013 and the quantitative antibiotic target has changed with the purpose that more county councils should be able to achieve their targets. All county councils which reduce antibiotic prescriptions during the measurement period compared with the previous measurement period can be reimbursed. The qualitative target is similar to previous measurement period but in one aspect more specified. An important requirement is that county councils must show that at least 50 percent of the health centres have provided the general practitioners their personal antibiotic prescribing and furthermore compare the personal prescribing of the practitioners at the health centre and also make structured comparisons between health centres in the county.

Antibiotics in dentistry

The sale of antibiotics prescribed by dentists decreases by 3% in 2012 compared with 2011, from 27 to 26 prescriptions per 1000 inhabitants and year. Penicillin V (J01CE02) is the most commonly prescribed antibiotic followed by amoxicillin (J01CA04) and clindamycin (J01FF01). These antibiotic substances represent 75%, 11% and 10% respectively of all antibiotics prescribed by dentists. In percentage terms, however, the greatest decrease in 2012 was seen for amoxicillin and erythromycin. Dentists account for approximately 7% of all antibiotic prescribing in outpatient care in Sweden. The proportion varies between 5% and 8% in different counties. The share is lowest in Västerbotten, Västernorrland, and Örebro Counties (5% respectively) and up to 8% in Skåne, Blekinge, Kalmar, Västmanland and Jämtland Counties. The total sale of antibiotic, measured as prescriptions per 1000 inhabitants, decreased in 17 out of 21 counties in 2012 compared with 2011.

Interventions addressed the overuse of antibiotics in outpatient care in Kalmar County

Worldwide, misuse and overuse of antibiotics is the most important reason for development of antimicrobial resistance and has become a major threat to public health.

The quote “No patient should have to suffer a harm that could have been avoided” was expressed by Minister of Social Affairs Göran Hägglund, during the negotiations between the Government and the Swedish Association of Local Authorities and Regions (SKL) in November 2010. The meeting ended in a deal agreement on a performance-based compensation model for patient safety work in the county councils, which became the start of an engaging process of change in all counties in Sweden.

In May of 2011, the local Strama – group of Kalmar County was given the commission to develop methods to be able to document, monitor and improve antibiotic prescriptions in outpatient and inpatient care in the County.

But it is a challenge to influence the Physician´s well established prescribing routines. Experience and studies show that feedback of prescribing patterns, combined with education, discussion and reflection is the most effective way to change the prescriber’s habits.

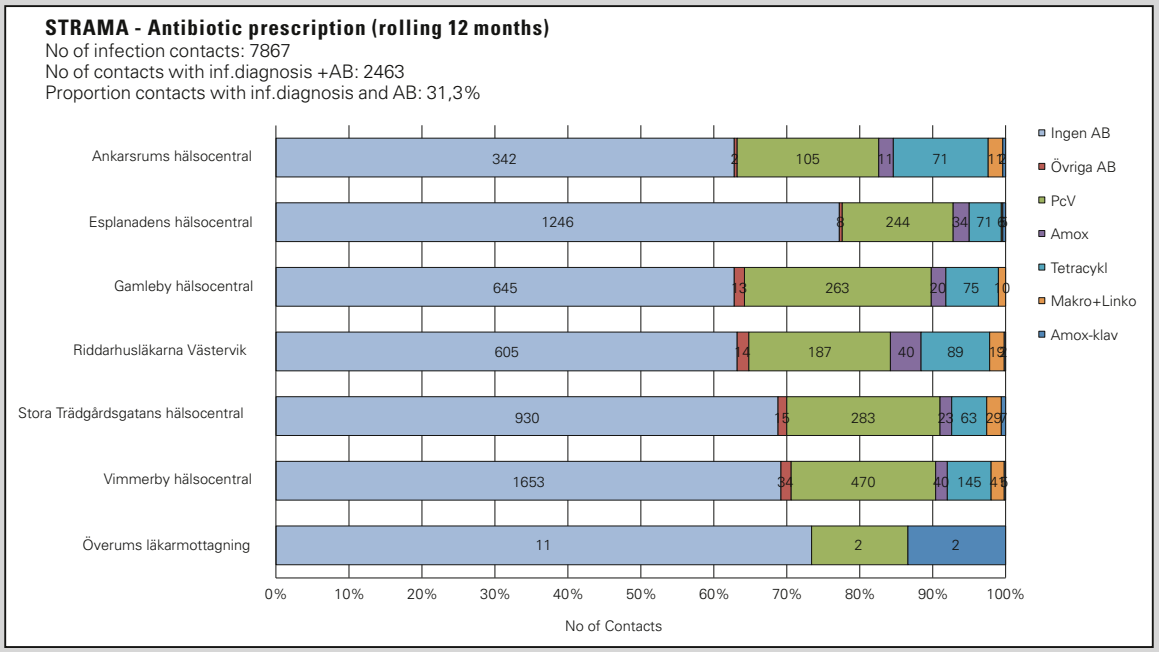


FIGURE 1. Visits for respiratory tract infections (RTI) to health care units in the northern part of Kalmar County during the past 12 month ((Contact date; 2012-04-02 to 2013-04-01, Analysis filter: RTI (LRTI+URTI))(Ingen AB= no antibiotics, Övriga AB=other antibiotics, PcV= penicillin V (J01CE02), Amox= amoxicillin (J01CA04), Tetracykl=tetracyclines (J01AA), Makro+Linko= macrolides (J01FA)+lincosamides (J01FF), Amox-klav= Amoxicillin with clavulanic acid (J01CR02)).

In the spring of 2012, intensive work began in order to develop data output tools for the monitoring and feedback of physicians' antibiotic prescribing related to diagnosis – new way to provide feedback to prescribers.

Simultaneously active implementation of existing guidelines took place around the County. Training days for doctors and nurses in both primary care and municipal health care were organized. Local "Strama"-homepage saw the light of.

From November 2012 until March 2013, the local Strama group representative, a specialist in family medicine along with a representative of the local drug and therapeutics committee, undertook a journey through the county visiting all the primary health care units, including all private health care providers, to inform and give feedback with the intent of changing/improving the prescribers' practices. The individual prescription statistics was shown and openly compared with the prescription of other colleagues / other providers, se example in figure 2. The presentation mostly resulted in constructive discussion about the decision to prescribe an antibiotic, the choice of antibiotic for bacterial infections or for a specific condition, the treatment duration and when the prescription can be considered to be inappropriate and not in agreement with the current guidelines. Questions about patient's demands and expectation and as well own incentives that control prescribing pattern, were frequently raised. It was very important to ensure that they agree that the discussed problem is important and the approach to managing the problem is appropriate.

The aforementioned journey has recently been completed. Renewed feedback of 24 months prescribing data starts again in September 2013. Meanwhile prescribers can obtain their prescription statistics in real-time via the local Strama-website.

Figure 1 and 2 shows example of reports from the local Strama-website. Figure 1 displaying visits for respiratory tract infection (RTI) at health care units in relation to antibiotic prescribing during April 2 2012-April 1 2013. The example shows that the share of all patients diagnosed RTI and treated with antibiotics vary between health care centers, from 27% to 37%.

The example shows that penicillin V is the most prescribed antibiotics for RTI in all health care centers. The example also shows that the share of patient diagnosed RTI and treated with penicillin V of all patients with RTI treated with antibiotic vary from 50% to 69% (Ingen AB = No antibiotics).

Figure 2 shows visits for Acute Bronchitis in relation to each doctor´s prescribing pattern for Acute Bronchitis during the period Mars 31 2012- April 2 2013. The result must of course be related to how many patient and what type of patient each doctor has exanimate during the period. The result is of great importance for the doctor when analyzing prescriber pattern and a great tool in quality work.

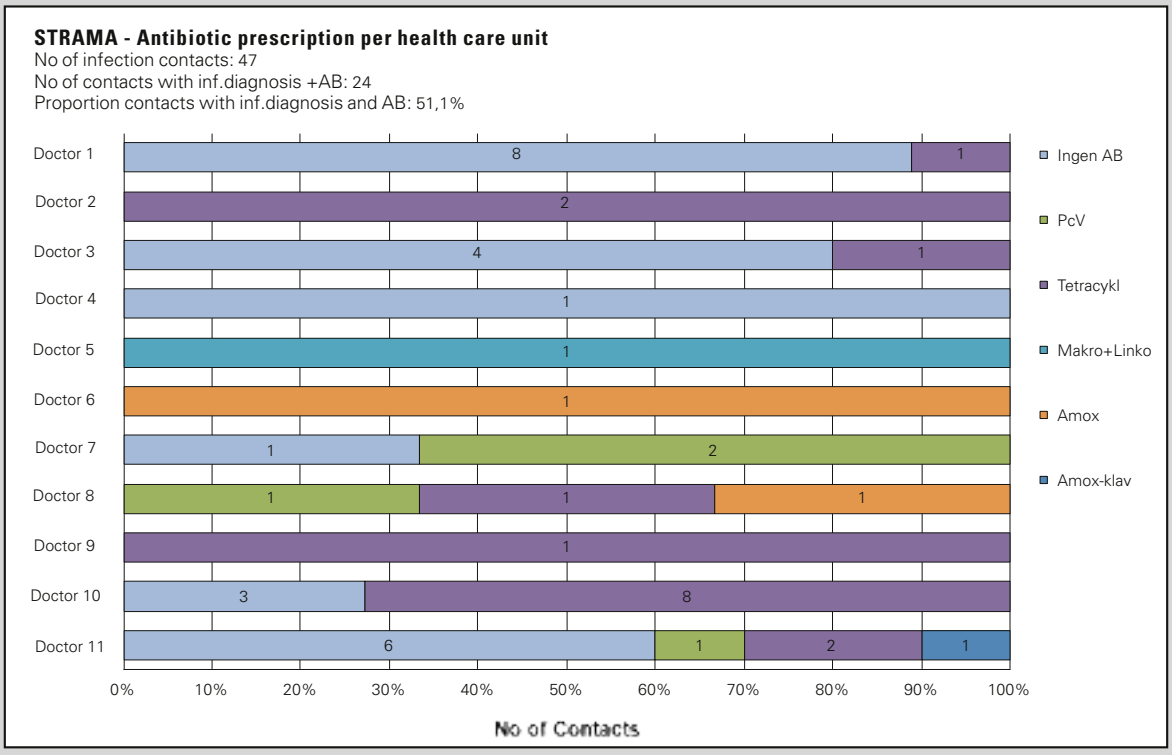


FIGURE 2. Treatment choice per doctor at one health care centers in Kalmar county, diagnosis; Acute Bronchitis (Contact date; 2012-04-02 to 2013-04-01, Analysis filter; LRTI - Acute brinchitis) (Ingen AB= no antibiotic, PcV= penicillin V (J01CE02), Tetracykl=tetracyclines (J01AA), Makro+Linko= macrolides (J01FA)+lincosamides (J01FF), Amox= amoxicillin (J01CA04), Amox-klav= Amoxicillin with clavulanic acid (J01CR02)).

Diagnose linked prescribing data from primary care

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

PRIS consists of data from 1 460 500 visits for infections during the years 2007-2012. PRIS is administrated by primary care R&D center in Jönköping County and is financed by the Swedish Institute for Communicable Disease Control and the R&D unit in Jönköping County.

In 2012, 66 health centers participated in PRIS and the population was 625157 patients listed at the participating health centers. During the year, 259 548 visits for infections were registered which represent 27% of all visits in this population, excluding visits during weekends. In total 415 visits per 1000 listed patient were registered whereof 145 received a prescription for an antibiotic. In addition, 44 prescriptions per 1000 listed were identified that could not be linked to a specific visit or diagnose. This might be due to prescriptions by phone, after worsening of illness, receiving a test result or simply administrative mistakes. The most common antibiotics prescribed without a registered diagnose were pcV, betalactamasresistant penicillins, tetracyclines and pivmecillinam.

Ten infection diagnoses represented 89% of all antibiotics (AB) prescribed in 2012. Urinary tract infection followed by throat infection and ear infection led to most antibiotic prescriptions, Table 1.

TABLE 1. The 10 diagnoses that represented 89 %of all antibiotic prescribing in 2011 in participating health centers.

Diagnose	% of total antibiotic prescribing	Prescriptions/1000 listed patients	% treated per diagnose
Cystitis	24	34	76%
Tonsillitis	17	24	80%
Acute otit media	10	15	74%
Skin infection	6	9	52%
Sinuitis	6	8	61%
Acute bronchitis	6	8	38%
Pneumonia	6	8	58%
Lyme disease	4	6	84%
Upper respiratory tract infection	4	5	7%
Impetigo	2	2	2%

According to treatment recommendations a Strep A test or a positive culture shall have been taken on most patients diagnosed with throat infections (tonsillitis and pharyngitis) before antibiotic treatment. In 2012, 57% of those who received antibiotics for throat infections had a positive Strep A test and 9% had a negative Strep A test, while in 34% no test had been taken at all. The corresponding figures for 2011 were 54%, 12% and 34%, Table 2.

TABLE 2. Use and result of strep A test in patients treated with antibiotics for tonsillitis/pharyngitis.

	2011		2012	
	Number	%	Number	%
Positive strep-A test	9847	54	9711	57
Negative strep-A test	2199	12	1569	9
No strep-A test	6232	34	5759	34

The proportion of positive Strep A tests of all taken was 36%. In 2012, 87% of those diagnosed with tonsillitis or pharyngitis and with a positive Strep test were treated with penicillin V (J01CE02), 5% with cephalosporins (J01DB-DE) and 3% with macrolides (J01FA) and lincosamides (J01FF), respectively.

In 2011, 77% of all children aged 1-12 years that were diagnosed with acute otitis media were treated with antibiotics. The corresponding figure for 2012 was 72% In 2007, 60% of all patients diagnosed with acute bronchitis were treated with antibiotics and the corresponding figure for 2011 was 42% and for 2012 was 38%. When antibiotics were prescribed for acute bronchitis, 57% of the patients were treated with tetracyclines, 23% with

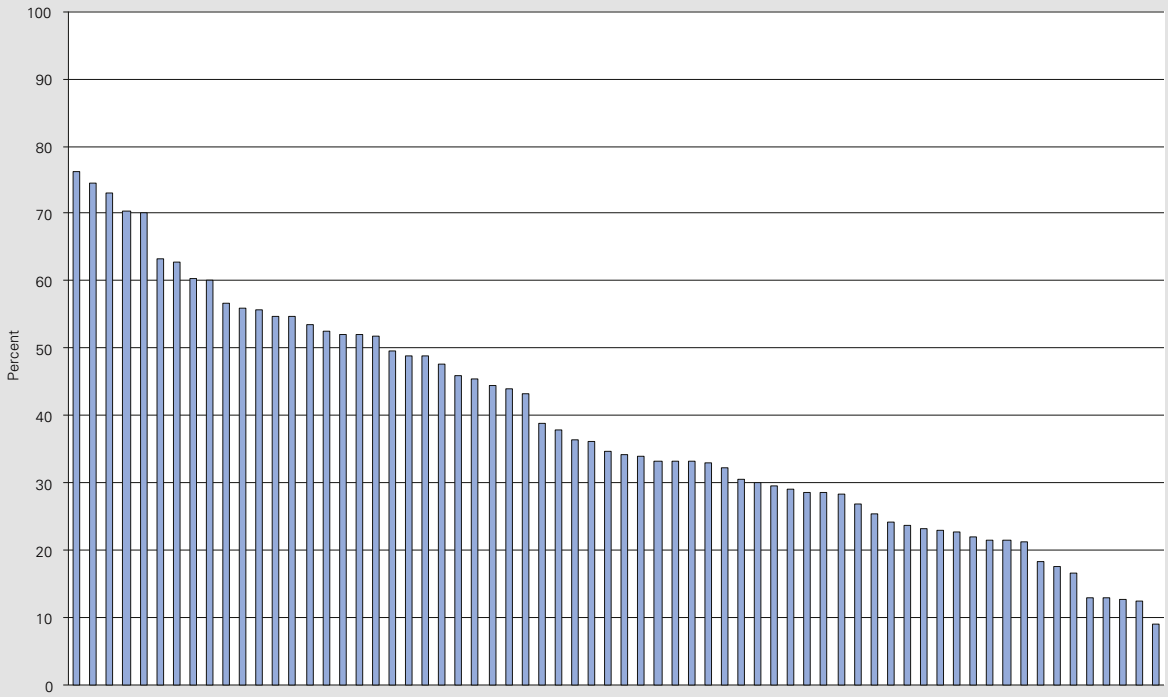


FIGURE 1. The proportion of all patients diagnosed with acute bronchitis and received antibiotic treatment per participating health centers (1-66).

penicillin V and 12% with amoxicillin. The proportion of all patients diagnosed with acute bronchitis and receiving antibiotic treatment varied between the participating health centers, from 9 to 76%, Figure 1. Such variation was noted for the majority of all diagnoses registered in PRIS.

The indication for antibiotic treatment in women with urinary tract infections cannot be analyzed by this kind of record. But the choice of antibiotic substance prescribed at the diagnose urinary tract infection can be analyzed and has changed over time. In 2007, the proportion of women diagnosed with a urinary tract infection and treated with the two first line substances, pivmecillinam or nitrofurantoin, was 55% and the proportion treated with trimethoprim or fluoroquionolones was 40%. In 2012, pivmecillinam was prescribed to 49% of all women diagnosed urinary tract infection and treated with antibiotics, nitrofurantoin to 36%, trimethoprim to 8% and fluoroquinolones to 3%. The proportion of women with urinary tract infections and treated with fluoroquinolones in PRIS can be compared with the goal launched by Strama in 2009; the proportion of fluoroquinolones should not exceed 10% of antibiotics commonly prescribed to treat urinary tract infections in women. When using sales data from pharmacies for the assessment of adherence to treatment recommendations less specific targets need to be applied, as prescribing for other diagnoses cannot be excluded effectively. This illustrates the value of registries like PRIS that approves for an accurate investigation of prescribing for a certain diagnosis.

Conclusion

PRIS is a valuable database for monitoring of the treatment of infections in primary care. All participating health centers receive a summary of their data in comparison with other units' data. There are several possible sources of error in this type of registry, but it can clearly illustrate trends over time and highlight differences in treatment between different units. It is quite clear that the management of especially respiratory tract infections can be improved. Anyone with a concrete question, for example for a student thesis, can access data from the record.

Antibiotics in hospital care

Hospital care

Hospital care includes data from all Swedish hospitals as well as data from those nursing homes and other care givers that order their antibiotics through requisitions. Patients in some nursing homes get their antibiotics through prescriptions and in these cases data are included in primary health care data, presented in the previous section. On the national level, the proportion of antibiotics to hospital care used by hospitals is about 75%, and has been so for the last five years. In some counties almost 100% of all antibiotics bought on hospital requisitions is actually used by hospitals and in other counties this proportion is as low as 55%.

The total sale of antibiotics to hospital care increased with 3% during 2012, from 1.59 DDD/1000 inhabitants and day in 2011 to 1.63 DDD/1000 inhabitants and day in 2012, Table 5.3.

inhabitants and day. Sales of third generation cephalosporins, mainly cefotaxime and ceftazidime, have replaced the use of second generation cephalosporins (cefuroxime). The decrease in DDD is partly explained by a shift from cefuroxime to cefotaxime since the prescribed daily dose, PDD, in Sweden of cefuroxime and cefotaxime do not correspond to the WHO definition of DDD (Appendix 2, Table 7.10). Cefuroxime has often a higher PDD and cefotaxime a lower PDD as compared with WHO´s DDD. Considering this the actual decrease is not that large. Taken together, the overall decrease in DDDs for cephalosporins indicates that these substances are actually replaced by other antibiotics.

Figure 5.18 shows eight groups of antibiotics often used within hospital care. The most pronounced changes in the figure is the decrease of cephalosporins and the increase of beta-lactamase resistant penicillins (J01CF), beta-lactamase sensitive penicillins (J01CE) and combinations of penicillins (J01CR). In the later group, piperacillin with tazobac-

TABLE 5.3. Antibiotic use in hospital care 2000-2012, DDD/1000 inhabitants and day.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
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
Total J01	1.21	1.25	1.27	1.37	1.43	1.50	1.56	1.62	1.57	1.52	1.55	1.61	1.65
Methenamine (J01XX05)	0.03	0.03	0.03	0.05	0.07	0.07	0.07	0.07	0.05	0.03	0.03	0.02	0.02

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

The decrease in the use of cephalosporins seen the latest years continues in 2012, Figure 5.17. From 2006 to 2012 the sales decreased by 46%, from 0.25 to 0.14 DDD per 1000

tam stands for 79%. Piperacillin with tazobactam still represents a small proportion (4%) of all antibiotic use in hospital care, but the use is increasing rapidly. In 2012 it increased with 13% measured as DDD per 1000 inhabitants and day compared to 2011. The increase in piperacillin with tazobactam could be a result of stewardship favoring piperacillin with tazobactam over cephalosporins since the former is more favorable in the situation with increasing ESBL. Carbapenems are also increasing, 12% in 2012, which probably is a result of an increased number of infections involving ESBL. To minimize the selection of ESBL producing bacteria, a decreased use of 2nd and 3rd generation´s cephalosporins is recommended in Sweden. According to recommenda-

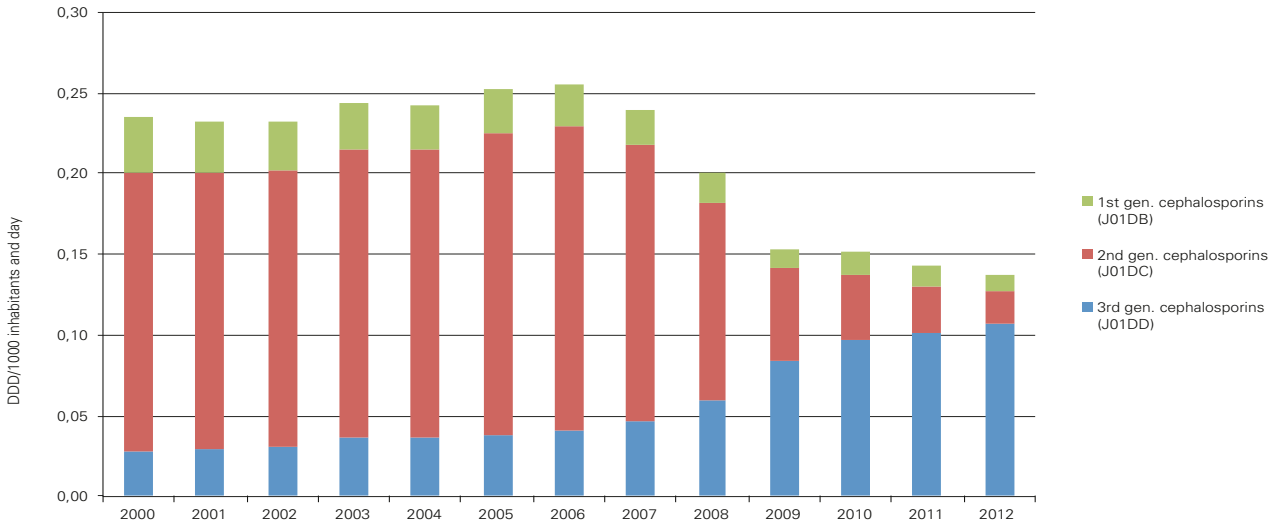


FIGURE 5.17. Cephalosporins in hospital care, DDD/1000 inhabitants and day, 2000-2012.

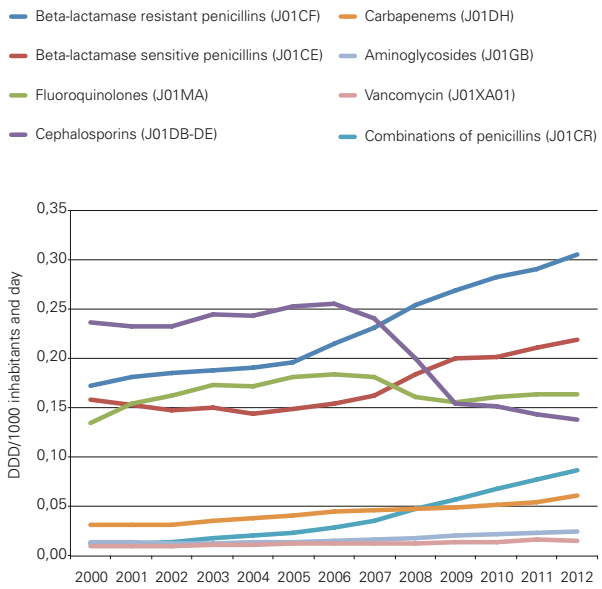


FIGURE 5.18. Antibiotic groups often used within hospital care 2000-2012, DDD/1000 inhabitants and day.

tions (Swedish Institute for Communicable Disease Control, 2013 and The Swedish Society of Infectious Diseases, 2011), cephalosporins should be replaced with benzylpenicillin in non-serious community acquired pneumonia (CRB 65 ≤2). In cases of febrile UTIs and abdominal infections, cephalosporins could be used, details of local resistance is crucial, and many local drug committees are emphasizing the use of piperacillin with tazobactam in these situations which contributes to the increase of J01CR over time.

Due to the rapid decrease in use of cephalosporins during the last years, the betalactamase-resistant penicillins (J01CF) are now the largest group of antibiotics in hospital care, Figure 5.18. These substances are largely used as prophylaxis before surgery. A single dose is recommended in nearly all kinds of surgical procedures for which antibiotic prophylaxis is indicated, or at most one-day prophylaxis. Communication about dosage regime of antibiotic prophylaxis before surgery has been in focus during the last years but still the use of betalactamase-resistant penicillins continues to increase. In 2012 the increase was 5% DDD/1000 inhabitants compared to 2012.

After several years with decreasing use of fluoroquinolones (J01MA) the use in 2012 was almost unchanged compared to 2011, Figure 5.18. Still, fluoroquinolones stands for 10% of all antibiotics within hospital care.

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

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

Antibiotic use measured as both DDD/100 patient-days and DDD/100 admissions has increased the last years, the former by 9% from 2009 to 2012 and the latter by 5% the same period. This could either be because patients receive more antibiotics or a result of shorter mean length of stay. When comparing the data with data from requisitions there are no big differences. Betalactamase resistant penicillins (J01CF) are the largest group and stands for about 19% of all antibiotics in both datasets. Table 5.4 and 5.5

The proportion of broad and narrow spectrum antibiotics used in hospitals varies greatly between counties, as seen in Figures 5.19-5.21. Only 6% of systemic antibacterials in hospitals in Uppsala County are penicillins V or G, whereas in Värmland County these substances represent 21%. Less variation is seen in sales of one of the most common broad spectrum substances, the fluoroquinolones, which constitute between 9% of all antibiotics in Skåne County to 14% in Södermanland County. After several years of decreasing use, the cephalosporins make up only 4% of antibiotics in Södermanland County. In Östergötland County the proportion is almost four times higher.

As seen in earlier figure 5.18 newer broad spectrum antibiotics such as carbapenems and piperacillin with tazobactam, represent a small but steadily growing proportion of the total use of antibiotics in hospitals. There are also great geographical differences. The proportion of carbapenems of all antibiotics in hospitals varies from 3% in Blekinge County to 8% in Östergötland County. Concerning piperacillin with tazobactam, sales vary from 4% in Halland County to 8% in Uppsala County, Figure 5.21.

TABLE 5.4. DDD/100 patient-days in somatic medical care in Swedish hospitals 2006-2012.

DDD/100 patient-days	2009	2010	2011	2012[a]
Tetracyclines (J01AA)	4.6	4.7	5.1	5.4
Penicillins with extended spectrum (J01CA)	5.9	6.1	6.5	6.7
Betalactamase sensitive penicillins (J01CE)	6.8	6.8	7.2	7.4
Betalactamase resistant penicillins (J01CF)	10.4	11.1	11.3	11.8
Combinations of penicillins (J01CR)	2.8	3.4	3.8	4.3
Cephalosporins (J01DB-DE)	7.4	7.2	6.8	6.6
Carbapenems (J01DH)	2.4	2.6	2.8	3.1
Trimethoprim (J01EA)	1.0	0.9	0.8	0.6
Trimethoprim with sulfonamides (J01EE)	2.0	2.1	2.3	2.2
Macrolides (J01FA)	0.9	0.9	1.1	1.0
Lincosamides (J01FF)	1.7	1.7	1.7	1.8
Aminoglycosides (J01GB)	1.0	1.1	1.2	1.2
Fluoroquinolones (J01MA)	5.9	6.1	6.2	6.2
Glycopeptides (J01XA)	0.8	0.8	0.9	0.9
Imidazole derivatives (J01XD)	1.4	1.3	1.2	1.1
Methenamine (J01XX05)	0.7	0.6	0.5	0.5
Linezolid (J01XX08)	0.1	0.1	0.1	0.1
All agents (J01)	56.5	58.0	60.1	61.6

[a]Denominator data from 2011.

TABLE 5.5. DDD/100 admissions in somatic medical care in Swedish hospitals 2006-2012.

DDD/100 admissions	2009	2010	2011	2012[a]
Tetracyclines (J01AA)	21.5	21.9	23.3	24.6
Penicillins with extended spectrum (J01CA)	27.7	28.2	29.6	30.8
Betalactamase sensitive penicillins (J01CE)	32.2	31.5	32.9	33.9
Betalactamase resistant penicillins (J01CF)	49.1	51.5	51.7	53.7
Combinations of penicillins (J01CR)	13.4	15.7	17.4	19.4
Cephalosporins (J01DB-DE)	34.8	33.7	31.3	30.1
Carbapenems (J01DH)	11.5	12.1	12.8	14.3
Trimethoprim (J01EA)	4.7	4.0	3.6	2.7
Trimethoprim with sulfonamides (J01EE)	9.6	9.9	10.4	10.3
Macrolides (J01FA)	4.1	4.1	5.0	4.4
Lincosamides (J01FF)	7.9	8.0	7.9	8.4
Aminoglycosides (J01GB)	4.8	5.1	5.3	5.7
Fluoroquinolones (J01MA)	27.8	28.5	28.4	28.3
Glycopeptides (J01XA)	3.6	3.7	4.1	4.1
Imidazole derivatives (J01XD)	6.4	6.0	5.5	5.1
Methenamine (J01XX05)	3.1	2.8	2.5	2.4
Linezolid (J01XX08)	0.3	0.4	0.3	0.4
All agents (J01)	266.5	269.9	274.6	281.2

[a] Denominator data from 2011.

Adverse reactions related to antibiotic use

Spontaneously reported drug-related adverse reactions are continuously entered into SWEDIS, a national database administered by the Swedish Medical Products Agency. The reports originate from health care professionals. The antibiotic related adverse reactions in the last five years, 2008-2012, 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=756), gastrointestinal disorders (n=286), hepato-biliary disorders (n=223), general disorders (n=174), blood disorders (n=131), neurological reactions (n=111), respiratory disorders (n=72), musculoskeletal disorders (n=69, and renal and urinary disorders (n=63).

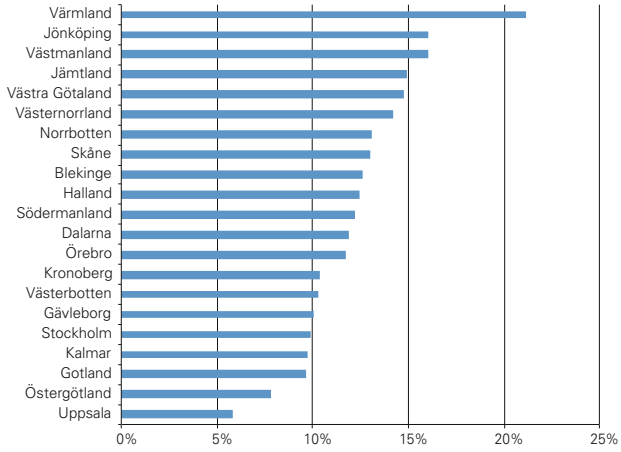


FIGURE 5.19. Percentage of narrow spectrum penicillins (penicillin V and G, J01CE) of all antibiotics in Swedish hospitals 2012, per county.

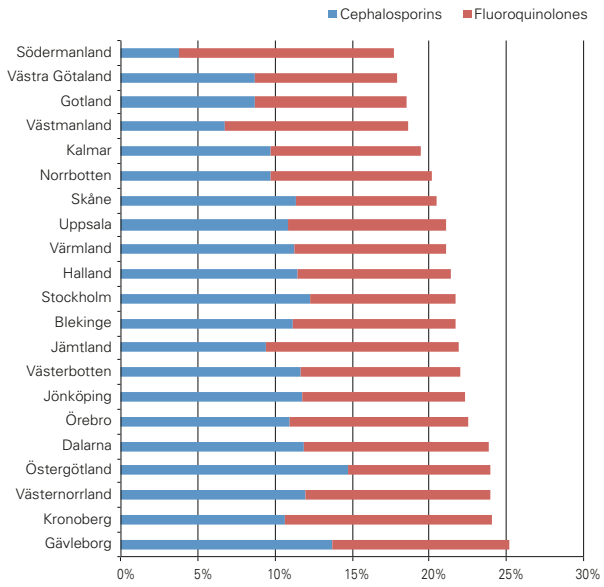


FIGURE 5.20. Percentage of broad spectrum antibiotics (cephalosporins, J01DB-DE, and fluoroquinolones, J01MA) of all antibiotics in Swedish hospitals 2012, per county.

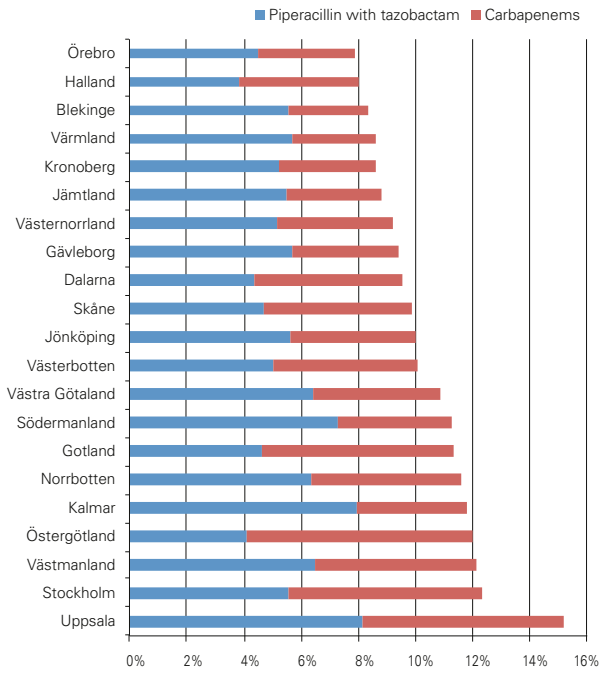


FIGURE 5.21. Percentage of carbapenems (J01DH) and piperacillin with tazobactam (J01CR05) of all antibiotics in Swedish hospitals 2012, per county.

The majority of the reports (59%) 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 5.6.

We have previously reported that amended treatment recommendations resulted in changed prescription patterns for uncomplicated urinary tract infections. There was a decreased consumption of fluoroquinolones which is reflected in a decrease in reported adverse events. For nitro-

TABLE 5.6. Most reported adverse drug reactions related to antibiotic agents to the Swedish Medical Products Agency 2008-2012.

Antibiotic	Total number of adverse drug reaction reports 2008 to 2012	Number of 'serious' reports	Number of fatal cases (causal relationship possible)
Flucloxacillin	147	88	6
Penicillin V	135	55	0
Nitrofurantoin	124	73	1
Trimethoprim with sulphonamides	115	65	1
Ciprofloxacin	110	62	4
Clindamycin	93	46	1
Doxycyclin	83	27	0
Amoxicillin	72	27	0
Piperacillin +tazobactam	68	34	2
Cefotaxime	56	33	0

TABLE 5.7 Number of most frequently spontaneously reported adverse events for fluoroquinolones and nitrofurantoin, during the period 2008 – 2012.

	2008	2009	2010	2011	2012	2008-2012
Fluoroquinolones (J01MA)						
Total no of reports	35	34	28	25	18	140
Number of reactions						
Musculoskeletal	9	10	5	6	6	36
tendinitis	2	3	3	2	2	12
tendon rupture	5	3	3	3	3	17
Skin- and subcutaneous tissue	4	8	11	6	4	33
Psychiatric disorders	4	2	1	3	3	13
Nitrofurantoin (J01XE01)						
Total no of reports	24	21	24	25	30	124
Number of reactions						
Respiratory system	7	9	6	4	14	40
dyspnoea	1	2	3	1	4	11
interstitial pneumonia	2	3	2	0	2	9
pulmonary fibrosis	0	0	0	0	3	3
Skin- and subcutaneous tissue	7	6	10	10	17	50
General disorders	7	7	10	8	8	40
fever	5	4	3	3	2	17

furantoin which was increasingly prescribed a weak trend of a corresponding increase in the reporting of adverse reactions was noted. Due to the low number of reports and to the fact that data are based on spontaneous reporting, no clear conclusions can be made regarding these trends, Table 5.7.

Use of antifungals

Antifungals in hospital care

For the first time since 2002 there has been a decrease in the total use of antifungal drugs for systemic use. Compared with 2011 the total consumption in 2012 decreased by 7%, yielding a national average of 60 DDD/one million inhabitants and day. Since the total use is very low, it is difficult to interpret whether this decrease represents a new trend in the use of antifungals in Sweden. Nevertheless there has previously been a small but steady increase in the use of antifungals for systemic use in Sweden for the past 12 years. In 2000 the total use was 40 DDD/ one million inhabitants and day, and this volume has increased almost every year, reaching the highest level in 2011 with 64 DDD/ one million inhabitants and day.

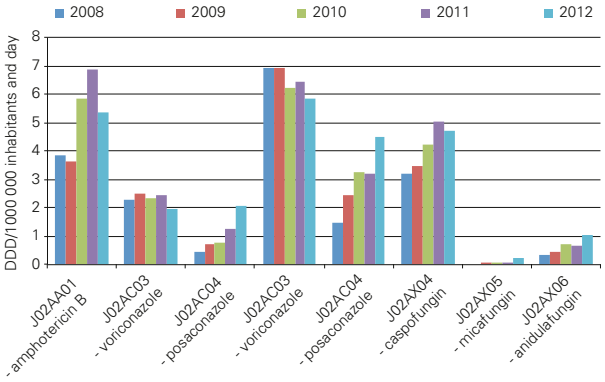
The figures vary between the different counties. Uppsala and Västernorrland, both counties with tertiary referral hospitals, have the highest consumption figures with an average of 136 DDD/ one million inhabitants and day. The lowest use was in Blekinge with 26 DDD/ one million inhabitants and day. Blekinge was also the county with the biggest decrease compared to 2011 - 40%.

Fluconazole still constitutes the absolute majority of the antifungals used, 70% or 42 DDD/ one million inhabitants and day. Amphotericin B and caspofungin are the two secondly most used compounds representing 8% and 7% respectively. The trend since 2000 shows that most of the described increase is due to an increased use of fluconazole. In the year 2000 the fluconazole use was 30 DDD/ one million inhabitants and day, representing 74% of the total use. Among antifungals with a broader spectrum, including both *Candida glabrata* and *Aspergillus sp* there has been a shift from amphotericin B that in year 2000 was the only broadspectrum antifungal available and constituted 20% of the total use, to the echinocandins that as a group today have 10% of the market.

Among the azoles with broad spectrum there has been a shift from itraconazole that in 2000 represented 3% of all antifungals to voriconazole and posaconazole that in 2012 has a marketshare of 7%. In 2012 itraconazole was hardly used at all.

Fluconazole which is a narrow spectrum antimycotic with effect towards candida species (excluding among others *C. krusei* and most strains of *C. glabrata*) stands for 70% of all consumption. It is a fungiostatic drug that is indicated for treatment of invasive non *krusei*, non *glabrata* candidosis in non neutropenic patients and for cryptococcosis. It is also used as prophylaxis against candida infection and as treatment for local infections such as thrush.

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



FIGUR 5.22. Use of broad spectrum antifungals in hospital care, 2008-2012, DDD/1000 000 inhabitants day.

which is an emerging pathogen in Sweden and now constitutes approximately 20% of all episodes of candidemia. *C.krusei* is always resistant.

The use of voriconazole is low in absolute numbers (1.94 DDD/ one million inhabitants and day), and the use decreased by 20% the last year, Figure 5.22. The total use in outpatient settings is three times higher and the absolute majority of voriconazole therapy is initiated and monitored by hospital physicians, so it is probably more correct to confer those data to hospital use rather than primary health care use. The amount of voriconazole on prescription has also decreased by approximately 20%.

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

Posaconazole can also be given orally, as a suspension, but in Sweden it is only licensed as second line therapy for invasive fungal infection refractory to the first line treatment and as prophylaxis, so it is mainly used as prophylaxis in haematologic units. The total use has increased by 162% since 2010 and now bypasses voriconazole. The total amount is still low 2.1 DDD/ one million inhabitants and day, Figure 5.22, and 4,5 DDD/ one million inhabitants and day are used 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 use of the echinocandins. In 2012 the use increased by 5%, making the total amount 6.0 DDD/ one million inhabitants and day, and the group now constitutes 10% of all systemic antifungals used in hospitals, making the echinocandin as a group the most commonly used broadspectrum antuifungal drug in Swedish hospitals. Caspofungin which has been available in Sweden since 2002 is the most commonly used (78%). Anidulafungin increased its share from 12% to 18% last year and the third member of the group micafungin has for the first year appeared in the statistics and constitutes 4% of the total echinocandin use. Micafungin has been used extensively in North America, Japan and many European countries for many years, but until 2012 it was hardly used at all in Sweden due to pre-clinical reports of an increased risk of livertumors in rats. The echinocandins have a fungicide effect against candida species and a fungiostatic effect against *Aspergillus fumigatus*. Therefore those agents are increasingly used as first line therapy for patient with febrile neutropenia when antibiotics alone have not been successful and when there is a suspicion of infection with yeasts or mold. Both indications and side effects differ a little between the different agents but the antifungal spectrum is similar.

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 amfotericin B is now mostly used in its liposomal form, which improves tolerability. The use has remained at the same level from 2005-2009 but increased substantially by 60 % during 2010, followed by an 18% increase in 2011. In the year 2012 the use decreased by 24%, Figure 5.22.

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

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

Antifungals in outpatient care

70% of all systemically administrated antifungal drugs are sold on prescription. The majority of those prescriptions took place in primary health care. The most commonly prescribed drug is fluconazole, mainly for mucocutaneal infections.

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

Data comparing sales of antimycotic drugs between different countries are rare but recently ESAC published comparative data from different European countries, showing that the Swedish figures of sale are comparably low.

Use of antimicrobials for animals

Statistics on total sales of antimicrobials for use in animals in Sweden are available since 1980. For a review of data from 1980-2000, see SVARM 2000. Data are derived from sales statistics and represent an approximation of the real use of antimicrobials, assuming that the amount sold is also used during the observation period. Details on data source and inclusion criteria are given in Appendix 2.

Trends in animal populations

Changes in the numbers of animals may affect trends in statistics on use of antimicrobials. The number of pigs slaughtered has decreased by 9% from 2011 to 2012 and by 15% in five years, while the number of broilers was 2% higher in 2012 than in 2008. The numbers of dairy and beef cows have decreased by 3 and 2%, respectively, in five years. The number of horses was 349 000 in 2010, an estimated increase by 10-20% since 2004. The number of dogs was 784 000 in 2012 and 729 000 in 2006. Further details on animal numbers are found in Appendix 1.

Completeness of data

The data coverage for products with general Swedish marketing authorisation is assumed to be 100%. Before 2011, data also covered most antimicrobial products sold with special licence (prescribed and sold on exemption from general Swedish marketing authorisation). In 2011, data coverage for these products was deemed to be somewhat incomplete (see SVARM 2011). From 2012 no information on sales of these products can be retrieved from the database of Apotekens Service. Efforts have been made to obtain information on sales of major products sold with special licence to the Swedish market (see Appendix 2). The data extracted from the database of Apotekens Service has thereby been complemented with a total of 1 166 kg active substance sold on special licence. Considering previous sales of these products, the data coverage after correction is probably ≥98% of the true total amounts expressed as kg active substance.

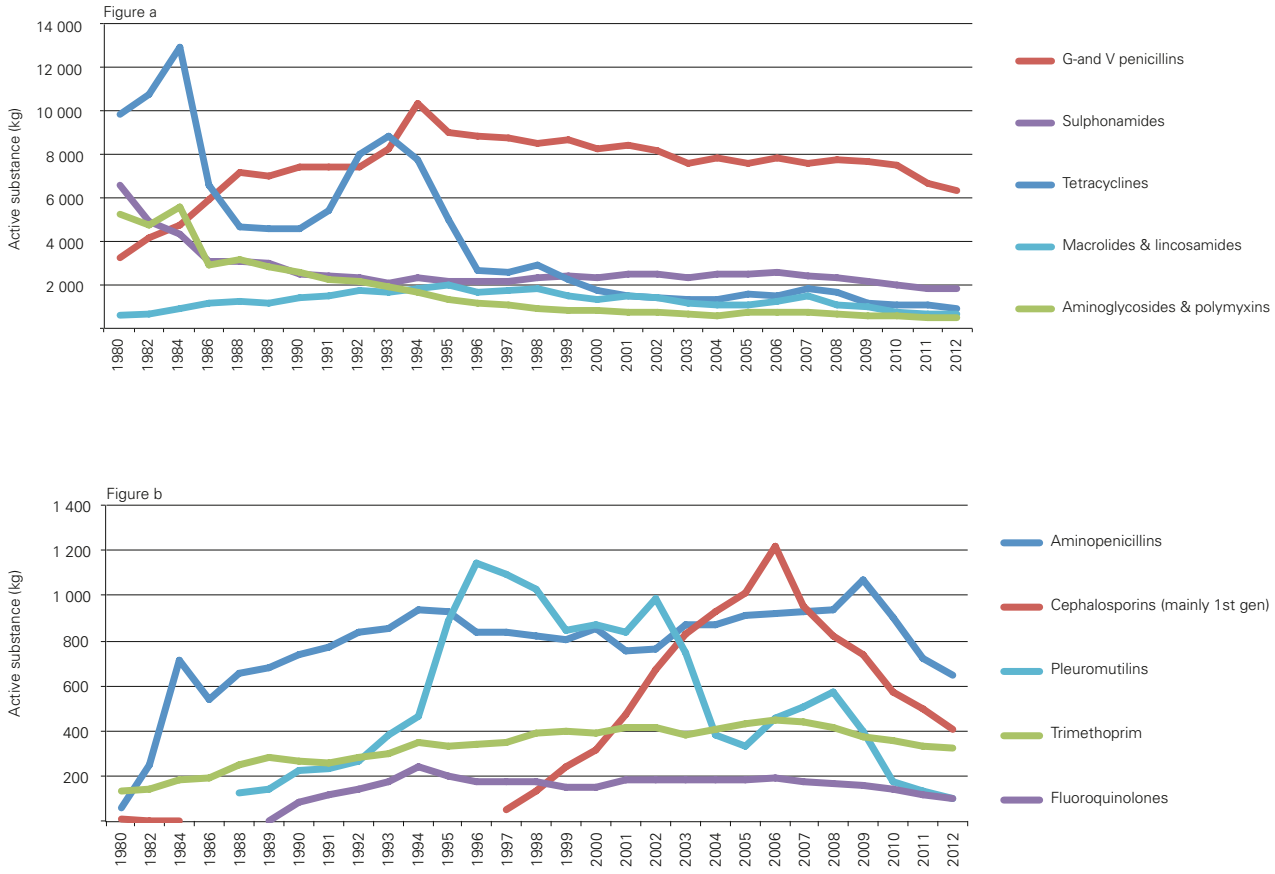


FIGURE 5.23. a&b. Sales of antimicrobials for animals. Nitroimidazoles, streptogramins, quinoxalines and other feed additives were withdrawn from the market during the time period and are not shown. Note that the scales on the Y-axis are different in figure a and b. For 2011, data on products sold with special licence with penicillins, tetracyclines and aminopenicillins may be incomplete.

Overall use

The total yearly sales of antimicrobials over the last decade are presented in Table 5.8. The potency of different antimicrobials is not equal and therefore each class should be evaluated separately. Trends in sales of individual classes from 1980 are shown in Figure 5.23. Of the total sales expressed as kg active substance, about 90% are products formulated for treatment of individual animals (injectables, tablets, intramammaries) and about 10% for treatment of groups or flocks (premixes, oral powders, solutions for in water medication).

To correct for changes in the numbers of animals over time, the population correction unit (PCU) described in a recent publication from the European Medicines Agency was applied (EMA 2011). The PCU is a purely technical term representing an approximation of the summed live-weight of the major animal populations, excluding companion animals. In Figure 5.24, the total sales of antimicrobials for animals (including sales for companion animals) from 1980 are presented as mg active substance per PCU. The overall sales have decreased by almost 60% compared to the average figures for 1980-1984 (*i.e.* before the Swedish ban on growth promoting antimicrobials in 1986). This is explained both by the removal of growth promoting antimicrobials in 1986 and by a major gradual decrease from the mid 90s of the sales of veterinary products for medication via feed or water (group medication). A decrease by about 26% since 2008 can be noted.

In Table 5.9, the sales of products for use in individual animals, excluding topical, intrauterine and intramammary use are presented. The sales of all classes have decreased in the last five years. The cephalosporins (almost entirely first generation cephalosporins) have decreased by 50% in

TABLE 5.8 Yearly sales of antimicrobial drugs for veterinary use expressed as kg active substance. For some classes data on sales of products sold with special licence may be incomplete for 2011 (indicated in red).

ATCvet code	Antimicrobial class	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
QJ01AA, QG01A	Tetracyclines[a]	1 307	1 329	1 562	1 516	1 853	1 649	1 174	1 115	1 073	881
QJ01BA	Amphenicols										<1
QJ01CE, -R, QJ51	Benzylpenicillin[a,b]	7 579	7 814	7 571	7 860	7 582	7 758	7 721	7 546	6 696	6 362
QJ01CA, QJ01CR	Aminopenicillins[a]	870	875	911	920	927	938	1 068	907	723	649
QJ01D	Cephalosporins	832	928	1 009	1 217	954	820	738	575	498	410
QA07AA, QJ01G, -R, QJ51R	Aminoglycosides and polymixins[a]	645	606	62	750	718	643	609	557	503	483
QA07AB, QJ01E	Sulphonamides[a]	2 326	2 462	2 535	2 543	2 427	2 303	2 128	1 998	1 867	1 812
QJ01E	Trimethoprim & derivatives	381	406	437	450	438	416	379	357	338	329
QJ01F	Macrolides & lincosamides	1 124	1 095	1 080	1 254	1 520	1 096	988	739	648	632
QJ01MA	Fluoroquinolones	184	187	184	195	180	169	164	148	120	106
QJ01XX92, - 94	Pleuromutilins	744	387	338	459	506	572	398	174	140	99
Total		15 992	16 089	16 389	17 164	17 106	16 364	15 368	14 117	12 606	11 763

[a] Includes drugs marketed with special licence prescription; [b] Also includes small amounts of penicillinase stable penicillins.

TABLE 5.9 Yearly sales of antimicrobial drugs authorised for individual treatment expressed in kg active substance. Only products for systemic use (QJ01) or for use as intestinal anti-infective (QA07) are included. For some classes, data on sales of products sold with special licence may be incomplete for 2011 (indicated in red)[a].

ATCvet code	Antimicrobial class	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
QA07A	Intestinal anti-infectives	594	586	496	434	372	364	355	302	280	274
QJ01A	Tetracyclines	606	611	623	609	632	605	576	538	520	471
QJ01A	Amphenicols										<1
QJ01CE	Benzylpenicillin[b]	7 536	7 769	7 493	7 777	7 504	7 671	7641	7 492	6 627	6 290
QJ01CA -CR	Aminopenicillins	870	875	911	909	899	828	802	742	742	644
QJ01D	Cephalosporins	832	928	1 009	1 212	950	817	735	575	575	410
QJ01E	Sulfonamides & trimethoprim	2 280	2 427	2 610	2 689	2 619	2 486	2 270	2 138	2 023	1 951
QJ01F	Macrolides & lincosamides	430	382	400	417	413	352	332	311	311	273
QJ01G	Aminoglycosides[b]	367	344	362	345	343	318	301	274	272	210
QJ01M	Fluoroquinolones	177	180	179	190	177	164	159	144	118	101
QJ01X	Pleuromutilins	77	32	29	39	36	36	28	17	13	14
Total		13 769	14 134	14 112	14 622	13 944	13 640	13 1 98	12 532	11 300	10 656

[a]Drugs marketed with special licence prescription include formolsulfatiazole and neomycin (QA07A) and benzylpenicillin,(QJ01CE); [b] The amount includes substances from QJ01R.

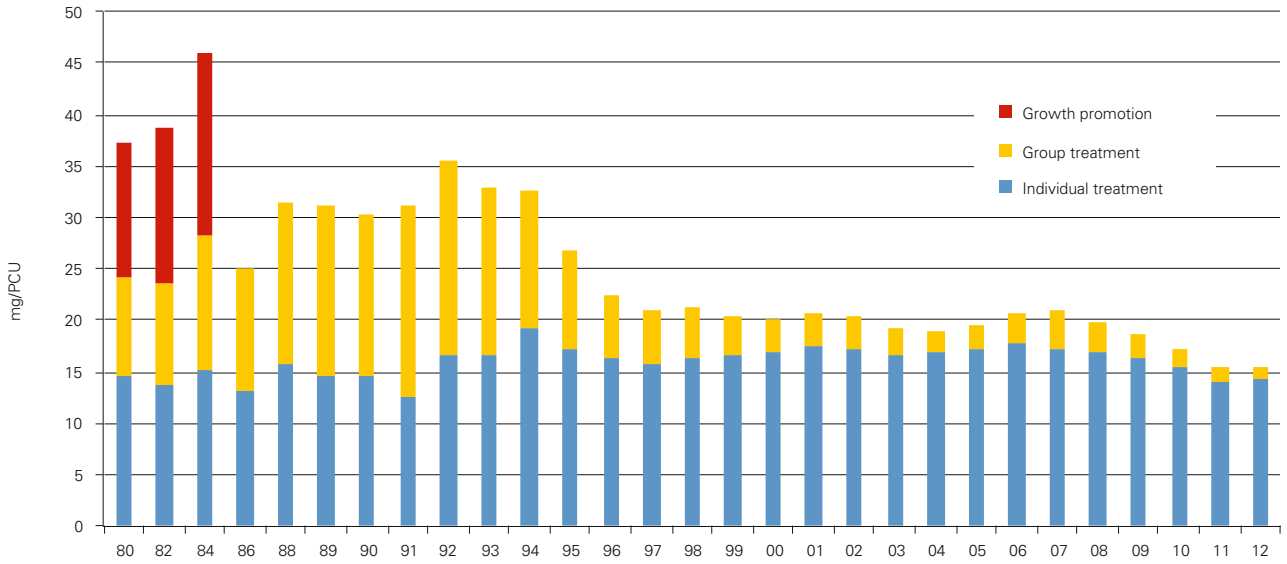


FIGURE 5.24. Sales of antimicrobials for animals expressed as mg per population correction unit (PCU)

TABLE 5.10. Yearly sales of antimicrobial drugs authorised for group treatment and ionophoric anticoccidials sold expressed as kg active substance. For some classes, data on sales of products sold with special licence may be incomplete for 2011 (indicated in red)[a].

ATCvet code	Antimicrobial class	1984	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
QA07A	Intestinal anti-infectives[a]				163	170	158	106	107	119	77	75
QJ01A	Tetracyclines	12 300	695	712	934	903	1 217	1 040	594	575	552	408
QJ01C	Penicillins incl. aminopenicillins					11	28	111	266	164	36	5
QJ01F	Macrolides & lincosamides	607	694	713	680	837	1 107	744	657	427	361	359
QJ01MA	Fluoroquinolones		8	7	5	5	3	5	5	4	2	6
QJ01MQ	Quinoxalines[b]	9 900										
QJ01XX91	Streptogramins[c]	8 800										
QJ01XX92, -94	Pleuromutilins		667	355	309	420	471	536	370	157	127	85
QP51AA	Nitroimidazoles	1 440										
	Feed additives[d]	700										
Total		33 747	2 064	1 787	2 091	2 346	2 984	2 543	1 999	1 447	1 154	937
QP51AH	Ionophoric antibiotics (coccidiostats)[d]	7 900	10 920	10 486	11 095	12 335	12 527	13 376	12 471	15 325	14 693	NA[e]

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

5 years, almost entirely related to decreased prescription of first generation cephalosporins for dogs. The sales of fluoroquinolones for therapy of individual animals have decreased by 39% since 2008. This is explained both by a marked decrease in sales of fluoroquinolones for oral use in dogs and cats (36% decrease of that subset) and of products for injection (42% decrease of that subset).

Data on sales of antimicrobials formulated for medication of groups of animals are given in Table 5.10. Data for 1984 are given as historical reference. As noted above, data on products sold with special licence is somewhat incomplete for 2011 which hampers assessment of trends of some classes. Today, the sales of products for medication of groups of animals are less than 10% of what it was on average before 1986 (counting the sum of veterinary medicines and growth promoters). For further comments see pig and poultry below.

Comments on trends by animal species

Dairy cows

The Swedish Dairy Association publishes a yearly report related to the organization's work to improve animal health and welfare in dairy cows (Swedish Dairy Association, 2012). For statistics on incidence of antimicrobial treatments of dairy cows enrolled in the Swedish milk recording scheme, data are retrieved from a database with veterinary reported disease events and treatments (Jansson Mörk, 2010).

The by far most common indication for treatment of dairy cattle is mastitis, 71% of all recorded treatments. In Sweden, mastitis is generally treated systemically and any changes in treatment incidence, treatment length or choice of antimicrobial for this condition will have a noticeable influence on the statistics on sales of antimicrobials. The reported inci-

dence of clinical mastitis in dairy cows has decreased over the last five years and was 11.2 per 100 completed/interrupted lactations in 2010/11. Treatment with penicillin was by far the most common (85%), and the decreased incidence of clinical mastitis tallies with a decrease in sales of penicillins for systemic use (Table 5.9).

In the sales statistics from pharmacies, 7 kg of third generation cephalosporins and 56 kg of fluoroquinolones were recorded as sold for cattle or unknown animal species. This represents a decrease since 2008 by 70 and 43%, respectively.

Pigs

In 2008 and 2012 the sales of antimicrobials for pigs were 4 150 and 3 118 kg active substance, respectively, or 15.3 and 13.3 mg/kg slaughtered pig (-13% in 5 years). Two thirds of the total sales in kg active substance were products for injection, and of those 62% were products containing penicillin. The sales of fluoroquinolones for pigs were 12 kg in 2012, 32% lower than in 2008. The sales of third generation cephalosporins were insignificant (0.01 kg).

In Sweden, products formulated for group medication are mostly used for pigs (Table 5.10). There has been an overall decrease by 50% of sales in mg/PCU of such products for pigs since 2008. The sales in mg/PCU of pleuromutilins have decreased since the mid 90s and were 82% lower in 2012 than in 2008. The main indication for pleuromutilins (tiamulin, valnemulin) is swine dysentery. Efforts to control the disease through *e.g.* eradication from affected farms and a certification programme have resulted in a decreased need to treat swine dysentery, reflected in overall declining sales figures (Figure 5.23). The continued drop in sales of macrolides for group medication (Table 5.10) 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.

Poultry

Antimicrobials are rarely used for treatment of bacterial diseases in commercially reared *Gallus gallus.* Localized outbreaks can therefore have a major influence on the sales in a specific year. Over the last five years, the yearly sales of fluoroquinolones for slaughter chickens and hens have been below or much below 1.5 kg and in 2012 there were no sales of this class for broiler. 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, only one of 2 853 broiler flocks (<0.1%) was treated with antimicrobials (amoxicillin). In addition to this, four flocks of parent or grandparent birds were treated, (three with fenoximethylpenicillin and one with amoxicillin). These figures are well in line with the sales statistics, keeping in mind that all the quantity sold will not be used.

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

Horses

Around two thirds of the sales of trimethoprim-sulphonamides are products for oral use in horses (paste or powder). The sales of such products increased steadily until 2007 but since, there has been a decrease by 28%. Over the same time period, the total number of horses has increased but the number of mares covered has decreased by about 30% (Anonymous 2012). Among the indications for trimethoprim-sulphonamides in horses are reproductive disorders and various conditions in foals. Thus, it is probable that the decrease in sales of trimethoprim-sulphonamides is explained by the lower number of mares covered and a lower number of foals born.

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

Dogs

In 2006, the total sales of antimicrobials for oral use in dogs corresponded to 563 packages per 1000 dogs. Since then, the sales have decreased to 330 packages per 1000 dogs (-42%). The dataset includes products authorised for oral use in animals (ATC vet code QJ01 and QA07) as well as for humans (ATC code J01) and corresponds to out-patient use for dogs.

In figure 5.25, the sales of the major classes of antimicrobials expressed as packages per 1000 dogs are shown. The most prominent changes relative to 2006 are noted for cephalosporins (-70%), aminopenicillins with clavulanic acid (-52%), and fluorquinolones (-51%).

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

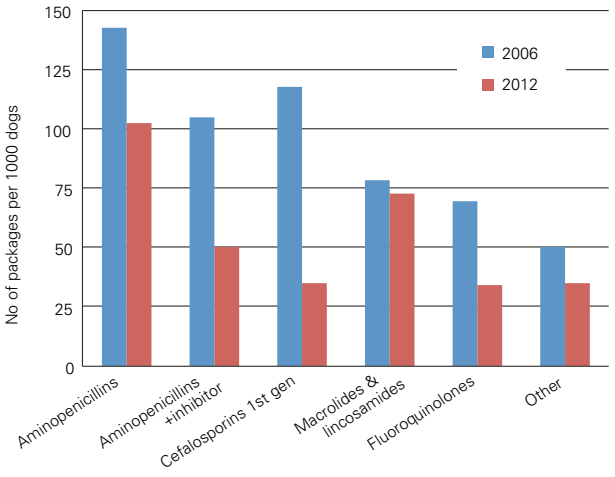


FIGURE 5.25. Sales of antimicrobials for oral use in dogs (QJ01, QA07 and J01) by class in 2006 and 2012 expressed as number of packages per thousand dogs.

Comparison of antimicrobial use in human and veterinary medicine

Data included and calculations

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

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

Comparison of use in tonnes active substance

In total, 64.9 and 11.6 tonnes of antimicrobials in included ATC classes were sold for use in humans and veterinary medicine, respectively. Figure 5.26 displays the sales of beta-lactam antibiotics. These substances are by far the most used antimicrobials in both human and veterinary medicine and also represent the largest amounts measured as kilograms. Penicillins represent most of the weight of antibiotics for both humans and animals; approximately 80 and 60% respectively. The substances shown in Figure 5.27 are sold in much 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 on the environment is probably more pronounced than that of the beta-lactams. In the figures, only antimicrobials sold in a total quantity exceeding 1000 kg during 2012 are included. The only class where use in animals outweighs human use is trimethoprim-sulphonamides, of which two thirds are sold for horses.

Comparison of use expressed as mg substance per kg body mass

When measuring the total antibiotic use in relation to estimated kg body mass in 2012, the sales were 103.7 and 15.3 mg per kg body mass in human and veterinary medicine, respectively. In Figure 5.28 a comparison of sales of antimicrobials for use in humans and animals are shown expressed as mg per kg body mass. Only classes where the total sales exceeded 1000 kg active substance are shown. Data on the total use does not take the heterogeneity of the likelihood of exposure within the population into account. This is especially true for data on sales for animals, as certain substances may only or mainly be sold for use in one particular animal species. This means that the selective pressure in a particular subset of the population (*i.e.* a particular animal species) can be far larger than in the total population. Nevertheless, in Figure 5.28 the largest difference is noted for the fluoroquinolones where use in humans is 36 times higher than in animals. For cephalosporins of the third and fourth generation, the corresponding figure was 70 times (data not shown).

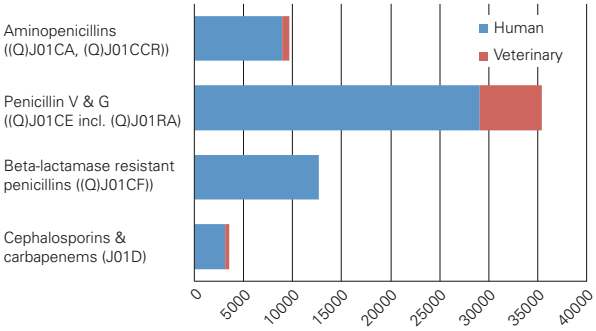


FIGURE 5.26. Amount of beta-lactam antibiotics in human and veterinary medicine, kg active substance, 2012. Please note the difference in indexation of the x-axis between figures 5.26 and 5.27.

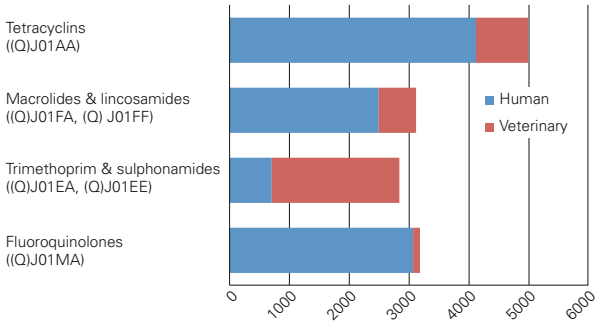


FIGURE 5.27. Amount of fluoroquinolones, macrolides, lincosamides, trimethoprim and sulphonamides, and tetracyclins in human and veterinary medicine, kg active substance, 2012. Please note the difference in indexation of the x-axis between Figures 5.26 and 5.27.

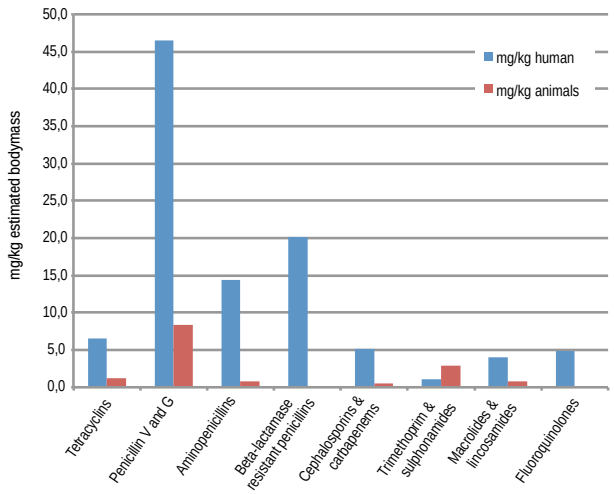


FIGURE 5.28. Use of antimicrobials in humans and animals expressed as mg active substance per kg body mass in 2012.

6. Occurrence of antimicrobial resistance

Antimicrobial resistance as notifiable diseases

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

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

In the following each of these bacterial pathogens are described.

ESBL-producing Enterobacteriaceae

ESBL-producing Enterobacteriaceae in humans

Background

In February 2007 ESBL-producing Enterobacteriaceae became notifiable by clinical laboratories according to the Communicable Disease Act. As no clinical data is available, information on ESBL cases is restricted to data on age, gender and cultured material. In 2007, an action plan with the aim to keep the proportion of *Escherichia coli* and *Klebsiella pneumoniae* producing ESBL in blood isolates as low as possible, and also in urine cultures in order to maintain the current treatment recommendations for lower urinary tract infections was presented. In 2009, a supplement to the action plan was published where the definition of ESBL was broadened (http://www.smittskyddsinstitutet.se/upload/Publikationer/antibiotika-och-vardhygien/implementering-av-en-ny-ESBL-definition.pdf). Valid from 2010, the definition of an ESBL included not only classical ESBLs (=$ESBL_A$), which are inhibited by clavulanic acid, but also plasmid-mediated AmpC-betalactamases (= $ESBL_M$) and metallo-betalactamases / carbapenemases (= $ESBL_{CARBA}$). In March 2012 the notifications of bacteria with $ESBL_{CARBA}$ were extended to include both a laboratory and a clinical report, coupled to a demand for contact tracing by the local authorities. An updated version of the action plan will be published in 2013.

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

A total of 7225 cases were notified in 2012, an increase with 28% compared to 2011. The increased incidence was seen in all Swedish counties, with the highest incidence found in Jönköping county (142 cases per 100 000 inhabitants; Figure 6.1).

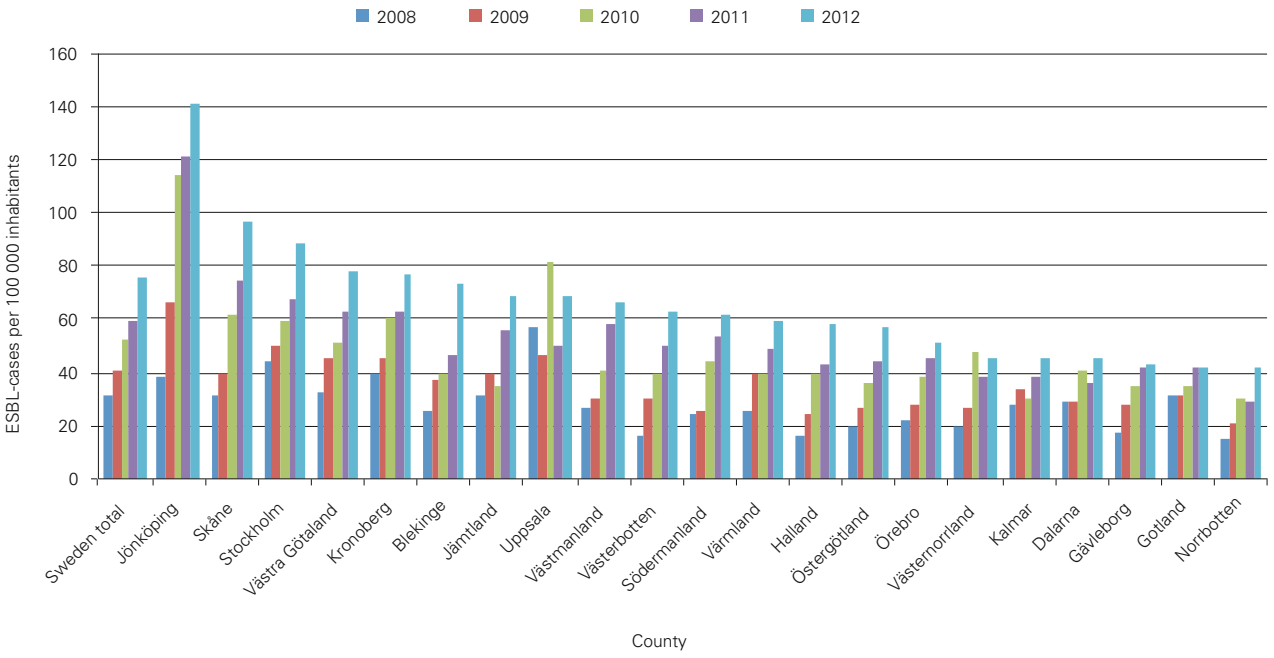


FIGURE 6.1. The incidence (cases per 100 000 inhabitants) of ESBL-producing Enterobacteriaceae in Swedish counties 2008-2012, arranged according to incidence figures 2012.

TABLE 6.1. Distribution of species among cases of ESBL-producing Enterobacteriaceae 2012.

Species	Number of cases
Escherichia coli	6538
Klebsiella pneumoniae	522
Citrobacter species	62*
Proteus mirabilis	36
Salmonella species	12
Enterobacteriaceae (not specified or species not reported)	284*
Total number reported	7454**

* Distinction between an ESBL and a chromosomally mediated AmpC was not made for these bacteria

** In 215 patients two or more ESBL-producing species were reported resulting in a higher number of isolates than number of cases reported.

The most commonly reported species was *Escherichia coli* with 88% of all cases, followed by *Klebsiella pneumoniae* with 7% (Table 6.1). Twelve cases of *Salmonella* species with ESBL were reported in 2012.

ESBL-producing bacteria were most often found in urine samples (60%). The second most common source was faecal samples with 16%. Isolates from rectum and wound samples constituted 8% and 3%, respectively, and blood isolates 4% of the cases. Invasive infections with ESBL-producing bacteria, all in blood, were notified in 390 persons during 2012, as compared to 312 persons in 2011. Among these, 337 were new cases for 2012 and 53 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.

The incidence in age groups and gender differed between species (Figure 6.2). ESBL-producing *E. coli* were derived from women in 67% of all *E. coli* cases. They had a median age of 52 years compared to 62 years for men. The *K. pneumoniae* ESBL cases were equally distributed between sexes, with median ages of 61 years for women and 62 years for men.

According to the national point-prevalence studies performed in 2007, 2009 and 2011 (SWEDRES 2011), ESBLs of CTX-M-type (=$ESBL_A$) dominated (> 90%).

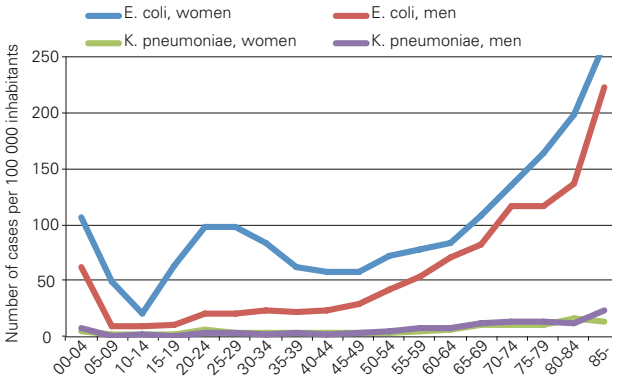


Figure 6.2. Age and gender distribution of *E.coli* and *K. pneumoniae* ESBL cases 2012

Isolates with plasmidmediated AmpC (=$ESBL_M$) were also found in 5-8% of these consecutively collected isolates. ESBL-producing isolates were often multiresistant, *i.e.* resistant to several other antibiotics, seriously limiting the options for treatment.

ESBL-producing Enterobacteriaceae in animals

Farm animals

In SVARM, active screening for ESBL-producing *E. coli* in healthy production animals is regularly performed using samples collected for the studies of indicator bacteria. During 2012, caecal samples from healthy broilers (n=200) and healthy laying hens (n=69) and in addition samples of broiler meat (n=97), were screened for *E. coli* resistant to third generation cephalosporins by selective culture on media supplemented with cefotaxime. Isolates with reduced susceptibility were further investigated by molecular methods.

$ESBL_A$ or $ESBL_M$, *i.e.* classical ESBLs and plasmid-mediated AmpC, respectively, were detected in 97 (49%) of the caecal samples from broilers, in 9 (13%) of the caecal samples from laying hens, and in 40 (41%) of the broiler meat samples (Table 6.2). Also, one isolate of indicator *E. coli* from laying hens obtained from non selective culture was resistant to third generation cephalosporins. This isolate carried the gene bla_{CMY-2} (=$ESBL_M$).

All isolates with $ESBL_A$ or $ESBL_M$ from broilers, broiler meat, and laying hens were susceptible to meropenem (MIC 0.008 – 0.016 mg/L).

TABLE 6.2. Occurrence of *Escherichia coli* resistant to third generation cephalosporins in healthy broilers, laying hens, dairy calves, and broiler meat, 2012.

Animal species	Sample material	No. of samples	No. of resistant isolates	No. of $ESBL_A$ / $ESBL_M$	Responsible beta-lactamase
Broilers	Caecal content	200	102	0 / 97	CIT[b] (n=97)
Broilers	Meat	97	41	0 / 40	CIT[b] (n=40)
Laying hens[a]	Caecal content	69	11	3 / 6	CMY-2 (n=6) CTX-M-1 (n=3)
Dairy calves[a]	Rectal swab	742	81	5 / 4	CTX-M-1 (n=1) CTX-M-15 (n=4) CMY-2 (n=4)

[a] Samples from laying hens were collected from October 2012 to January 2013 and samples from dairy calves from October 2011 to November 2012;
[b] All isolates from broilers or broiler meat with a CIT-group enzyme in previous years possessed the gene bla_{CMY-2}.

The proportion of samples from broilers and broiler meat positive for $ESBL_A$ or $ESBL_M$ was comparable to data from previous years. There are no previous data on occurrence of $ESBL_A$ or $ESBL_M$ in laying hens in Sweden. Most likely, the occurrence of $ESBL_A$ and $ESBL_M$ among poultry in Sweden is due to introduction via imported animals for breeding purposes, and efforts are being made to improve the situation.

In addition to the screening for *E. coli* resistant to third generation cephalosporins described above, data on the presence in dairy calves was obtained via an ongoing research project using similar methods as in SVARM. In this project, rectal swabs from 742 calves aged 7-28 days from 249 farms were cultured. $ESBL_A$ or $ESBL_M$ was detected in 9 (1%) of the samples (Table 6.2). These are the first described findings of ESBL-producing *E. coli* from calves in Sweden.

Enterobacteriaceae with carbapenemases ($ESBL_{CARBA}$), the most recent threat

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

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

The total number of cases with an $ESBL_{CARBA}$-producing Enterobacteriaceae in 2012 was 23. Cases were reported from seven Swedish counties but more than half of the cases were reported from Stockholm and Skåne counties. Seventeen cases were reported as acquired abroad and 16 of those were healthcare related. Three cases were reported as domestic, and were related to healthcare or care outside the hospital. Two of these cases had clinical symptoms and one was found by contact tracing. The majority of the imported cases were detected through targeted screening (15) and two due to clinical symptoms. For one patient no country of acquisition could be given. This case was detected through contact tracing.

The $ESBL_{CARBA}$-producing Enterobacteriaceae were mostly detected in fecal (6) or urine samples (6).Two isolates each were from rectum, wound and blood samples. The distribution between sexes was even and the median ages were 66 and 61 years for women and men, respectively.

A total of 58 $ESBL_{CARBA}$ –producing isolates were identified in Sweden in 2007-2012. *K.pneumoniae* have dominated, but in 2012 isolates of *E. coli* accounted for half of the cases (Figure 1). Four different types of $ESBL_{CARBA}$ have been identified so far, and the enzyme types OXA-48 and NDM dominated in 2012 (Figure 2). Both these types of enzymes appeared in *E. coli* and *K.pneumoniae* isolates and in most cases together with CTX-M (=$ESBL_A$) and/or pAmpC CIT (=$ESBL_M$) enzymes. Countries from the Middle East were often mentioned in relation to OXA-48, and the Indian subcontinent in relation to NDM. All isolates with $ESBL_{CARBA}$ were multiresistant, leaving very few options for treatment.

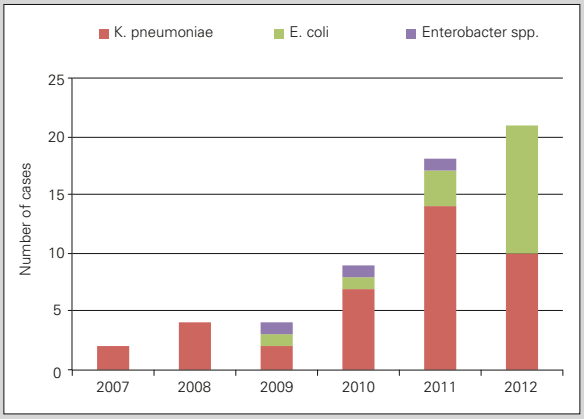


FIGURE 1. Bacterial species of Enterobacteriaceae carrying $ESBL_{CARBA}$ in Sweden 2007-2012.

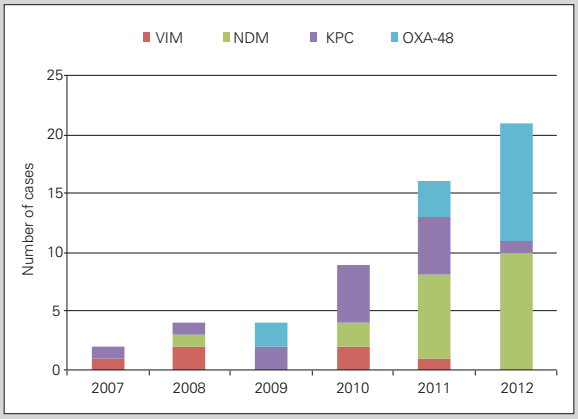


FIGURE 2. Numbers and types of $ESBL_{CARBA}$ in Enterobacteriaceae in Sweden 2007-2012.

TABLE 6.3. Bacterial species of Enterobacteriacae isolated from cats, dogs and horses, producing $ESBL_A$ or $ESBL_M$ enzymes. Isolates from clinical samples, with phenotypic resistance to third generation cephalosporins, were submitted 2008-2012.

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

[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.

Companion animals and horses

During 2012, a total of 23 isolates of Enterobacteriaceae with phenotypic resistance to third generation cephalosporins from cats (n=3), dogs (n=15) and horses (n=6) were submitted to the Section of Antibiotics, SVA for further analysis. The majority were isolated from wounds or from the urogenital tract. Eighteen of the isolates were confirmed to produce $ESBL_A$ or $ESBL_M$ and are presented in Table 6.3 together with isolates from previous years.

In addition, in a research project using similar methods as in SVARM, healthy dogs were screened for *E. coli* resistant to third generation cephalosporins. In this project rectal swabs from 84 healthy dogs were cultured and one isolate with $ESBL_M$ (CIT group) was detected.

Considering the low number of isolates producing $ESBL_A$ and $ESBL_M$ submitted to SVA, the prevalence appears to be low. However, since isolates producing $ESBL_A$ or $ESBL_M$ from companion animals are generally multiresistant, they pose a challenge for the veterinarian in the clinical situation when the animal needs antibacterial treatment. Increased awareness of the need for infection control and antimicrobial stewardship is essential to minimize the spread of these resistant bacteria.

ESBL-producing Enterobacteriaceae, zoonotic aspects

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

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. Furthermore, a recent Swedish study (summarized in "No indication of spread of *Escherichia coli* carrying bla_{CMY-2} from broilers to human clinical settings"), investigating the potential overlap between clinical human isolates and isolates from healthy broilers concluded that the overlap was limited and restricted to similar plasmids, and that no closely related *E. coli* carrying $ESBL_M$ isolates were identified (Börjesson et al., 2013).

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

No indication of spread of *Escherichia coli* carrying bla_{CMY-2} from broilers to human clinical settings

During the last couple of years studies have concluded that broiler production is a potential reservoir for ESBL and pAmpC-producing Enterobacteriaceae in human clinical settings (Leverstein-van Hall et.al., 2011). Furthermore, The European Food Safety Authority (EFSA) concluded in a recent report that there is indirect evidence for transmission of ESBL- and pAmpC-producing Enterobacteriaceae and the corresponding genes between farm animals, especially broilers, and humans (EFSA 2011). Due to the high occurrence of foremost pAmpC producing *E. coli* in the Swedish broiler production, we investigated if there was an overlap between isolates from broilers and human clinical isolates. To establish the relatedness between human and broiler isolates a selection of bla_{CMY-2} -containing *E. coli* isolates from intestinal content of broilers in Sweden and isolates from human clinical isolates were characterised using both genotypic and phenotypic methods.

Twenty-two *E. coli* isolates obtained from a screening programme described in SVARM 2010 were characterised using MLST, PFGE, PCR based plasmid replicon typing and for antimicrobial susceptibility using VetMIC GN-mo plates. The plasmid carrying the bla_{CMY-2} was identified using conjugation and/or transformation with subsequent PCR-based plasmid replicon typing, and the size of the plasmid was determined by nuclease-S1 treatment and PFGE. In addition, 72 human clinical isolates carrying bla_{CMY-2} collected by the Swedish Institute for Communicable Disease Control (SMI) from clinical laboratories were selected to mirror the sampling period for the broilers, and 6 isolates from a point prevalence study in 2009 were also included. The human clinical isolates were screened for the plasmid replicon type identified to carry the bla_{CMY-2} in broiler isolates and isolates that tested positive were subjected to PFGE, PCR based plasmid replicon typing and antimicrobial susceptibility testing. To identify the plasmid carrying bla_{CMY-2} in human clinical isolates, transformation was performed with subsequent PCR-based plasmid replicon typing and the size of the plasmid was determined by nuclease-S1 treatment and PFGE.

The broiler isolates belonged to 11 STs, with ST10, ST68 and ST2167 (4 isolates, respectively) being the most common. Ten isolates were resistant to beta-lactam antibiotics only and two isolates were defined as multi-resistant. There was an association between ST and resistance pattern and isolates belonging to the same ST generally showed identical or closely related PFGE patterns. Six of the isolates were non-typeable by PFGE. The bla_{CMY-2} was identified on an incK plasmid 60–100 kb in size that transferred no resistance except for beta-lactam resistance. For one broiler isolate the bla_{CMY-2} could not be transferred. Of the 72 human clinical isolates it was shown that an incK plasmid carried bla_{CMY-2} in 19 of the isolates. No other resistance phenotypes were transferred and the incK plasmids were in the same size range as those from broilers, with one exception, a 200 kb plasmid. Of the human isolates 17 were typeable with PFGE, but none of them showed similarity to the broiler isolates. The human isolates also showed a higher heterogeneity, and they were generally resistant to a wider range of antimicrobials and carried more plasmid replicon types than the broiler isolates.

The study demonstrated that Swedish human clinical isolates and broiler isolates were distinct from each other, indicating that so far there seems to have been no direct transmission between humans and broilers in Sweden. These results are in contrast to the results by Leverstein-van Hall et al. (2011), who demonstrated relatedness between human and broiler isolates in the Netherlands. Nevertheless it is possible that transfer of the plasmid has occurred between the settings in Sweden. A recent study in Sweden found that only a minority (~6%) of cephalosporin-resistance in *E. coli* was due to pAmpC (SWEDRES 2011), and in the present study only ~26% of the human pAmpC producing *E. coli* isolates actually carried bla_{CMY-2} on an incK plasmid. In conclusion, it was shown that the overlap between isolates of *E. coli* producing ESBL and pAmpC in Sweden from humans and broilers appears to be limited.

The results of this study were published in:

Börjesson S, Jernberg C, et al. 2013, Characterisation of plasmid-mediated AmpC-producing *E. coli* from Swedish broilers and association to human clinical isolates. *Clin Microbiol Infect*, DOI: 10.1111/1469-0691.12192

Methicillin resistant *Staphylococcus aureus* (MRSA)

MRSA in humans

Background

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

Notifications of MRSA according to the Communicable Disease Act

In 2012 a total of 2097 cases of MRSA were notified, an increase by 213 cases (11%) compared to 2011 (Figure 6.3).

In 2012, seven of the Swedish counties, Kalmar, Skåne, Stockholm, Jämtland, Jönköping, Uppsala and Västra Götaland, had a higher incidence than the average national incidence of 22 cases/100 000 inhabitants (Table 6.4).

In 2012, 43% (n=894) of all reported MRSA cases were domestically acquired and 39% (n=814) were acquired abroad. Iraq (69), Philippines (61), Thailand (53), Egypt (40) and Spain (36) made up the five most common countries for imported MRSA infection.

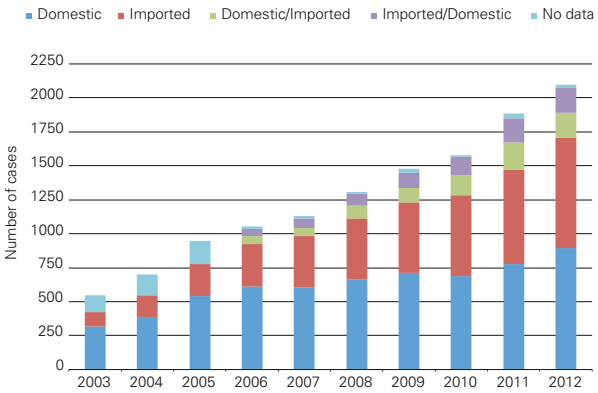


FIGURE 6.3. Number of MRSA cases annually notified in Sweden 2003-2012 by country of infection. "Domestic/Imported" and "Imported/Domestic" indicate several mentioned countries of infection with the most likely mentioned first.

TABLE 6.4. MRSA notifications according to the Communicable Disease Act 2003-2012 by county.

County	2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc *	No	Inc*	No	Inc*	No	Inc*
Blekinge	2	1.3	3	2,0	9	5.9	4	2.7	16	10.5	10	6.6	11	7.2	8	5.2	17	11.1	19	12.5
Dalarna	2	0.7	3	1.1	6	2.1	11	4,0	15	5.4	23	8.3	28	10.1	27	9.7	38	13.7	32	11.6
Gotland	2	3.5	1	1.7	10	17.3	4	6.9	8	14,0	6	10.5	6	10.5	5	8.7	9	15.7	10	17.5
Gävleborg	5	1.8	5	1.8	24	8.6	17	6.1	12	4.4	26	9.4	12	4.3	26	9.4	36	13.0	30	10.8
Halland	13	4.6	9	3.2	21	7.4	23	8.1	18	6.2	16	5.5	45	15.2	40	13.4	51	16.9	46	15.1
Jämtland	5	3.9	1	0.8	8	6.2	4	3.1	24	18.9	31	24.4	18	14.2	28	22.1	19	15.0	33	26.1
Jönköping	24	7.3	14	4.3	40	12.1	44	13,0	17	5.1	20	6.0	66	19.6	54	16,0	61	18.1	86	25.4
Kalmar	6	2.6	16	6.8	23	9.7	26	11.1	36	15.4	29	12.4	42	18.0	72	30.8	45	19.3	78	33.4
Kronoberg	5	2.8	17	9.5	11	6.1	14	7.8	13	7.2	19	10.4	26	14.2	23	12.5	40	21.7	40	21.5
Norrbotten	9	3.6	7	2.8	8	3.1	5	2,0	10	4.4	16	6.4	13	5.2	21	8.4	20	8.0	30	12.1
Skåne	104	9.1	128	11.3	162	13.9	179	15.5	166	13.8	273	22.5	284	23.1	313	25.2	369	29.5	380	30.1
Stockholm	228	12.3	277	14.8	315	17.1	356	18.9	351	18,0	342	17.3	375	18.6	412	20,0	502	24.0	595	28
Södermanland	2	0.8	8	3.1	11	3.8	9	3.4	26	9.8	20	7.5	23	8.5	30	11.1	34	12.5	31	11.3
Uppsala	12	4,0	26	8.6	28	9.2	24	7.9	33	10.2	40	12.2	33	9.9	41	12.2	42	12.4	79	23.1
Värmland	11	4,0	18	6.6	9	3.2	13	4.8	32	11.7	22	8.0	33	12.1	28	10.2	48	17.6	43	15.7
Västerbotten	13	5.1	16	6.2	10	3.8	7	2.7	23	8.9	22	8.5	28	10.8	39	15,0	20	8.0	18	6.9
Västernorrland	10	4.1	5	2,0	4	1.6	9	3.7	22	9,0	35	14.4	43	17.7	30	12.4	24	9.9	36	14.9
Västmanland	11	4.2	12	4.6	35	13.4	48	18.4	54	21.7	23	9.2	46	18.3	32	12.7	28	11.0	35	13.7
Västra Götaland	63	4.2	118	7.8	125	8.1	177	11.6	178	11.5	245	15.7	258	16.4	264	16.7	347	21.8	361	22.6
Örebro	8	2.9	11	4,0	16	5.8	35	12.8	25	9.1	46	16.6	45	16.1	40	14.3	44	15.6	55	19.4
Östergötland	14	3.4	14	3.4	101	24.3	48	11.5	49	11.6	43	10.2	45	10.5	47	10.9	71	16.5	60	13.8
Total	**549**	**6.1**	**709**	**7.8**	**975**	**10.8**	**1057**	**11.7**	**1128**	**12.3**	**1307**	**14.1**	**1480**	**15.8**	**1580**	**16.8**	**1884**	**19.9**	**2097**	**21.9**

[a]Inc = Incidence (cases/100 000 inhabitants)

Among the domestic MRSA cases 2012, the incidence was highest in the age group 80 years and older, followed by the age group 0-6 years (Figure 6.4). Among children (0-6 years), the infants (0 years) were clearly overrepresented (data not shown). The incidence of MRSA among the very old and the very young was substantially higher (≥ 20) than in the other age groups. In these groups the incidence had remained at a low but slightly increasing level, in 2012 reaching 7-8. In Figure 6.5 the numbers of domestic MRSA cases of the same age groups are presented. The majority of domestic cases were not surprisingly reported from the largest age-group 20-59, whereas the numbers were fairly even in the other age groups.

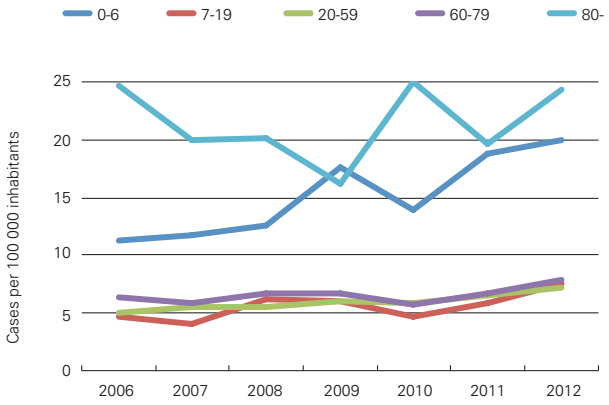


FIGURE 6.4. Age group adjusted incidence of notified domestic MRSA cases in Sweden 2006-2012.

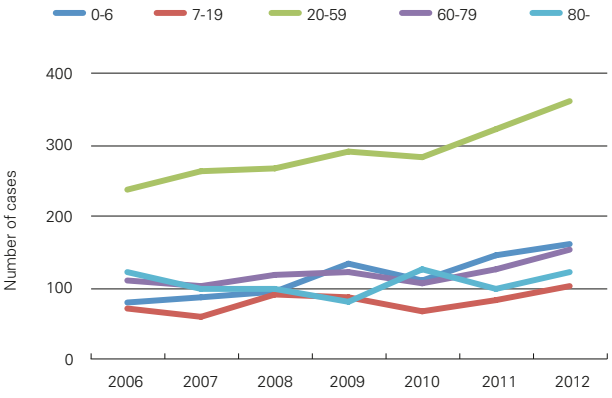


FIGURE 6.5. Numbers per age group of domestic notified MRSA cases in Sweden 2006-2012.

In 2012, 41% of the domestic cases were identified through contact tracing, 11% in targeted screening, and 46% during investigations of clinical symptoms (Figure 6.6 A). For imported cases the corresponding figures were 11%, 52%, and 36%, respectively (Figure 6.6 B). The majority of samples from investigations of clinical symptoms were wound samples. Invasive MRSA infection was reported in 36 cases 2012. 23 of those were newly notified persons 2012 and 13 occurred in patients already known to carry MRSA.

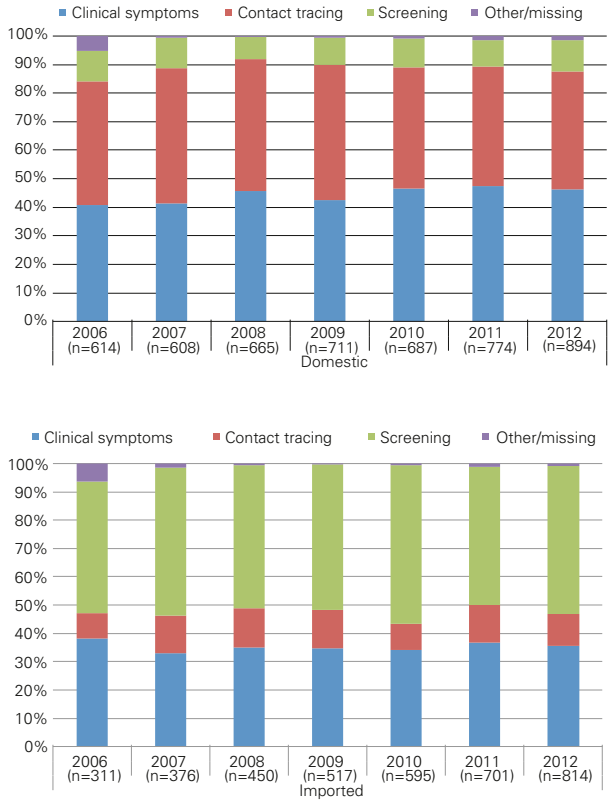


FIGURE 6.6, A AND B. The reasons for detection of domestic (A, top) and imported (B, bottom) MRSA cases in Sweden 2006-2012. n = number of reported cases each year.

Epidemiological classification of the acquisition of MRSA was based on information in the clinical notifications and from subsequent investigations by the CMOs, Figure 6.7, A and B. Community-acquired infections dominated among domestic cases 2012 and comprised 68% (n=610) of all domestic cases, Figure 6.7 A. There has been a continuous increase in the proportion of community acquired cases since 2006, and in Sweden today MRSA is acquired primarily in the community. Among the imported cases the proportion of community acquired infections was 44% (n=361), Figure 6.7 B. Hospital acquired MRSA was comparatively more common in imported cases, 34% (n=280), than among domestic cases, 8% (n=72). The number of domestic cases with hospital acquired MRSA increased from 52 (2011) to 72 (2012), but still the number of domestic hospital acquired cases has more than halved as compared to 2006 when 135 cases were reported. The number of domestic cases with MRSA acquired in healthcare/care outside the hospital increased to 130 (15%) in 2012 compared to 75 (10%) in 2011.

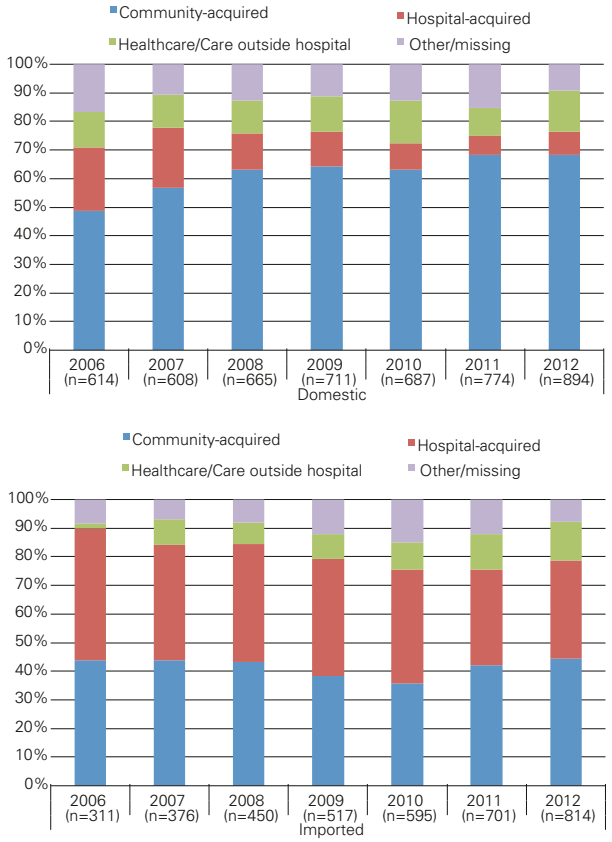


FIGURE 6.7, A AND B. Epidemiological classification of the acquisition of domestic (A, top) and imported (B, bottom) MRSA, Sweden 2006-2012. n= number of reported cases each year.

During 2012 more than 25 outbreaks (2-11 cases/outbreak) were reported in different counties from the Swedish healthcare system and from long-term care facilities. More outbreaks were reported from healthcare outside hospitals than from hospitals.

Epidemiological typing of MRSA

The primary method used at SMI for epidemiological typing of MRSA isolated from newly reported cases is *spa*-typing. This method replaced pulsed-field gel electrophoresis (PFGE) in 2006. An important advantage of *spa*-typing is that it is a sequence based method with a standardised nomenclature (http://spaserver.ridom.de/). This nomenclature (Ridom nomenclature) is unambiguous, easy to communicate and internationally well recognised. In addition to *spa*-typing all isolates are tested by PCR for presence of genes encoding the PVL-toxin.

In 2012, *spa*-typing results were available for MRSA isolated from 2017 cases (96%). The total number of *spa*-types seen was 348. The ten most common *spa*-types in 2007-2012 are listed in Table 6.5. Six *spa*-types have been among the top ten since 2007. These are t002, t008, t019, t044, t437 and t015. In 2012, 864 cases (42%) had an MRSA of a top ten *spa*-type. New for 2012 was t304. New for 2011 was t790, but this *spa*-type was only seen in 23 cases in 2012. Three of the top ten *spa*-types in 2007 were not seen among the top ten in 2012. These three were t032 (n=28), t037 (n=28) and t024 (n=24).

Table 6.6 shows a comparison of the top ten *spa*-types seen among MRSA from domestic and imported cases in 2012. Seven of these *spa*-types were present in both groups; t002, t223, t008, t044, t127, t019 and t304. The most common of the remaining three top ten *spa*-types was t015 among domestic cases (position 4) and t437 among imported cases (position 6).

PVL-results were available for MRSA isolated from 2037 cases. Of these, 34% were PVL-positive (n=691). This was a decrease from 41% in 2011. In 2012, a PVL-positive MRSA was most often of *spa*-type t008 or t019. MRSA of the two most common *spa*-types, t002 and t008, were seen both as PVL-positive and PVL-negative variants.

TABLE 6.5. The ten most common *spa*-types in 2007-2012, listed in decreasing order per year. For 2012, numbers of isolates are shown in brackets and numbers of PVL-positive and PVL-negative isolates are shown in square brackets [PVL-positive / PVL-negative].

2007	2008	2009	2010	2011	2012
t032	t002	t008	t008	t008	t002 (176) [64 / 112]
t008	t008	t044	t002	t002	t008 (132) [109 / 23]
t044	t044	t002	t044	t019	t019 (107) [107 / 0]
t002	t019	t019	t019	t044	t223 (105) [1 / 104]
t037	t032	t015	t223	t223	t044 (81) [77 / 4]
t015	t127	t437	t437	t127	t127 (68) [1 / 67]
t437	t437	t127	t127	t437	t437 (56) [29 / 27]
t690	t024	t223	t032	t690	t015 (55) [0 / 55]
t024	t015	t032	t015	t015	t304 (46) [2 / 44]
t019	t037	t037	t021	t790	t690 (38) [22 / 16]

TABLE 6.6. The ten most common *spa*-types among MRSA isolated from domestic and imported cases in 2012. Numbers of isolates are shown in brackets and numbers of PVL-positive and PVL-negative isolates are shown in square brackets [PVL-positive / PVL-negative].

Domestic	Imported
t002 (86) [28 / 58]	t002 (61) [22 / 39]
t223 (52) [1 / 51]	t008 (60) [49 / 11]
t008 (50) [40 / 10]	t019 (53) [53 / 0]
t015 (39) [0 / 39]	t223 (36) [0 / 36]
t044 (33) [33 / 0]	t044 (30) [27 / 3]
t127 (31) [0 / 31]	t437 (30) [13 / 17]
t019 (30) [30 / 0]	t127 (19) [0 / 19]
t304 (23) [0 / 23]	t304 (19) [1 / 18]
t690 (21) [11 / 10]	t037 (14) [1 / 13]
t692 (20) [20 / 0]	t005 (13) [7 / 6]

MRSA in animals

In Sweden, MRSA in animals was first verified in 2006 and was made notifiable in 2008. During 2012, MRSA was isolated from two horses, two cats and in samples from a dairy herd. Up to and including 2012 a total of 52 cases in animals have been confirmed at SVA (Table 6.7).

Most cases were detected in passive monitoring when animals with clinical infections were sampled. Isolates of *S. aureus* with resistance to oxacillin were further analysed with confirmatory tests. Screening studies for active monitoring have been performed in pigs, cattle, horses and dogs during different years.

Farm animals

In pigs, there was no active monitoring of MRSA in 2012 and no clinical isolates were detected. Screening studies have been performed four times in pigs since 2006 with only one positive sample in slaughter pigs in 2010, indicating a favourable situation in the Swedish pig population.

In dairy cattle, active monitoring of selected isolates of penicillinase producing *S. aureus* has been ongoing since 2010. In this monitoring, four isolates of PVL-negative MRSA with *mecC* (Ito et al., 2012), also known as $mecA_{LGA251}$, of *spa*-types t524 and t9111 were detected in 2010-2011 (Ericsson Unnerstad et al., 2013), and one PVL-positive MRSA with *mecA* of *spa*-type t002 in 2012.

In addition, sampling for MRSA was performed in 40 dairy cattle herds in South-east Sweden during two months in 2012. Bulk tank milk sample, milk samples from five cows, hock skin samples from the same five cows and nasal swabs from five preweaned calves were analysed with selective methods. MRSA was not identified in this study.

Companion animals and horses

In horses, there was no active monitoring of MRSA during 2012. Screening studies in horses have been performed twice, in 2007 and 2010, with only one positive sample in 2007. A screening for MRSP and MRSA of 58 healthy dogs was performed in 2012 without detection of MRSA. In 2012, MRSA was detected in clinical samples from two cats and two horses, all with wound infections. Since MRSA was first detected in 2006, *spa*-type t032 has dominated in companion animals, and *spa*-type t011, CC398, in horses. Most isolates from horses were from clinical cases with postoperative wound infections (Table 6.7), and all isolates from both companion animals and horses have been PVL-negative.

Zoonotic aspects on MRSA

Zoonotic transmission of MRSA occurs by direct or indirect contacts, making farmers, animal owners, veterinarians and other persons in close contact with animals the population at risk. MRSA is reported globally in farm animals, mostly in pigs but also in veal calves, broilers and dairy cows.

MRSA CC398

Internationally, the livestock-associated MRSA CC398 dominates in farm animals and can be of importance for the overall human MRSA burden in countries with low prevalence of MRSA in humans (EFSA, 2009). In countries with high prevalence of MRSA CC398 in pigs, the pig population constitutes a reservoir of MRSA with continuous transmission to people in close contact with pigs. MRSA CC398 also occurs among horses and *spa*-type t011 is by far the most common type among Swedish horses.

Four PVL-negative MRSA CC398-associated *spa*-types (t034, t011, t571 and t108) were seen among 40 human cases in 2006-2012. The two dominating *spa*-types were t034 (n=20) and t011 (n=15). Nine of the 40 cases were from 2012, four with *spa*-type t034 and five with t011. The epidemiological information on these cases is however scarce.

MRSA with *mecC* (also known as $mecA_{LGA251}$)

Isolates of MRSA with *mecC*, also known as $mecA_{LGA251,}$ were first reported internationally from dairy cows and humans in 2011 (García-Álvarez et al., 2011 and Shore et al., 2011). Such MRSA isolates were detected in Swedish dairy cows in 2011 and in 40 human cases 2011-2012. Fourteen *spa*-types were seen among the human isolates, the two most common being t843 (9 cases) and t373 (7 cases). The *spa*-types detected in cows were t524 and t9111, the latter of which has also been found in two human cases.

Other types of MRSA

Initiated by the detection of PVL-positive MRSA of *spa*-type t002 in a dairy farmer, cattle in a dairy farm were sampled in 2012. Milk samples from lactating cows and body samples from nostrils and groin from other cattle were taken in this herd. MRSA of the same *spa*-type as in the farmer was detected in milk samples from several cows and one nasal swab from a dry cow. An isolate of the same *spa*-type was earlier detected in the anonymous monitoring. It is probable that this isolate came from the same herd. Since MRSA of this *spa*-type is common among humans in Sweden, it is likely that transmission has occurred from the farmer to cows. As *S. aureus* is prone to persist in bovine udders, a reservoir in the cows was established with risk of spread to other cows and to humans. Investigations on the farm, with competent authorities involved, aim to minimise transmission and, eventually, get the herd free from MRSA.

MRSA in companion animals

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

Conclusion

The prevalence of MRSA in Sweden is still low both in humans and in animals. If the favourable situation in animals is preserved, spread from animals to humans can be prevented. Infection control and caution in trade of live animals are important strategies for preventing introduction and spread of MRSA in animal populations.

TABLE 6.7. Isolates of methicillin resistant *Staphylococcus aureus* (MRSA) in Swedish animals 2006-2012. 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	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*
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*
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*
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*

[a] tested with 2% NaCl.

Methicillin resistant *Staphylococcus pseudintermedius* (MRSP)

MRSP in animals

Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) was first isolated in Sweden from a healthy dog in a screening for MRSA in 2006. Since 2008, methicillin-resistant coagulase positive staphylococci are notifiable in Sweden. On suspicion of MRSP, diagnostic laboratories are advised to send the isolate to SVA for confirmation by PCR for the presence of the *mecA* gene.

Figure 6.8 shows the yearly numbers of cases notified to the Board of Agriculture in Sweden since year 2008. During 2006-2007 the numbers correspond to the number of *mecA*-positive isolates confirmed at SVA. MRSP has mostly been isolated from dogs but also from a few cats and horses. The numbers of notified cases have declined during recent years. Whether this reflects a true reduction in the number of animals infected with MRSP is uncertain.

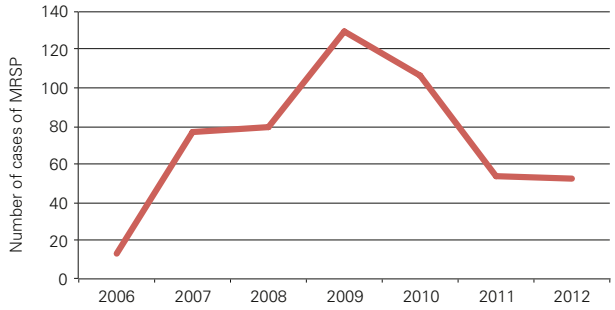


FIGURE 6.8. The number of cases with methicillin resistant *Staphylococcus pseudintermedius* (MRSP) in Sweden notified to the Swedish Board of Agriculture 2008-2012. In 2006-2007 the numbers represent the isolates that were sent to SVA and confirmed as *mecA*-positive.

In 2012, 39 MRSP isolates were confirmed at SVA and all were isolated from dogs. In 41% of the cases, MRSP was isolated from skin including ear samples, in 18% from wounds, and in the remaining cases from miscellaneous sampling sites. Thirty isolates were randomly selected for further investigations. A majority belonged to *S. pseudintermedius spa*-type t02. PFGE analysis of 30 isolates revealed that isolates in Sweden were related and that they showed a high relatedness with the European clone ST71-J-t02-II-III described by Perreten and co-workers (2010).

In 2006 and 2007, most of the MRSP isolates had a characteristic antibiogram, being susceptible only to two antibiotics of those licensed for use in dogs in Sweden, fusidic acid and tetracycline (SVARM 2007). In 2008, the first isolates resistant to tetracycline were detected. In 2012, 23 MRSP isolates were tested for susceptibility on wide range MIC panels, and all isolates were found to be multiresistant. Of the 23 isolates, 14 (61%) were resistant to erythromycin, clindamycin, ciprofloxacin, gentamicin and trimethoprim. Four (17%) isolates were also resistant to tetracycline. Another three (13%) isolates were additionally resistant to fusidic acid.

In 2012, 58 healthy dogs were screened for MRSP and MRSA. None of the dogs were positive.

Since the first cases of MRSP, there have been discussions among veterinarians on how to prevent further spread of this pathogen and on the prudent use of antimicrobials. For instance, in many animal clinics and hospitals, infection control programmes have been implemented with focus on strict hand hygiene routines. Also, veterinarians with special interest in dermatology have agreed on an antimicrobial policy for treatment of dogs with dermatological disorders.

Zoonotic aspects

In the literature, there is limited information on zoonotic transmission of MRSP and regarding *S. (pseud)intermedius* sporadic cases are described (van Duijkeren *et al.*, 2011; Barbarini *et al.*, 2013). In 2011, an outbreak was described among patients at Uppsala Akademiska hospital (Starlander *et al.*, 2011).

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

VRE In humans

Background

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

Notifications of VRE according to the Communicable Disease Act

From 2000 to 2006 only low numbers (18-35 per year) of VRE-cases were reported in Sweden. In 2007, reports came from Stockholm County about an increase in the number of VRE-cases, and the total yearly count was 53 cases (Table 6.8, Figure 6.9). 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. In Västernorrland County an outbreak of another strain of *E. faecium* with *vanB* lasted 2010-2011 with an estimated number of 100 cases.

TABLE 6.8. VRE notifications according to the Communicable Disease Act 2006-2012 by species and van-gene.

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

During 2012 a total of 152 cases were reported, an increase by 25% compared to 2011 (Table 6.8). VRE cases were reported from 15 of the 21 Swedish counties. The average national incidence of VRE was 1.6 with higher than average incidence figures in Jönköping County (4.4), Stockholm (3.9), Halland (3.3) and Kronoberg (2.2). Of all cases, 61% (n=93), were reported as domestic (Figure 6.9), and 91% of those (n=85) were healthcare related. In 32% (n=48) VRE had been acquired abroad. The five most common countries for imported VRE infection were Turkey (6 cases), Iran (5), Bosnia-Hercegovina, Germany and India (4 each). Fourty-five (94%) of the imported cases were healthcare related.

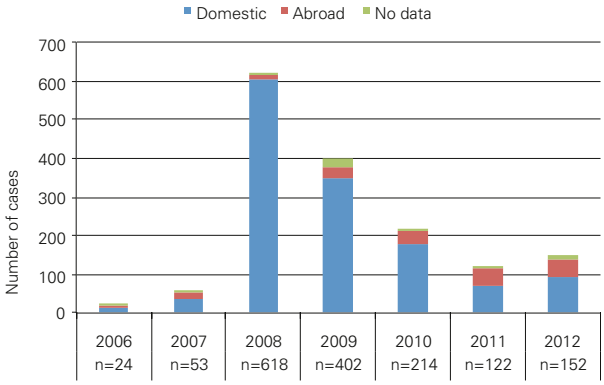


FIGURE 6.9. Number of VRE cases annually notified in Sweden 2006-2012 by country of infection.

The domestic VRE cases were detected through contact tracing (73%), screening (15%) or clinical symptoms (12%). The majority of the imported cases (94%) were detected through screening, 2% due to clinical symptoms and 2% due to contact tracing. Accordingly a majority of the isolates (77%) in the first laboratory notifications were from feces and rectum, and only 3% from urine samples. Distribution of the notified cases between genders was even, with the median age for women 77 years and for men 70 years.

In 2012, *Enterococcus faecium* was reported in 148 cases and *E. faecalis* in 8 cases. Four out of the 152 VRE cases were infected with both *E. faecium* and *E. faecalis*. In contrast to previous years, the dominating resistance gene 2012 was *vanA* (Table 6.8). One case of an invasive VRE infection, *E. faecium* with *vanA*, was reported in 2012.

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. It 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 were caused by strains of different PFGE-types, and they have been given names retrospectively. The extensive outbreak 2010-2011 in Västernorrland County was caused by a strain with the PFGE pattern SE-EfmB-1001.

In 2012, outbreaks of *E. faecium* with *vanA* gene were reported from Jönköping, Halland and Stockholm counties with 2-22 patients affected in each outbreak. The counties of Jönköping and Halland had one outbreak each (www.smi.se; Newsletter 53, 2012), whereas Stockholm had three. All of the outbreaks were healthcare related, but there were no known connections between the counties. In Jönköping and Halland counties the respective index patients had been hospitalised abroad. Isolates from the index cases as well as from all affected patients were typed by PFGE. The strains were named SE-EfmA-1203 (Jönköping) and SE-EfmA-1204 (Halland), respectively. The outbreaks in Stockholm were caused by three different strains according to their PFGE patterns.

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. This has become more important recently with the dramatic increase in numbers of *E. faecium* with *vanA*.

VRE in animals

No specific screening for vancomycin resistant enterococci (VRE) was performed in SVARM 2012. However, when monitoring antibiotic resistance in indicator bacteria from healthy animals all isolates of *E. faecalis* and *E. faecium* are tested for susceptibility to vancomycin. No resistant isolates have been detected.

Historically, vancomycin resistant *E. faecium* with the *vanA* gene has been isolated from intestinal content of healthy broilers but not from the other farm animals studied in SVARM, *i.e.* slaughter pigs and cattle.

Occasional VRE have been found in the studies of indicator *E. faecium*, where isolates are selected at random from cultures of intestinal content of broilers sampled at slaughter. However, using selective culture of intestinal content on agar supplemented with vancomycin, VRE have been readily isolated from broilers in Sweden. In the latest screening in 2010, VRE were isolated from 49 (23%) of 200 samples collected at slaughter. For more information, please read previous SVARM reports and especially 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, most cases of VRE in Swedish healthcare have been caused by *E. faecium* with the *vanB* gene (Table 6.8), and only during 2012 VRE with *vanA* have outnumbered VRE with *vanB*. Many of the recent cases of *E. faecium* with *vanA* were patients that had received healthcare in other countries, and a connection to the presence of VRE in Swedish broiler production seems unlikely. Also, it has been shown by PFGE that the VRE found in broilers have never been identified among human isolates. Accordingly, there are no indications that the presence of VRE in broilers in Sweden has affected the situation in Swedish healthcare.

Streptococcus pneumoniae with reduced susceptibility to penicillin (PNSP)

PNSP in humans

Background

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

Notifications according to the Communicable Disease Act

In 2012 a total of 239 PNSP cases were reported in Sweden, 196 during the first 6 months and 43 cases after implementation of the new definition, *i.e.* penicillin MIC > 1 mg/L. Forty-three percent of the cases had been infected domestically and 15% of the cases in a foreign country. For the remaining 101 cases (42%) no country of acquisition was given.

The incidence of PNSP in Sweden 2012 was 2.5 cases per 100 000 inhabitants. The majority of PNSP cases (39% in 2012), independent of year observed, were found in the age group 0-4 years. There was no difference in the proportion of the reported cases with regard to sex.

PNSP were reported from all Swedish counties except from Halland, with Stockholm (87 cases) and Skåne (35 cases) accounting for 51% of all notifications (but only 35% of the Swedish population). The remaining counties reported 1-27 cases each. Due to regional differences in general culturing propensity, case finding intensity as well as presence of targeted screening programmes, a comparison of regional incidences is not meaningful.

The majority, 59% of all notifications of PNSP, were found in cultures from the nasopharynx. In 46% of all cases the detection of PNSP was due to clinical infection, and in 10% due to targeted screening including contact tracing. In the remaining cases another reason for sampling was stated (5%) or the information was missing (39%).

Serotype distribution

In 2012, 12 cases of invasive PNSP infection, with bacteria isolated from blood, were reported. Of these isolates four were serotype 9V and four serotype 19A. For all cases of PNSP with MIC ≥ 0.5 mg/L (239 isolates serotyped at SMI so far) the most commonly found serotypes were in descending order: 19F (23%), 35B (17%), NT (14%), 19A (7%), 6B (6%), 23F (5%); 9V and 14 (4% each).

Resistance in zoonotic pathogens

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

Salmonella

Salmonella from human clinical specimens

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

Blood culture isolates of *Salmonella* are always tested, and in 2012 we used the complete data sets of positive blood cultures from ten laboratories (Appendix 3) as one source of information on antibiotic susceptibility in *Salmonella*. In 2012, 82 isolates of *Salmonella* were found among a total of 18 117 blood cultures. The most common serovars were *S.* Enteritidis (15), *S.* Typhimurium (10), *S.* Paratyphi A (9), *S.* Typhi (7), *S.* Virchow (6), *S.* Newport (3) and *S.* Stanley (3) (Table 6.9). The remaining 20 isolates were reported as S. other serovars. 60 of the cases were reported as travel associated with Thailand, Turkey, Africa (north or central regions), and India being the countries/regions most frequently mentioned.

Susceptibility testing by disk diffusion and application of NordicAST breakpoints was performed by local clinical laboratories. One isolate was resistant to cefotaxime and produced an $ESBL_A$. Resistance to trimethoprim-sulphamethoxazole was found in 6 isolates (7.7%) and resistance to ciprofloxacin in as many as 25 (31%). Typically, all isolates of *S.* Paratyphi A were resistant to ciprofloxacin, 4/6 of *S.* Virchow, 2/7 of *S.* Typhi, and 10 of other serovars (Table 6.9).

TABLE 6.9. *Salmonella* from blood cultures in Sweden 2012. Data collected from 10 laboratories, covering approximately 55% of the Swedish population.

Salmonella serovar	No. of isolates	No. of Cip-R[a]	No. of Ctx-R[a]	Countries reported
S. Agona	2			Sweden
S. Corvallis	3	1		China, Thailand, Indonesia
S. Enteritidis	15	4		Turkey and several other
S. Newport	3			Tanzania, Sweden
S. Paratyphi A	9	9		India, Nepal
S. Stanley	2	1		Thailand, Sweden
S. Thompson	2			Turkey, Sweden
S. Typhi	7	2		Pakistan, India, Libanon
S. Typhimurium	10	1	1	Argentina, Spain, Egypt, Sweden
S. monophasic Typhimurium	3			Sweden, Venezuela
S. Virchow	6	4		Africa, Sweden
S. other serovars	20	3		
Total	**82**	**25**	**1**	

[a] Cip-R = ciprofloxacin resistant; Ctx-R = cefotaxime resistant

Salmonella in animals

Findings of *Salmonella* in animals are notifiable in Sweden and antimicrobial susceptibility is tested in one isolate from each warm-blooded animal species (wild and domesticated) involved in an incident. In incidents involving more than one serovar or phage type, one isolate of each serovar and phage type is tested. In SVARM 2012, isolates from incidents notified in 2012 are included but also isolates from incidents previously notified but still under restrictions. In addition, isolates obtained in the salmonella surveillance programme from samples collected at slaughter are included.

All animals 2012

Altogether, 71 isolates were tested of which 51 were *S.* Typhimurium and three of these were of the monophasic serovar O 4,5:i:- (Table 6.10). Distributions of MICs and resistance for all isolates are presented in Table 6.11 and for the subset *S.* Typhimurium in Table 6.12. The majority of isolates (70%) were susceptible to all antimicrobials tested, but 21 isolates were resistant to at least one substance, and eight isolates (11 %) were multiresistant (Table 6.13).

Of the multiresistant isolates, two from incidents in cattle and two from incidents in pigs, had the classic penta-resistance found in *S.* Typhimurium DT 104. One isolate of *S.* Typhimurium (not phagetyped) from an incident in cattle had a rare resistance phenotype; ampicillin, streptomycin, and sulphonamide. So far this is the only incident in Sweden where this phenotype has been found. Three multiresistant isolates were monophasic *S.* Typhimurium isolated from dogs. All three isolates had a phenotype common for this serovar; ampicillin, streptomycin, sulphonamide and tetracycline.

Farm animals 2000-2012

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 2000-2012, isolates from the vast majority of notified incidents in farm animals were tested in SVARM, in total 570 isolates. About half of the isolates, 281 (49%) were *S.* Typhimurium and of these, 39% were from pigs, 32% from cattle, 27% from poultry and 2% from sheep.

The majority (74%) of *S.* Typhimurium isolates were susceptible to all antimicrobials tested and only 28 isolates (10%) were multiresistant (Table 6.14). The most common resistance traits were ampicillin, streptomycin, tetracycline, sulphonamide, chloramphenicol or florfenicol. These were also the most common traits in isolates of *S.* Typhimurium from all animals in the period (Fig 6.10). Resistance to third generation cephalosporins has not been found and resistance to ciprofloxacin has been confirmed only in one isolate. Six isolates (2%) of other serovars than Typhimurium were multiresistant.

The 28 multiresistant isolates of *S.* Typhimurium were from 26 separate incidents of which 15 involved cattle, 6 pigs, 2 poultry and 1 incident involved both pigs and cattle. Of the remaining incidents, one was in sheep and one in ducks in a hobby flock. Three incidents in 2004 involving cattle were epidemiologically linked through trade of calves. An epidemiological link is also suspected between four incidents 2007-2008 involving cattle, pigs and sheep. There are no known links between the other incidents.

Eight incidents of monophasic *Salmonella* subspecies I (O 4,5,12:i- /O 4,5:i:- / O 4:i:-) have been confirmed in farm animals since this variant was first found in Swedish animals in 2006 (Table 6.14). Two incidents involved cattle, three incidents pigs, one incident ducks, and one incident involved both cattle and poultry. Monophasic *Salmonella* has also been isolated from three dogs and a wild bird. Epidemiological links between some of the incidents have been confirmed. Most isolates have had the characteristic resistance phenotype: ampicillin, streptomycin, sulphonamide and tetracycline.

TABLE 6.10. Number of *Salmonella enterica* tested for antimicrobial susceptibility, 2012.

Serovar	Cattle	Pigs	Sheep	Poultry	Horses	Dogs	Cats	Wild birds	Wild mammals	Total
S. Agona	1									1
S. Dublin	2									2
S. Duesseldorf	1									1
S. Enteritidis									2	2
S. Gallinarum				4						4
S. Hadar				1						1
S. Infantis				1						1
S. Livingstone				1						1
S. enterica subsp. *arizonae* (IIIa)						2				2
S. enterica subsp. *diarizonae* (IIIb)	1								2	3
S. enterica subsp.*enterica* (I)									2	2
S. Typhimurium DT 104	3	3								6
S. Typhimurium DT110b								1		1
S. Typhimurium DT 195								1		1
S. Typhimurium DT 40				1				1		2
S. Typhimurium DT 41				1						1
S. Typhimurium NST 1:3	2									2
S. Typhimurium NST 3:10	1									1
S. Typhimurium NST 11:7 (U277)	1						8	6	1	16
S. Typhimurium NST 11:72				1						1
S. Typhimurium NST 12:16	1									1
S. Typhimurium NST 18:3	1									1
S. Typhimurium not phagetyped	3	1					7	2	2	15
Monophasic *S.* Typhimurium 4,5:i:-						3				3
Total	**17**	**4**	**0**	**10**	**0**	**5**	**15**	**11**	**9**	**71**
Percent of total	24%	6%	0%	14%	0%	7%	21%	15%	13%	

TABLE 6.11. Distribution of MICs and resistance (%) in *Salmonella enterica* (n=71) from all animals, 2012.

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	11							16.9	70.4		1.4					11.3				
Cefotaxime	0				47.9	52.1														
Chloramphenicol	6									29.6	64.8					1.4	4.2			
Ciprofloxacin	0		1.4	25.4	73.2															
Florfenicol	6									32.4	60.6	1.4		5.6						
Gentamicin	0						8.5	43.7	46.5	1.4										
Kanamycin	0							2.8	2.8	56.3	38.0									
Nalidixic acid	0									8.5	85.9	5.6								
Streptomycin	27										5.6	5.6	62.0	14.1	4.2	2.8	2.8	2.8		
Sulphonamide	14													5.6	25.4	49.3	5.6	1.4		12.7
Tetracycline	11							1.4	54.9	32.4			5.6	1.4		4.2				
Trimethoprim	0						40.8	53.5	5.6											

TABLE 6.12. Distribution of MICs and resistance (%) in *Salmonella* Typhimurium (n=51) from all animals, 2012.

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							7.8	74.5		2.0					15.7				
Cefotaxime	0				43.1	56.9														
Chloramphenicol	8									31.4	60.8					2.0	5.9			
Ciprofloxacin	0			15.7	84.3															
Florfenicol	8									37.3	54.9			7.8						
Gentamicin	0						3.9	45.1	51.0											
Kanamycin	0									56.9	43.1									
Nalidixic acid	0									3.9	90.2	5.9								
Streptomycin	27										2.0	2.0	68.6	11.8	3.9	3.9	3.9	3.9		
Sulphonamide	20													2.0	15.7	56.9	5.9	2.0		17.6
Tetracycline	14							2.0	52.9	31.4			7.8			5.9				
Trimethoprim	0						33.3	62.8	3.9											

TABLE 6.13. MICs (mg/L) of *Salmonella enterica* resistant to three or more antimicrobials, 2012. Shaded fields indicate resistance.

Animal species	Zoonosis	Amp	Ctx	Cip	Nal	Chl	Flo	Gen	Kan	Str	Sul	Tet	Tmp
Cattle	*S.* Typhimurium, not phagetyped	>64	≤0.06	0.06	4	4	4	1	2	256	>1024	1	≤0.25
Dog	Monophasic *S.* Typhimurium 4,5:i:-	>64	0.12	0.06	8	4	4	1	2	>256	>1024	>64	≤0.25
Dog	Monophasic *S.* Typhimurium 4,5:i:-	>64	≤0.06	0.06	4	4	4	1	4	256	>1024	>64	≤0.25
Dog	Monophasic *S.* Typhimurium 4,5:i:-	>64	0.12	0.06	4	4	4	0.5	4	>256	>1024	>64	≤0.25
Pig	*S.* Typhimurium DT 104	>64	0.12	0.06	4	128	32	1	4	128	>1024	16	≤0.25
Pig	*S.* Typhimurium DT 104	>64	0.12	0.06	4	256	32	1	2	128	>1024	16	≤0.25
Cattle	*S.* Typhimurium, not phagetyped	>64	0.12	0.06	4	256	32	1	4	64	>1024	16	0.5
Cattle	*S.* Typhimurium DT 104	>64	0.12	0.06	4	256	32	1	4	64	>1024	16	0.5

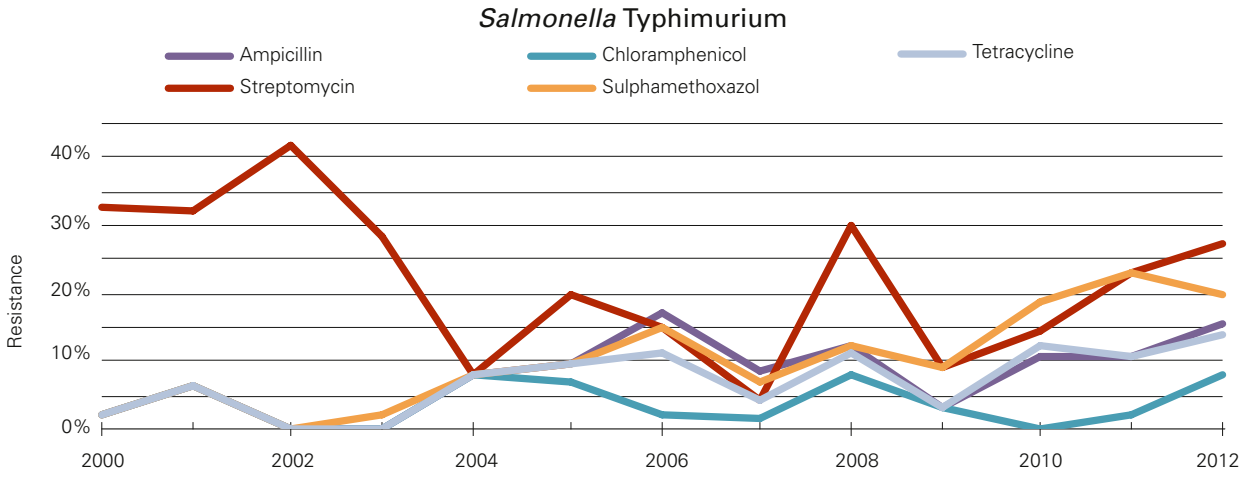


FIGURE 6.10. Resistance (%) in *Salmonella* Typhimurium from all animals, 2000-2012. The number of isolates each year varies (n=31-85).

TABLE 6.14. Resistance phenotypes of *Salmonella* Typhimurium (n=281) from incidents in farm animals, 2000-2012. All isolates were tested for susceptibility to ampicillin, ceftiofur/cefotaxime, florfenicol, gentamicin, chloramphenicol, nalidixic acid, streptomycin, sulphametoxazole, tetracycline, and trimethoprim. Monophasic *S.* Typhimurium (O 4,5,12:i:-) are included.

Phenotype	Animal species	Phage type																								
		1	7	9	10	12	15a	39	40	41	99	110b	104	120	125	126	146	193	195	NST (U277)	NST	NT	Monophasic	Not phagetyped	Total
AmpStrSulTetNalChlFlo	**Pigs**												1												**1**
AmpStrSulTetChlFlo	**Cattle**												6	1										2	**9**
AmpStrSulTetChlFlo	**Pigs**												4											1	**5**
AmpStrSulTetChlFlo	**Sheep**												1												**1**
AmpStrSulTetChl	**Cattle**												1												**1**
AmpStrSulTet	**Cattle**													1								2	2		**5**
AmpStrSulTet	**Pigs**																						1		**1**
AmpStrSulTet	**Poultry**																					1	2		**3**
AmpStrSul	**Cattle**													1											**1**
StrSulTet	**Cattle**																				1				**1**
AmpSul	**Cattle**												2												**2**
AmpSul	**Pigs**												1												**1**
StrGen	**Cattle**									1															**1**
StrGen	**Pigs**								1																**1**
StrGen	**Poultry**									1															**1**
StrSul	**Pigs**																						2		**2**
StrSul	**Poultry**						2																		**2**
SulTm	**Cattle**																1				1				**2**
Amp	**Poultry**																				2				**2**
Gen	**Poultry**																				1				**1**
Nal	**Pigs**					1																			**1**
Str	**Cattle**												1	1		1					4			1	**8**
Str	**Pigs**								4	3			2	1							4	1		1	**16**
Str	**Poultry**									2											3				**5**
Susceptible	**Cattle**	4			2		1	1	1	6			2	5	1	1				1	26	1	1	6	**59**
Susceptible	**Pigs**	1	1			2			33	5	1		1	8					1	1	17	2		9	**82**
Susceptible	**Poultry**	1		1		1			5	1		1		2				1	1	1	42	4		2	**63**
Susceptible	**Sheep**	1																						3	**4**
Total		**7**	**1**	**1**	**2**	**4**	**3**	**1**	**44**	**19**	**1**	**1**	**22**	**20**	**1**	**2**	**1**	**1**	**2**	**3**	**101**	**11**	**8**	**25**	**281**

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, resistance to third generation cephalosporins has not been found and resistance to fluoroquinolones is rare. Thus, the overall situation regarding *Salmonella* among animals in Sweden is favourable. This is largely due to the effective strategies in the Swedish *Salmonella* control programme since the 1950-ies.

To relate the situation in Swedish animals to the situation in humans is however not possible because compiled data on occurrence and susceptibility of *Salmonella* from humans in Sweden is largely lacking. However, of the most common serovars presented for human invasive infections 2012 (Table 6.9), *S.* Typhi is not associated with animals. Moreover, *S.* Enteritidis, *S.* Paratyphi A, *S.* Virchow, *S.* Newport and *S.* Stanley are most rare in animals in Sweden.

Also, nearly one third of the human isolates were resistant to ciprofloxacin and this high rate was in contrast to the rare findings of ciprofloxacin resistance in *Salmonella* from animals in Sweden. Taken together, this strongly suggests that *Salmonella* causing human infections rarely originate from Swedish animals, which is in agreement with epidemiological information available for the human cases.

Campylobacter

Human

Information on *Campylobacter* from humans was not available for 2012.

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 2012. For details on methodology see Appendix 4.

Results and comments

Of the 100 isolates tested, 80 were susceptible to all six antimicrobials. Resistance to fluoroquinolones only (ciprofloxacin and nalidixic acid) was the most common phenotype (Table 6.15).

In comparison to previous years quinolone resistance has increased notably in 2010 and 2012 (Figure 6.11). The reasons for this are not known but selection through use of antimicrobials 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*.

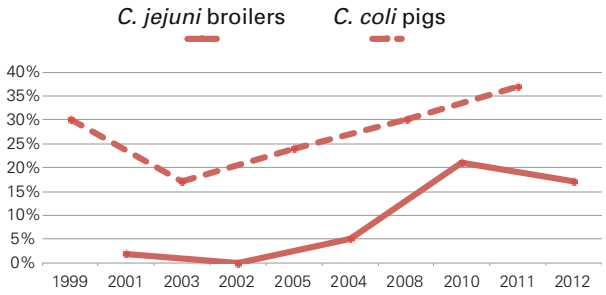


FIGURE 6.11. Ciprofloxacin resistance (%) in *Campylobacter jejuni* from broilers and *Campylobacter coli* from pigs 1999-2012. The number of isolates per year has varied between 83 and 100.

Zoonotic aspects

No data for *Campylobacter* from humans were available for 2012 but data for 2002-2011 were presented in SWEDRES 2011. However, comparisons to data for *Campylobacter* from animals is hampered because the human isolates are not separated by species or by infections acquired in Sweden or abroad. *Campylobacter* spp. isolates acquired within the country are expected to have a lower level of resistance.

In 2011 higher resistance percentages were reported for human isolates of *Campylobacter* spp. for fluoroquinolones (69%), tetracycline (37%) and erythromycin (7%) than for isolates of *C. jejuni* from broilers 2012 or for *C. coli* from pigs 2011 (SVARM 2011). Notably, resistance to erythromycin, the drug of choice for treatment of human campylobacteriosis, is not found in *Campylobacter* 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.

TABLE 6.15. Distribution of MICs and resistance (%) in *Campylobacter jejuni* from broilers, 2012.

Antimicrobial	Resistance (%) 2012	Distribution (%) of MICs (mg/L)											
	(n=100)	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Ciprofloxacin	17	17	52	13	1				10	7			
Erythromycin	0				78	20	2						
Gentamicin	0			11	86	3							
Nalidixic acid	17						5	57	20	1			17
Streptomycin	1				3	75	21						1
Tetracycline	2		85	11	2					2			

Resistance in 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, Appendix 3). Commercially available tests for MIC determination are also used, and in recent years there has also been an increase in the use of automated methods for susceptibility testing and categorization.

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

Ten of these Swedish laboratories, with coverage of approximately 55% of the Swedish population, also deliver data on invasive isolates from all their positive blood cultures (Appendix 3). 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.**

Isolates from blood cultures reported to ECDC/EARS-Net

Background

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

EARSS turned into EARS-Net

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

A summary of the data reported from Sweden 2006-2012 is presented in Figure 6.12 in which numbers of isolates are shown, and in Table 6.16 where the proportions of resistance to certain antibiotics are included. The numbers of isolates of *E. coli* and *S. aureus* were much greater than the other pathogens, and they also showed increasing trends over the years, whereas the numbers of the other five pathogens were stable.

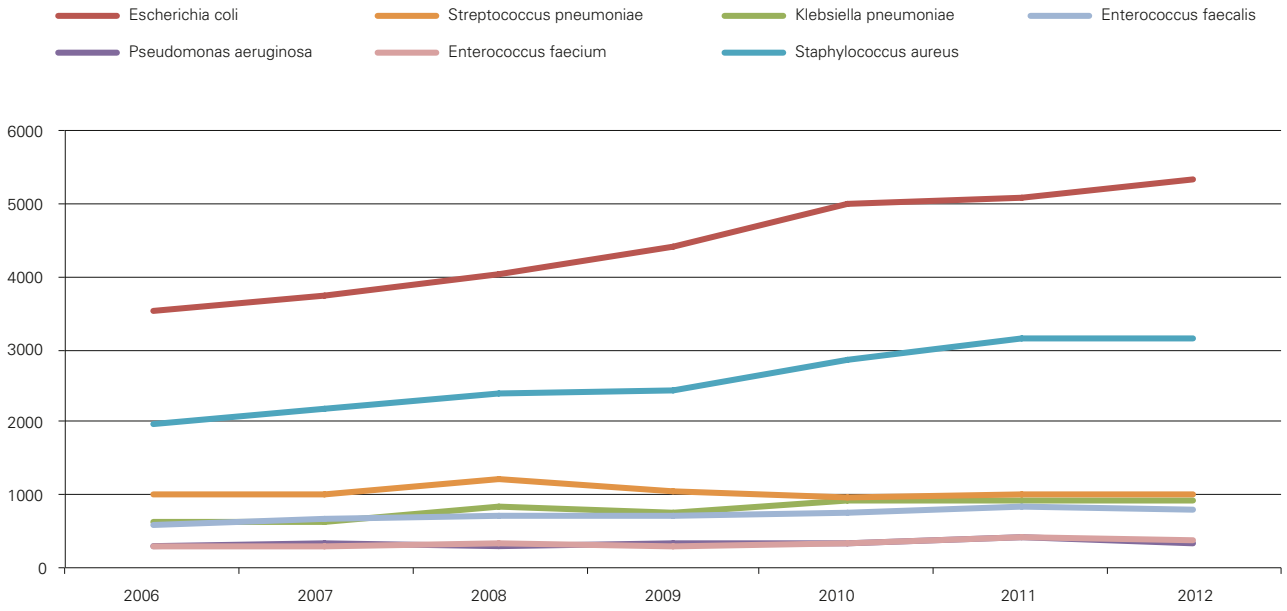


FIGURE 6.12. Yearly numbers of bloodstream infections by seven pathogens reported to EARS-Net from Sweden (20 laboratories, covering approximately 80% of the population).

TABLE 6.16. Antimicrobial resistance in invasive isolates of pathogens included in EARSS/EARS-Net surveillance during seven years (2006-2012).

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

Results and comments

In general the proportions of resistance to clinically important antimicrobials were low, and this has been the typical situation for Sweden and its neighbouring Nordic countries all through the EARSS/EARS-Net history (www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/). However, increasing trends of resistance to third-generation cephalosporins are seen for both *E. coli* and *K. pneumoniae*. This increase is due to an increasing prevalence of ESBL-producing isolates, whereas the mechanism causing resistance to ceftazidime in *P. aeruginosa* has a non-ESBL explanation (Figure 6.13). In *E. coli*, aminoglycoside resistance has shown an increasing trend for the last couple of years and the level of resistance reached 5.5% in 2012 (Table 6.16). Genes coding for aminoglycoside resistance often co-exist with genes for ESBL enzymes on plasmids, but it is obvious from the data presented here that there must be a pool of genes coding for resistance also outside the ESBL plasmids. The same situation is however not seen in *K. pneumoniae*.

Reduced susceptibility and resistance to fluoroquinolones (I+R) seems to have stabilized on a level of approximately 10% in both *E. coli* and *P. aeruginosa* but approximately 5% in *K. pneumoniae*.

For the grampositive bacteria the levels of resistance were similar to previous years with 0.8% MRSA among *S. aureus*. There were no VRE reported in the two enterococcal species but high-level aminoglycoside resistance (HLAR) of 14-18%, and in *S. pneumoniae* the level of nonsusceptibility to penicillin (I+R) was 5%, which is the highest level noted in Sweden ever since the start of EARSS/EARS-Net.

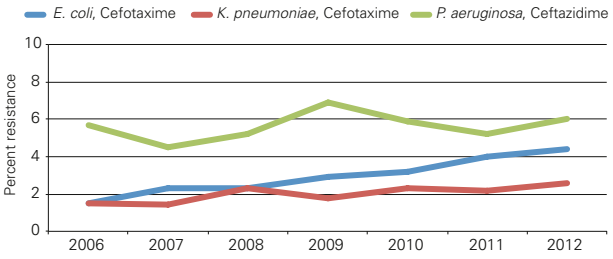


FIGURE 6.13. Proportion of resistance to third-generation cephalosporins in *E. coli*, *K. pneumoniae* and *P. aeruginosa*. Swedish data in EARS-Net 2006-2012 (20 laboratories, covering approximately 80% of population).

Resistance in other bacterial species from blood cultures

Streptococcus pyogenes, Streptococcus agalactiae and *Haemophilus influenzae*

Data on all positive blood cultures were obtained from ten laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is at present 5 millions, thus representing more than 55% of the Swedish population. From these laboratories data for the pathogens specified by EARS-Net are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In previous SWEDRES reports (2008-2011) data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* were presented, and they are summarized in Table 6.17 together with the most recent data from 2012.

Results and comments

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.

There were two important findings in the 2012 data when compared to previous years. First, the number of GAS infections had increased by almost 70 cases compared to 2011, reflecting the present situation in Sweden with high prevalence of severe cases of this disease (www.smi.se). The proportions of isolates with erythromycin- or tetracycline resistance had not changed, however (Table 6.17). The other important finding was the frequency of resistance to erythromycin in GBS, which had doubled from 6.8 in 2011 to 13.2% in 2012.

Salmonella

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

The annual resistance surveillance and quality control programme (ResNet)

Background

One part of the national surveillance programme on antimicrobial resistance makes use of the web-based software ResNet to receive aggregated data from laboratories and to present them in the form of resistance frequencies in their respective geographical areas on a map of Sweden, and also as individual zone histogram graphs as a tool for internal quality assurance (Appendix 3).

In 2012 six pathogens were included in the programme, and the results for these pathogens are presented here using the same type of graphs as in previous SWEDRES reports to illustrate trends.

TABLE 6.17. Antimicrobial resistance in blood culture isolates of *Streptococcus pyogenes, Streptococcus agalactiae* and *Haemophilus influenzae* during five years (2008-2012).

		2008 (n=11115)[a]		2009 (n=11416)		2010 (n=12296)		2011 (n=16969)		2012 (n=18117)	
Species	**Antibiotic**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**	**n (% of tot)**	**% R**
Streptococcus pyogenes	Ery	196 (1.8)	0.5	134 (1.2)	2.2	118 (1.0)	1.7	188 (1.1)	3.2	257 (1.4)	2.3
	Tet		14.6		9.7		12.7		13.3		12.5
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
	Cli		6.5		3.8		5.4		5.8		13.7
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
	Beta+ [b]		23.8		20.4		6.6		nd		8.7
	Ctx		nd		nd		nd		2.5		1.9
	Tsu		14.3		14.3		13.3		15.8		22.3

[a] Total number of positive blood cultures from ten laboratories. [b] Beta+ = betalactamase producing isolates.

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 2001. 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 2012, 22 laboratories delivered data according to the recently introduced EUCAST methodology (Appendix 3), and 8360 isolates were included in the analysis (Figure 6.14). The average resistance rates for all tested antibiotics were very similar between 2011 and 2012. It should be noted that nalidixic acid is no longer recommended as a screening disk for fluoroquinolone resistance. Ciprofloxacin 5 µg is the recommended disk, and the resistance figure 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.

Klebsiella pneumoniae

Klebsiella pneumoniae is one of the most important bacterial species from a hospital infection control point of view. Bacteria mainly derived from urine samples have been included in the surveillance programme since 2005. In 2012, 21 laboratories delivered data according to the recently introduced EUCAST methodology (Appendix 3), and 2241 isolates were included in the analysis (Figure 6.15). The results indicate that the rates of resistance to all tested antibiotics were the same or slightly lower than in 2011.

Pseudomonas aeruginosa

Pseudomonas aeruginosa has since 2003 been included yearly in the surveillance programme, except for 2005 and 2008. Laboratories have been asked to test 100 consecutive isolates of *P. aeruginosa* with the exclusion of respiratory isolates. In 2012, 19 laboratories delivered data according to the recently introduced EUCAST methodology (Appendix 3), and 1980 isolates were included in the analysis (Figure 6.16). Aminoglycoside resistance (gentamicin and/or tobramycin

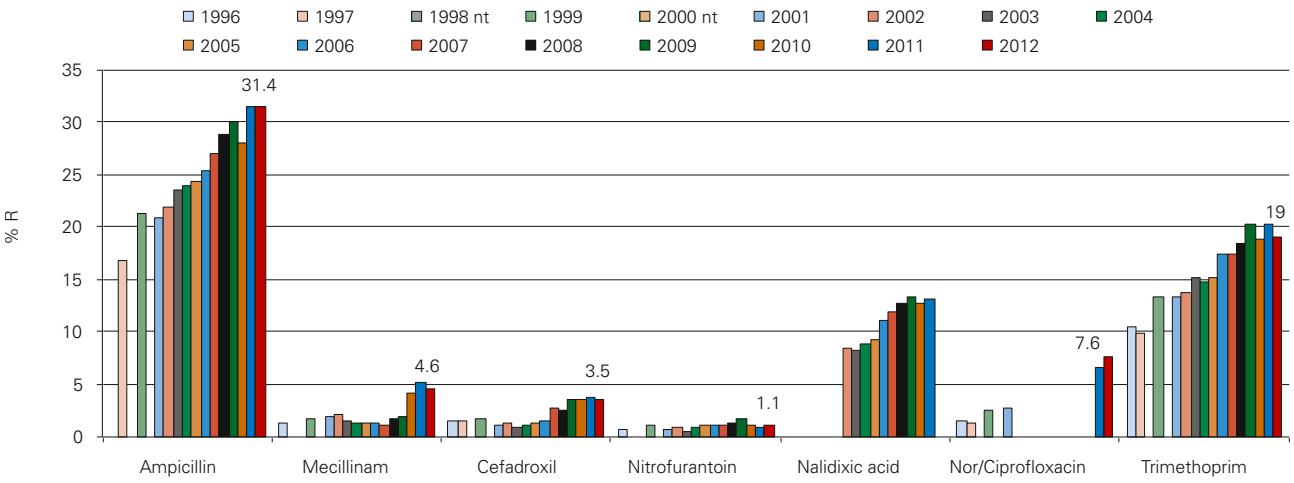


FIGURE 6.14. Resistance rates for UTI antibiotics in *Escherichia coli* 1996-2012. Resistance (R) to fluoroquinolones was tested by norfloxacin 1996-2001, by nalidixic acid (screening for I+R) 2002-2011, and by ciprofloxacin from 2011 and onwards. Zone breakpoints relevant at the time of testing were always used.

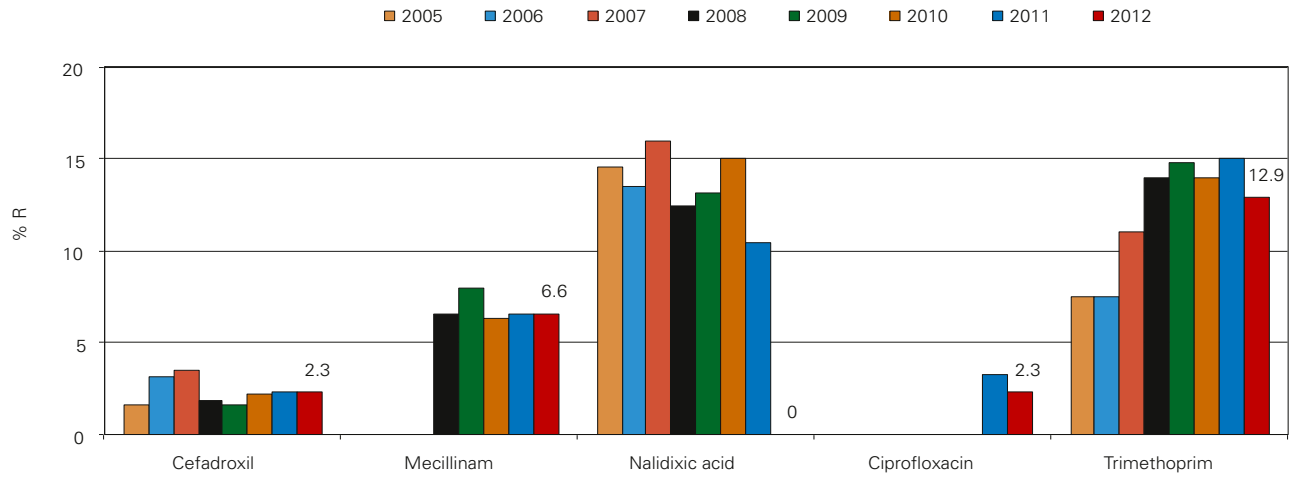


FIGURE 6.15. Resistance rates for UTI antibiotics in *Klebsiella pneumoniae* 2005-2012. Resistance (R) to fluoroquinolones was tested by nalidixic acid (screening for I+R) 2005-2011, and by ciprofloxacin from 2011 and onwards. Zone breakpoints relevant at the time of testing were always used.

tested) seemed stable around 1%. Four beta-lactam antibiotics were tested; one cephalosporin, one penicillin-inhibitor combination, and two carbapenems. For ceftazidime, rates of resistance have increased and now exceed 5%, and for piperacillin-tazobactam (not tested before 2010) the rates of resistance seems stable around 7%. For the carbapenems, resistance to imipenem continued to be higher (8.6%) than to meropenem (5.8%) in 2012. Resistance to ciprofloxacin seems to have stabilized around 10%.

Staphylococcus aureus

Staphylococcus aureus from skin and soft tissue infections has been included in the annual surveillance programme since 2001 (Appendix 3). In 2012, 23 laboratories provided data on 200 consecutive isolates each using the disk diffusion method for cefoxitin (screening disk for detection of MRSA), clindamycin, erythromycin, fusidic acid, and an aminoglycoside (gentamicin or tobramycin). Norfloxacin was used as screening disk for detection of fluoroquinolone resistance. The average resistance rates, as retrieved from ResNet, are shown in Figure 6.17.

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 2012. The average resistance rates for erythromycin, clindamycin, fusidic acid and norfloxacin were almost the same as in the previous 2 years. Resistance to aminoglycosides had increased but 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 3000 consecutive isolates from all clinical laboratories have been tested for suscepti-

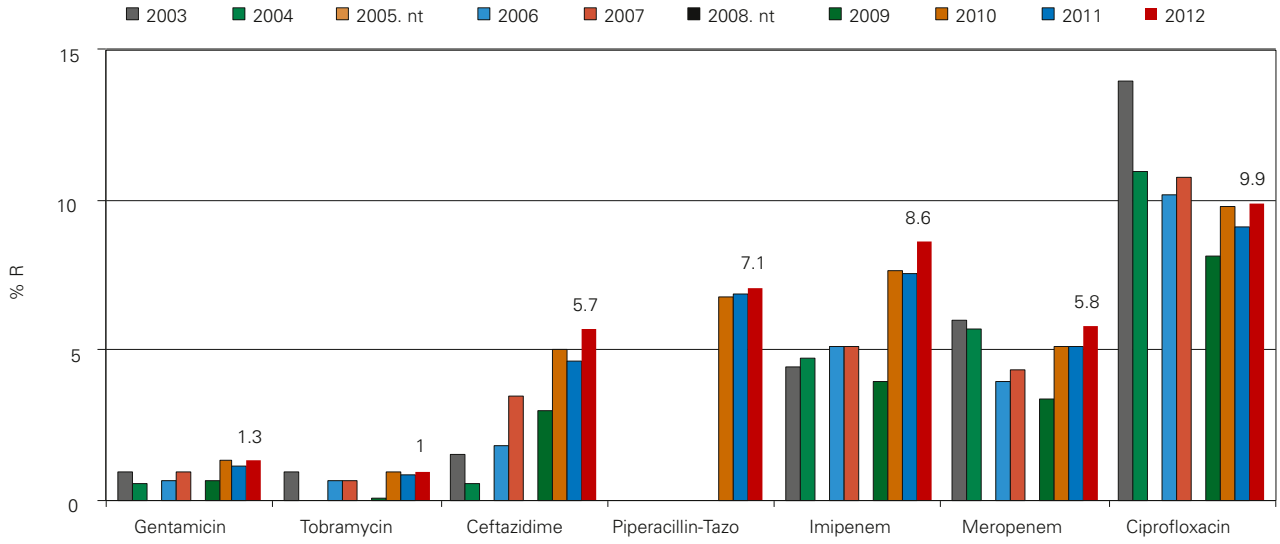


FIGURE 6.16. Resistance rates for four groups of antibiotics tested against *Pseudomonas aeruginosa* 2003-2012 (no data collected in 2005 and 2008).

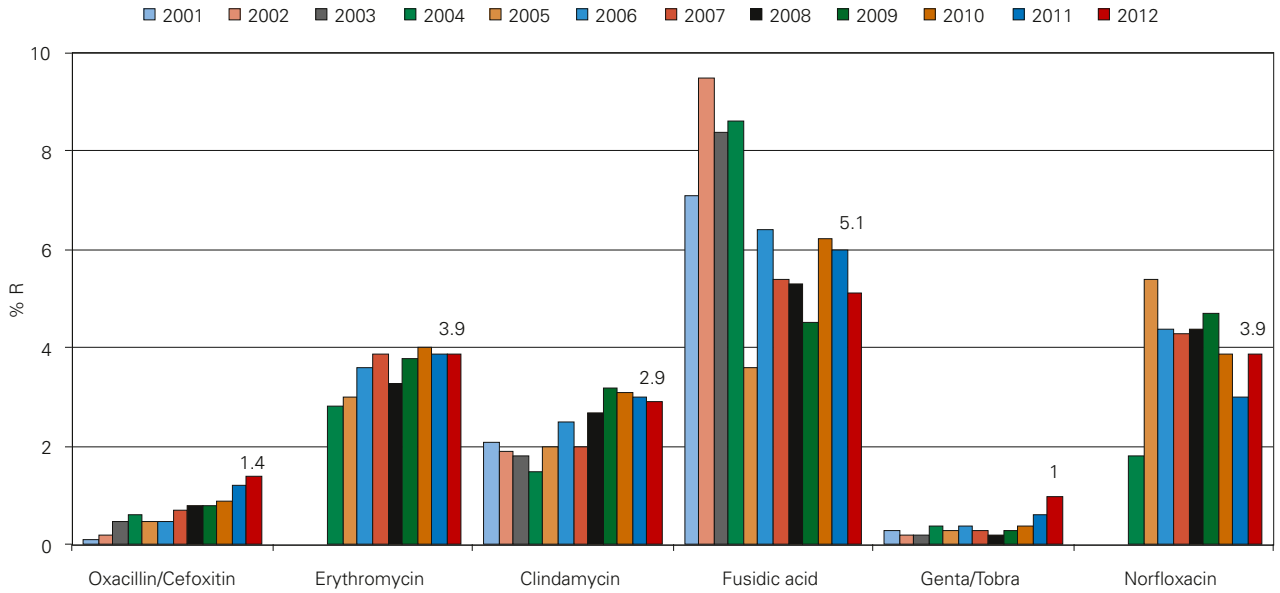


FIGURE 6.17. Resistance rates for *Staphylococcus aureus* from skin and soft tissue infections 2001-2012. In 2005 resistance rates were recorded in S. aureus infections from elderly (> 65 years) people only.

bility 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 2012, 21 laboratories delivered data according to the newly introduced EUCAST methodology (Appendix 3), and 2123 isolates were included in the analysis. The national summary of the results, as retrieved from ResNet, are shown in Figure 6.18. During the first 15 years of surveillance there had been an increase in the rates of resistance for all tested antibiotics. However, since 2010 this successive increase has stopped, and in 2012 there was even a substantial decrease in levels of resistance for all tested antibiotics.

Haemophilus influenzae

Haemophilus influenzae was included in the surveillance programme on antibiotic resistance in 2012 as a follow-up to 2008-2011 when a marked increase in rates of penicillin-resistant and trimethoprim-sulfamethoxazole-resistant isolates was seen (Figure 6.19). In 2012, 21 laboratories delivered data according to the newly introduced EUCAST methodology (Appendix 3), and 2149 isolates were included in the analysis. In 2010 methodological changes were introduced (for description see www.nordicast.org) which made results for beta-lactam resistance more difficult to interpret, but by correlating beta-lactamase producing isolates to 6 mm only of penicillin G 1 unit disk, it was possible to get a percentage of the prevalence of this resistance mechanism (Figure 6.19). Other mechanisms of betalactam resistance were then assumed if zones of penicillin G 1 unit disk measured 7-11 mm, allowing for a rough estimation of the frequencies of BLNAR. By doing so the results indicated a dramatic increase in BLNAR during the last couple of years. 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 2012 the previously high rates of resistance to trimethoprim-sulfamethoxazole had increased further and reached more than 25%. Tetracycline resistance in *Haemophilus influenzae* was still rare (less than 1%) as was resistance to fluoroquinolones, detected by the nalidixic acid screening disk.

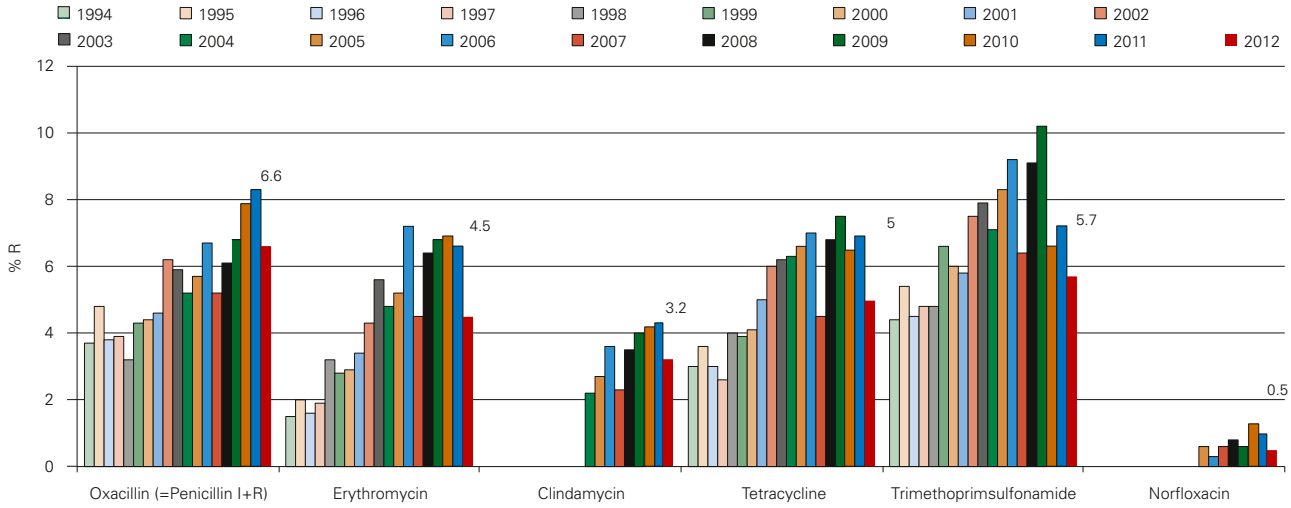


FIGURE 6.18. Resistance rates for *Streptococcus pneumoniae* isolated from respiratory tract specimens 1994-2012.

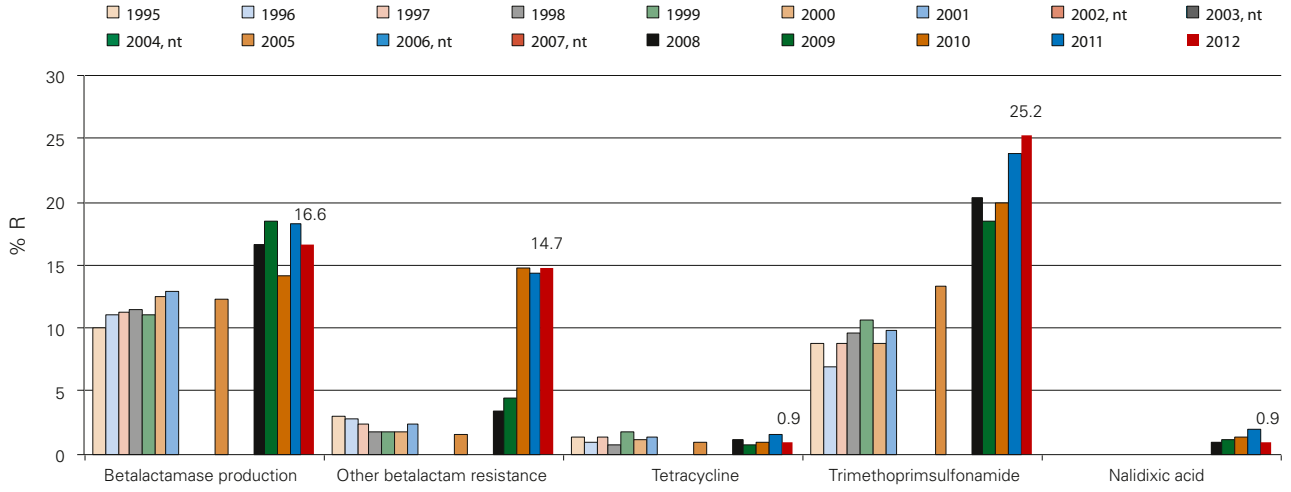


FIGURE 6.19. Resistance rates for *Haemophilus influenzae* 1995-2012 (no data collected in 2002-04 and 2006-07). In 2010-2012 betalactamase producing isolates were separated from isolates with other betalactam resistance mechanisms by use of penicillin G 1 unit disk using the following interpretation: 6 mm = betalactamase production, 7-11 mm = other betalactam resistance.

Clostridium difficile

The *Clostridium difficile* surveillance programme in Sweden

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 collected from the clinical microbiology laboratories. All *C. difficile* strains isolated during week no. 11 and 39 were sent to SMI for PCR ribotyping and antibiotic susceptibility testing. Primarily metronidazole and vancomycin resistance was monitored, *i.e.* the recommended treatment choices for CDI. However, since antibiotic use is a risk factor for acquiring CDI, also three other antibiotics were included as indicators of selective pressure, currently moxifloxacin, clindamycin and erythromycin. All isolates were tested using Etest on Mueller Hinton agar and MICs interpreted according to ECOFFs proposed by EUCAST.

Distribution of resistant *Clostridium difficile* isolates in 2012

In the surveillance programme 2012 a total of 491 isolates were collected from all Swedish counties. None of the isolates were resistant to the current treatment options metronidazole or vancomycin. The proportions of *C. difficile* isolates resistant to moxifloxacin, clindamycin, or erythromycin increased in 2012 compared to 2011 (Table 6.18) and displayed the highest proportions since the surveillance programme started in 2009 (Akerlund et al., 2011). Similar to previous years, *C. difficile* isolates with resistance to moxifloxacin and the other tested antibiotics continued to be clustered in geographical regions, strongly suggesting ongoing local outbreaks of resistant isolates of the PCR ribotypes 012, 017, 046 and 231. (Fig. 6.20 and Table 6.18).

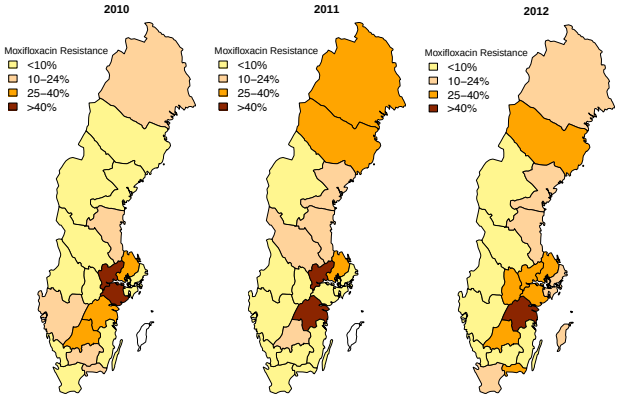


FIGURE 6.20. Proportion of *Clostridium difficile* isolates with resistance to moxifloxacin per county 2010-2012.

TABLE 6.18. Distribution of MICs and resistance (%) in *Clostridium difficile* of different PCR ribotypes tested against erythromycin, clindamycin and moxifloxacin, Sweden 2012 (n=491).

Antimicrobial	PCR ribotype	Resistance (%)	Distribution (no. of strains) per MIC (mg/L)													
			≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Clindamycin	012	94						1				1	1			31
	017	88									1					7
	046	76			1				1	2	1					16
	231	94								1						16
	Other	5				8	37	59	136	102	44	6		1		18
	Total	**18 (15)** [a]			**1**	**8**	**37**	**60**	**137**	**105**	**46**	**7**	**1**	**1**		**88**
Erythromycin	012	91				1	1	1		1	2		4	5	1	18
	017	100												2		6
	046	76					1	3	1							16
	231	94							1				3	1		12
	Other	7	1	1	7	73	123	138	38							30
	Total	**21 (15)**	**1**	**1**	**7**	**74**	**125**	**142**	**40**	**1**	**2**		**7**	**8**	**1**	**82**
Moxifloxacin	012	91						3					31			
	017	75						2					6			
	046	43					5	6	1				9			
	231	94						1					16			
	Other	6				2	67	243	59	5	2	1	22			
	Total	**18 (14)**				**2**	**72**	**255**	**60**	**5**	**2**	**1**	**84**			

[a] Corresponding figure for 2011 in parenthesis.
Shaded areas indicate resistance based on ECOFFs proposed by EUCAST for *C. difficile*: clindamycin R > 16, erythromycin R > 2, moxifloxacin R > 4.

Neisseria gonorrhoeae

Notifications according to the Communicable Diseases Act

Gonorrhoea is a notifiable infection and in 2012, 1098 cases (11.5 cases per 100 000 inhabitants) of gonococcal infections were reported. Most of the cases were identified in the three largest counties of Sweden, including the cities Stockholm, Gothenburg, and Malmö, respectively. In this report we present data on clinical isolates obtained at four different sites: a) WHO Collaborating Centre for Gonorrhoea and other Sexually Transmitted Infections, Swedish Reference Laboratory for Pathogenic Neisseria (an external body of the Swedish Institute for Communicable Disease Control), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital, Örebro; b) Clinical Microbiology Malmoe, Skåne University Hospital, Malmoe; and c) Karolinska University Hospital, site Huddinge and site Solna, Stockholm.

In 2012, a total of 877 different N. *gonorrhoeae* strains from the notified cases were fully characterised at these laboratories, representing 80% of the notified cases.

Antimicrobial susceptibility testing was performed according to standardized methodology using Etest for MIC determination of ampicillin, cefixime, ceftriaxone, azithromycin, ciprofloxacin, and spectinomycin. Clinical breakpoints for SIR categorization were defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Production of betalactamase was examined by nitrocefin disks.

Results and comments

Results for 2012 are compared with those from 2005 to 2011 in Table 6.19**.** Notably, the rates of resistance to all antimicrobials previously used as first-line treatment options for gonorrhoea (penicillins and ciprofloxacin) remained high. The rates of resistance to azithromycin and cefixime have increased substantially during the last 4-5 years. Notably, most of the azithromycin resistant cases were identified in Stockholm, which may reflect an overuse of azithromycin in the treatment of gonorrhoea and/or other sexually transmitted infections, in particular urogenital chlamydial infections. It is of grave concern that also resistance to ceftriaxone, the last remaining option for empirical antimicrobial monotherapy of gonorrhoea, has been increasingly detected during the last three years. No resistance to spectinomycin has still been detected in Sweden, however, the availability of spectinomycin is limited (in Sweden as well as worldwide), and the drug is not suitable for treatment of pharyngeal gonorrhoea.

Neisseria meningitidis

Notifications according to the Communicable Diseases Act

Invasive meningococcal disease is a notifiable disease, and in 2012 a total of 106 clinical cases (1.1 cases per 100 000 inhabitants) of the disease were reported. All together 90 clinical 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 Swedish Institute for Infectious Disease Control [SMI]), Department of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital.

Antimicrobial susceptibility testing was performed according to standardized methodology using Etest for determinations of MICs of penicillin G, cefotaxime, meropenem, chloramphenicol, ciprofloxacin and rifampicin. Production of betalactamase was examined by nitrocefin disks.

None of the isolates produced betalactamase. Fifteen (17%) isolates had reduced susceptibility to penicillin G (MIC >0.064 mg/L). All isolates were susceptible to cefotaxime (MICs 0.002-0.032 mg/L), meropenem (MICs 0.004-0.032 mg/L), chloramphenicol (MICs 0.125-2 mg/L), and rifampicin (MICs 0.002-0.064 mg/L). One (1.1%) isolate displayed intermediate susceptibility to ciprofloxacin (MIC 0.064 mg/L) and one (1.1%) isolate was resistant (MIC=0.25 mg/L).

Mycobacterium tuberculosis

Notifications according to the Communicable Diseases Act

During 2012 in total 645 cases of tuberculosis (TB) were reported compared to 595 cases during 2011 which is an increase by 8%. The number and proportion of culture confirmed cases were 503 (78%) compared to 476 (80%) in 2011. *Mycobacterium tuberculosis* was identified in 497 cases, *Mycobacterium africanum* in one patient and *Mycobacterium bovis* in five patients. The proportions of cases diagnosed with isoniazid resistant TB in 2012 were 10% (49/498) and MDR 2.8% (14/498) out of which two were XDR-TB.

TABLE 6.19. Antibiotic resistance rates (%) and beta-lactamase production of Swedish *Neisseria gonorrhoeae* isolates 2005-2012.

	2005 (n=497)	2006 (n=352)	2007 (n=406)	2008 (n=447)	2009 (n=384)	2010 (n=618)	2011 (n=805)	2012 (n=877)
Beta-lactamase producing	23	30	30	28	44	29	23	23
Ampicillin	23	30	30	28	44	31	24	23
Cefixime[a]	0	0	<1	1	5	6	8	10
Ceftriaxone[a]	0	0	0	<1	0	2	2	1
Azithromycin[a]	<1	5	7	13	6	12	11	10
Ciprofloxacin	49	61	70	63	75	56	55	62
Spectinomycin	0	0	0	0	0	0	0	0

[a] For cefixime, ceftriaxone and azithromycin, new SIR criteria were introduced in 2009 and the results from previous years have been recalculated.

Isolates of *M. tuberculosis* and *M. africanum* resistant to at least one of the four first line drugs (isoniazid, rifampicin, ethambutol or pyrazinamid) were identified in 60 patients corresponding to 12% of the 498 with culture confirmed TB, Table 6.20. The five patients with *M. bovis* were not included since these strains are naturally resistant to pyrazinamid. As always the most common resistance found was isoniazid resistance. Among the patients born in Sweden 5 (6.8%) had resistant TB and two of those had MDR-TB. They were the first two cases with MDR-TB among cases born in Sweden since many years. They had both spent a long time abroad in high-incidence settings and were probably infected there. None of them had a history of previous TB treatment. Around 85% of the TB patients in Sweden are born in another country. In this group 13% (55/425) had some kind of resistant TB and 12 of those 55 had MDR- or XDR-TB, which makes 3% (12/425).

Of the culture confirmed cases 34 (7%) had a history of previous treatment for TB after 1949, at which time effective medication became available. Out of those 34 cases, 7 (21%) had strains resistant to any of the first line drugs including 3 (9%) MDR-TB. The corresponding figures for cases with no reported previous treatment were 11.4 % (53/464) out of which 11 (2.4%) were MDR-TB.

None of the two cases with XDR-TB were born in Sweden. Twelve cases with MDR/XDR-TB were not of Swedish origin and ten of them came to Sweden in 2009 or later. In total nine of the 14 cases had pulmonary manifestations and among them seven were smear positive.

Genetic typing with MIRU-VNTR (Mycobacterial Interspersed Repetitive Units - Variable Numbers of Tandem Repeat) has been performed on 59 of the 60 resistant strains so far. This is done to help detect clusters which could indicate ongoing spread of resistant strains. Twenty-three of the 59 examined strains belong to 20 different clusters with two or more patients in each cluster. The majority of the clustering cases belong to clusters with no resistant strains which make recent spread unlikely, the common factor in the cluster most often being the same country of origin.

The proportion of patients with *M. tuberculosis* resistant to isoniazid has gradually increased from 7.5% in 2003 to 12% in 2011, but in 2012 there was a decrease to 9.8%. The annual proportion of MDR-TB increased from 0.8% in 2006 to 4.2% in 2007, dropped in 2009 but increased again to 3.6% in 2011. In 2012 it has decreased to 2.8% but two XDR-TB cases are included in this which is a serious sign of the increasing problem with resistant TB world-wide.

TABLE 6.20. Drug resistant tuberculosis in Sweden 2003-2012.

Year of diagnosis	2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
Culture confirmed *M. tuberculosis* or *M. africanum*	345		368		448		395		361		434		510		523		473		498	
	No	%	No	%	No	%	No	No	%	%	No	%	No	%	No	%	No	%	No	%
Any resistance	32	9.3	43	11.7	52	11.6	43	68	13.0	13.6	57	13.1	58	11.4	68	13	73	15.4	60	12
Isoniazid	26	7.5	35	9.5	46	10.3	38	57	10.9	12.7	51	11.8	51	10.0	57	10.9	57	12	49	9.8
Rifampicin	10	2.9	6	1.6	5	1.1	6	1.5	15	4.2	15	3.5	14	2.7	20	3.8	19	4	15	3
Ethambutol	5	1.4	3	0.8	3	0.7	1	0.3	7	1.9	6	1.4	7	1.4	12	2.3	10	2.1	12	2.4
Pyrazinamid	7	2.0	12	3.3	6	1.3	6	1.5	11	3.0	18	4.1	15	2.9	20	3.8	27	5.7	23	4.6
Isoniazid + rifampicin (MDR)	8	2.3	5	1.4	4	0.9	3	0.8	15	4.2	14	3.2	13	2.5	18	3.4	17	3.6	14	2.8

Resistance in clinical isolates from animals

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

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

Pigs

Escherichia coli

Isolates are from clinical submissions of samples from the gastro-intestinal tract. In general only *E. coli* isolates that harbour genes coding for virulence factors are tested for susceptibility. The presence of genes coding for the following proteins are determined by PCR: enterotoxin (LT), heat-stable enterotoxin a and b (STa and STb), verocytotoxin (VT2e) and adhesion factors F4, F5, F6, F18 and F41. Isolates with at least one of these genes are generally tested for antimicrobial susceptibility. Before October 2007, *E. coli* isolates from the gastro-intestinal tract were tested regardless of presence of virulence factors.

As in previous years, resistance to ampicillin, streptomycin, tetracycline or trimethoprim-sulphonamides was most commonly occurring (Table 6.21). Multiresistance occurred in 24% of the isolates in 2012, 25% in 2011, 15% in 2010, 19% in 2009 and 14% in 2008. The combination of resistance to ampicillin, streptomycin and trimethoprim-sulphonamides was the most common trait in 2012, as in previous years, occurring in 56% of the multiresistant isolates. Seven percent of all isolates were resistant to four antimicrobials.

TABLE 6.21 Distribution of MICs and resistance (%) in *Escherichia coli* from pigs 2012. Isolates are from clinical submissions of faecal samples or samples taken post mortem from the gastro-intestinal tract.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2012 n=74	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	27				8.1	59.5	5.4		27.0		
Ceftiofur	0		32.4	63.5	4.1						
Enrofloxacin	7	93.2	2.7	1.4	2.7						
Florfenicol	0					12.2	52.7	31.1	4.1		
Gentamicin	0					98.6	1.4				
Neomycin	4						93.2	2.7			4.1
Streptomycin	36						17.6	28.4	17.6	6.8	29.7
Tetracycline	27				18.9	40.5	9.5	4.1	27.0		
Trim-Sulph.[a]	26			74.3			1.4	24.3			

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

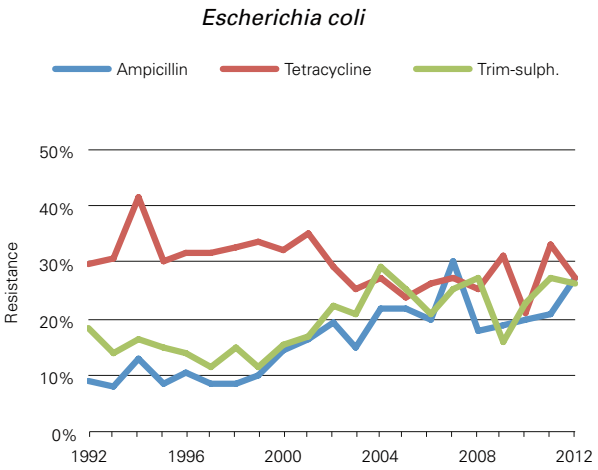


FIGURE 6.21. Percent resistance to ampicillin, tetracycline and trimethoprim-sulphametoxazole in *Escherichia coli* from pigs, 1992-2012. The number of isolates each year varies (n=74-482).

Brachyspira hyodysenteriae

Isolates are from clinical submissions of faecal samples. Analysis of antimicrobial susceptibility data from isolates of *B. hyodysenteriae* from Sweden 1990-2010 has resulted in the proposal of epidemiological cut-off values for the antimicrobials tested at SVA (Pringle et al., 2012). For more information on cut-off values for *B. hyodysenteriae*, see "Antimicrobial susceptibility of *Brachyspira hyodysenteriae* isolated from pigs between 1990 and 2010". In Table 6.22 these cut-off values are used and historical data have been adjusted. With the new epidemiological cut-off value >0.25 mg/L for tiamulin, some isolates are classified as resistant or with decreased susceptibility. However, with the previously used clinical cut-off value >2 mg/L, no isolate was classified as resistant. The cut-off value 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 are from clinical submissions of faecal samples. Epidemiological cut-off values for *B. pilosicoli* are not available for the antimicrobials tested. As guide for the choice of antimicrobial for treatment of spirocheatal diarrhoea, a clinical breakpoint for tiamulin of >2 mg/L and for tylosin of >16 mg/L are used at SVA. With these clinical breakpoints, 12% of the isolates are resistant to tiamulin and 61% to tylosin (Table 6.23). Only tiamulin and tylosin are currently licensed for treatment of spirocheatal diarrhoea in pigs in Sweden and isolates with high MICs of both these substances are detected.

TABLE 6.22. Resistance (%) in *Brachyspira hyodysenteriae* from pigs 2005-2012 and distribution of MICs for isolates from 2009-2012. Isolates are from clinical submissions of faecal samples.

Antimicrobial	Resistance (%)			Distribution (%) of MICs (mg/L)												
	2005-06 n=54[a]	2007-08 n=38[b]	2009-12 n=47[d]	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline	9	3	4			10.6	72.3	12.8		4.3							
Tiamulin	7	18	6		44.7	34.0	14.9	4.3	2.1								
Tylosin	81	76	55								23.4	19.1	2.1			2.1	53.2
Tylvalosin	-	93[c]	53				2.1	19.1	25.5	4.3	8.5	23.4	12.8		4.3		
Valnemulin	0	18	2	89.4	8.5			2.1									

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

TABLE 6.23 Distribution of MICs for *Brachyspira pilosicoli* from pigs 2005-2012, n=264. Isolates are from clinical submissions of faecal samples.

Antimicrobial	Distribution (%) of MICs (mg/L)													
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128
Doxycycline			37.9	49.2	4.5	3.0	4.9	0.4						
Tiamulin		30.7	28.0	12.9	8.3	6.4	1.9	0.4	1.9	9.5				
Tylosin							5.3	19.3	11.0	3.4	4.9	3.4	4.9	47.7
Tylvalosin[a]					10.9	19.8	26.7	5.9	2.0	5.0	16.8	12.9		
Valnemulin	43.9	21.6	6.4	9.1	6.4	4.5	2.3	1.5	4.2					

[a] 101 isolates tested.

Actinobacillus pleuropneumoniae

Isolates are from post mortem investigations of lungs. Most isolates from 2011 and 2012 are isolated from lung samples taken at slaughterhouses within the monitoring programme SVARMpat. The resistance situation is favourable and almost no resistance is detected (Table 6.24). 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.

Isolates are from post mortem investigations of lungs or 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 post mortem investigations of lungs are most likely from pigs with respiratory disease. Antimicrobial resistance is rare among isolates of *Pasteurella* spp. (Table 6.25).

TABLE 6.24 Distribution of MICs and resistance (%) in *Actinobacillus pleuropneumoniae* from pigs 2005-2012. Isolates are from post mortem investigations of lungs. The number of isolates each year varies (n=16-57)

Antimicrobial	Resistance (%) 2005-12 n=253	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	>128
Ampicillin	0						100									
Cefotaxime	0		75.1	24.9												
Chloramph.	0								100							
Ciprofloxacin	0	0.8	72.3	26.9												
Florfenicol	0									100						
Gentamicin	0							0.4	6.7	78.7	14.2					
Nalidixic acid	0							3.2	61.7	35.2						
Penicillin	0				4.7	66.4	28.9									
Streptomycin	2								0.4		2.4	45.8	49.8	1.9		
Tetracycline	0							99.6	0.4							
Trimethoprim	0				20.2	62.8	13.4	2.4	1.2							

TABLE 6.25 Distribution of MICs and resistance (%) in *Pasteurella* spp. from pigs 2005-2012. Isolates are from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs.

Antimicrobial	Resistance (%) 2005-12 n=138	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	>64
Ampicillin	0								100							
Chloramph.	0[a]									100						
Ciprofloxacin	0[a]	21.6	58.8	18.6	1.0											
Enrofloxacin	0[b]					97.6	2.4									
Florfenicol	0[c]										97.8	2.2				
Gentamicin	1									72.5	23.2	3.6	0.7			
Nalidixic acid	0[a]								50.5	40.2	8.2		1.0			
Penicillin	0					29.7	63.0	7.2								
Streptomycin	6										3.6	40.6	37.0	13.0	5.8	
Tetracycline	0								97.8	2.2						
Trimethoprim	0[a]						68.0	25.8	3.1		3.1					

[a] 97 isolates tested; [b] 41 isolates tested; [c] 134 isolates tested.

Cattle

Escherichia coli

Isolates are from the gastro-intestinal tract of calves. In 2012, 21 isolates are from samples investigated at SVA and 37 isolates emanate from post mortem investigations of calves at a regional laboratory in the southern part of Sweden. There are differences in resistance in the two collections of isolates with more resistance to enrofloxacin, neomycin and trimethoprim-sulphonamides and less to tetracycline in the material from the regional laboratory compared to the material from SVA. For example geographical origin, type of herds and indication for sampling may influence the differences in resistance, but no conclusions can be drawn. In the whole material from 2012, resistance to streptomycin, tetracycline and ampicillin was most commonly occurring (Table 6.26) Multiresistance occurred in 50% of the isolates compared to 40% in 2007-2011.

Two isolates from 2010 and one isolate from 2012 had a MIC of ceftiofur above the cut-off value. The isolates from 2010 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.

Pasteurella spp.

Isolates are from nasal swabs from calves with respiratory disease or from post mortem investigations of lungs. Antimicrobial resistance is rare among isolates of *Pasteurella* spp. (Table 6.27) and penicillin is considered the substance of choice for treatment of pneumonia in calves in Sweden. Isolates of betalactamase producing *Pasteurella* spp. have been confirmed in one herd in 2003 and betalactamase producing *Mannheimia haemolytica* in one herd in 2010.

TABLE 6.26 Resistance (%) in *Escherichia coli* from cattle 1992-2002 and 2005-2012. Distribution of MICs for isolates from 2012. Isolates are from diagnostic submissions of faecal samples or samples taken post mortem from the gastro-intestinal tract.

Antimicrobial	Resistance (%)				Distribution (%) of MICs (mg/L)									
	1992-02 n=220	2005-06 n=63	2007-11 n=70	2012 n=58	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	24	32	33	48				3.4	37.9	8.6	1.7	48.3		
Ceftiofur[a]	0[g]	0	3	2		5.2	82.8	10.3	1.7					
Enrofloxacin[b]	10	13	10	19	81.0	3.4	1.7	1.7	12.1					
Florfenicol	0[g]	0	1	0						34.5	63.8	1.7		
Gentamicin[c]	5	0	1	2					77.6	20.7		1.7		
Neomycin	8	13	24	19						60.3	20.7	3.4	1.7	13.8
Streptomycin[d]	42	54	49	74						3.4	20.7	1.7	3.4	70.7
Tetracycline	31	49	64	69				8.6	17.2	5.2		69.0		
Trim/Sulph.[e,f]	11	21	17	24			75.9			1.7	22.4			

[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/sulphametoxazole); [f] Cut-off value >4 mg/L until 2006; [g] 16 isolates tested.

TABLE 6.27 Distribution of MICs and resistance (%) in *Pasteurella* spp. from calves 2005-2012. Isolates are from the respiratory tract, isolated from nasal swabs or from post mortem investigations of lungs.

Antimicrobial	Resistance (%)	Distribution (%) of MICs (mg/L)									
	2005-12 n=215	≤0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Ampicillin	0					100					
Enrofloxacin	0[b]		95.8	4.2							
Florfenicol	0							100			
Penicillin	0		47.4	43.3	9.3						
Tetracycline	0					97.7	2.3				
Trim/Sulph.[a]	0				96.7	1.9	0.9	0.5			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphametoxazole); [b] 190 isolates tested.

Antimicrobial susceptibility of Brachyspira hyodysenteriae isolated from pigs between 1990 and 2010

The anaerobic spirochete *Brachyspira hyodysenteriae* is the causative agent of swine dysentery, a major disease of pigs world-wide. Antimicrobial agents such as pleuromutilins, macrolides and lincosamides are important in the control of the infection. However, resistance to these antimicrobial agents is an increasing threat to the treatment options and there are recent reports on multiresistant isolates of *B. hyodysenteriae* (Hidalgo et al. 2011; Sperling et al., 2011). Antimicrobial susceptibility tests of *B. hyodysenteriae* are not always performed routinely and there are no generally approved or recommended standards. However, a broth dilution method has been evaluated (Karlsson et al., 2003) and is used in SVARM for monitoring susceptibility in *Brachyspira* spp. Quality control MIC ranges for the type strain of *B. hyodysenteriae*, B78^{T} (ATCC 27164^{T}), has been established for this method (Pringle et al., 2006) but no criteria for interpretation of the results have been officially established.

Here, MICs of five antibiotics for *B. hyodysenteriae* isolated between 1990 and 2010 are compiled and wild type cut-off values based on MIC distributions and the current knowledge on mechanisms of resistance in this species are proposed. The antimicrobial agents in the test panels have changed during those years why the numbers of isolates tested for each antimicrobial agent varies (Figure). Arrows indicate the proposed cut-off values for tiamulin >0.25 mg/L, valnemulin >0.125 mg/L, tylosin >16 mg/L, tylvalosin >1 mg/L and doxycycline >0.5 mg/L.

A gradual increase in tiamulin MICs was seen between 1990 and 2003 although this increase has ceased during the last years and the results from 2004-2010 are comparable to the results from 2002-2003. In *Brachyspira* spp. decreased susceptibility to tiamulin develops in a stepwise manner for which the genetic background is only described in part (Pringle et al., 2004; Hidalgo et al., 2011). Several mutations altering the binding site at the ribosome can be present in different combinations causing varying increases of tiamulin MIC but there are also isolates with high tiamulin MICs in which none of the known changes can be found. This mix of clones with different susceptibility causes a trailing endpoint in MIC distribution diagrams and difficulties to define a wild type cut-off value to separate the wild type from isolates with acquired decreased susceptibility. For valnemulin the MICs follow the tiamulin MICs in most cases but are generally a few dilution steps lower. In Figure the MICs of tiamulin for *B. hyodysenteriae* are shown in two diagrams, one with all 582 isolates together and one with three subpopulations of in total 457 isolates (1990-1997, 1998-2001 and 2002-2003). For the first subpopulation, 1990-1997, the peak of the susceptible population is at an MIC of 0.031-0.063 mg/L but in the whole population, 1990-2010, the peak appears to be at 0.125 mg/L thus masking a decreased susceptibility of the wild-type population. Because the mechanisms of tiamulin resistance are only partly known this masked decreased susceptibility can only be detected if monitoring begins in time when a sufficient proportion of a population under selection pressure is still of wild type.

For monitoring of resistance it is more important to detect the low-level resistance (or decreased susceptibility) than to find the isolates with the highest MICs. The low-level resistance could be the first step towards higher MICs and hence more important to control. To monitor a gradual decrease in susceptibility such, as for tiamulin in *Brachyspira* spp., a wild type cut-off value close to the edge of the susceptible wild type distribution is needed, which would be at 0.125-0.25 mg/L. In previous SVARM reports a tiamulin cut-off for resistance in *B. hyodysenteriae* of >2 mg/L has been used. This cut-off is also used at SVA as a clinical breakpoint for resistance.

The results of this study have previously been published in: **Pringle M, Landen A, et al.** 2012, Antimicrobial susceptibility of porcine *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli* isolated in Sweden between 1990 and 2010. *Acta Vet Scand*, 54:54.

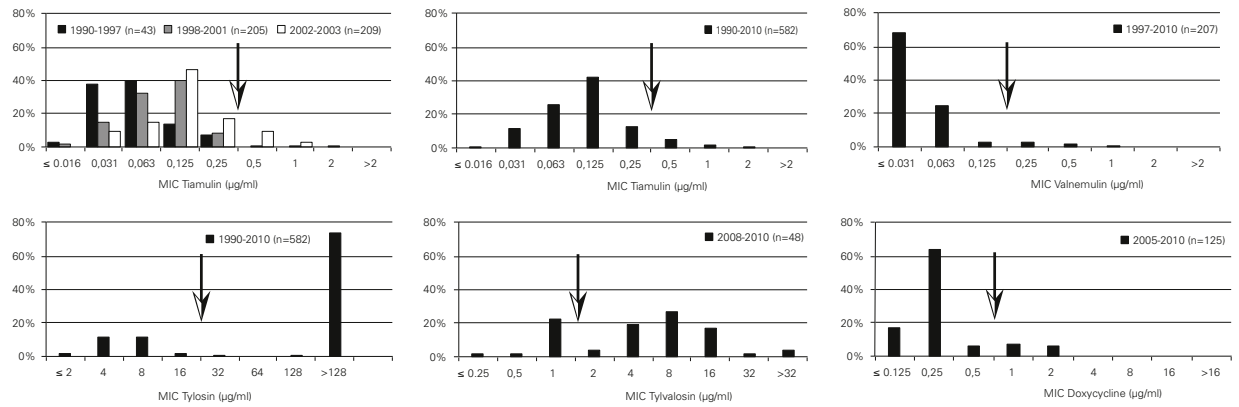


FIGURE. Distribution of MIC of five antimicrobial agents for Swedish field isolates of *B. hyodysenteriae*. Arrows indicate proposed wild type cut-off values.

SVARMpat

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

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

Studies performed include sampling of animals for defined bacterial pathogens and subsequent susceptibility testing. The programme also encourages practitioners and laboratories to routinely submit certain samples from clinical cases and post mortem investigations. Such continuous clinical submissions yield isolates of *Actinobacillus pleuropneumoniae* and *Brachyspira* spp. from pigs and *Pasteurella* spp. from cattle and pigs. Susceptibility testing of these isolates is performed within SVARMpat.

SVARMpat projects 2012:

Screening for MRSA in milk samples from cows was started in 2010 and is still ongoing. Selected isolates of beta-lactamase producing *Staphylococcus aureus* from routine submissions to SVA are investigated for methicillin resistance. During 2010-2012, 441 isolates were tested and MRSA with *mecC* was confirmed in three isolates from 2010 and one from 2011, and MRSA with *mecA* was confirmed in one isolate from 2012.

MRSA-sampling in dairy herds in South-east Sweden. One bulk tank milk sample, milk samples and hock skin samples from five cows and nasal swabs from five preweaned calves from each of 40 dairy herds were analysed for MRSA with selective methods. MRSA was not detected.

Studies in herds with respiratory disease in calves. Investigation of possible reasons to therapeutic failure, including bacteriological sampling and post mortem investigations, are performed.

Enteritis in young calves. Analysis of virulence factors in *E. coli* isolates from post mortem investigations of calves is performed.

***Mycoplasma ovipneumoniae* in sheep.** During 2010-2012, samples were taken at post mortem investigations of lungs from sheep with pneumonia. Altogether, about 100 samples were analysed and *M. ovipneumoniae* was detected in 35 of them.

Exudative epidermitis in piglets. Piglets with exudativ epidermitis are sampled and isolated strains of *Staphylococcus hyicus* are susceptibility tested. Since 2011, pigs from 10 herds have been sampled and *S. hyicus* was isolated from all sampled pigs but one. Penicillin resistance was detected in four out of 14 isolates.

Otitis media in pigs. Post mortem investigations are performed on pigs with tilted heads and bacteriological samples are taken from the middle ear and nasal cavity. Eleven pigs have been investigated since 2011.

ESBL-producing *E. coli* in broilers. The occurrence and epidemiology of ESBL-producing *E. coli* are studied in several projects.

Farmed fish

Isolates presented are from clinical submissions of farmed fish. In 2012, data for 5 isolates of *Aeromonas salmonicida* subsp. *achromogenes*, 3 of *Flavobacter columnare* and 31 of *Flavobacter psychrophilum* were available. Data for 2009-2012 are compiled and presented as distributions of MICs in Table 6.28. The majority of the isolates from the two former species is from brown trout whereas most isolates of *F. psychrophilum* are from rainbow trout.

At present there are no accepted interpretative criteria for MIC data of bacteria from aquaculture. However, deviating high MICs of some isolates indicates the presence of acquired resistance. For example, in *A. salmonicida* and *F. psychrophilum* MIC distributions for the quinolone nalidixic acid are bimodal. Likewise, among *F. psychrophilum* there are some isolates with deviating MICs for tetracycline. Acquired resistance to these antimicrobials is plausible since there is a limited therapeutic use of the oxolinic acid as well as of tetracycline in aquaculture in Sweden.

Horses

Escherichia coli

Isolates included are from the genital tract of mares. In 2012, resistance to trimethoprim-sulphonamides or streptomycin were the two most common resistance traits (Table 6.29). In Figure 6.22, rates of resistance from 2003 and onwards are shown for ampicillin, gentamicin, streptomycin and trimethoprim-sulphametoxazole.

Multiresistance occurred in 6% of the isolates which is

a lower figure compared to last year. A majority of multiresistant *E. coli* isolates was resistant to ampicillin, streptomycin and trimethoprim-sulphonamides. None of the isolates were resistant to five or more substances.

In 2012, two isolates had MICs of ceftiofur >1 mg/L and they tested positive for production of ESBL. These two *E. coli* isolates produced CTX-M-1enzyme. Besides being resistant to betalactams, these two isolates were also resistant

TABLE 6.28. Distribution of MICs for *Aeromonas salmonicida* subsp. *achromogenes* (n=50), *Flavobacter columnare* (n=26) and *Flavobacter psychrophilum* (n=103) from farmed fish 2009-2012.

Bacterial species	Antimicrobial	Distribution (%) of MICs (mg/L)									
		≤0.25	0.5	1	2	4	8	16	32	64	>64
Aeromonas salmonicida subsp. *achromogenes*	Florfenicol				96.0	2.0		2.0			
	Nalidixic acid		80.0	2.0					2.0	6.0	10.0
	Tetracycline	78.0	14.0	4.0		2.0		2.0			
Flavobacter columnare	Florfenicol				100						
	Nalidixic acid		76.9	15.4	3.8	3.8					
	Tetracycline	76.9	23.1								
Flavobacter psychrophilum	Florfenicol				99.0		1.0				
	Nalidixic acid				16.5	19.4	2.9	1.0	3.9	6.8	49.5
	Tetracycline	33.0	9.7	30.1	5.8	18.4	2.9				

TABLE 6.29 Distribution of MICs and resistance (%) in *Escherichia coli* from horses 2012. Isolates are from clinical submissions of samples from the female genital tract.

Antimicrobial	Resistance (%) 2012 n=196	Distribution (%) of MICs (mg/L)									
		≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	7				3.6	46.9	39.8	2.6	7.1		
Ceftiofur	1		7.7	75.0	16.3		1.0				
Enrofloxacin	4	95.9	2.6	0.5	0.5	0.5					
Florfenicol	<1					3.6	40.3	53.6	2.0	0.5	
Gentamicin	2					94.4	3.6	1.0		1.0	
Neomycin	<1						98.0	1.5	0.5		
Streptomycin	12						13.3	31.6	43.4	2.0	9.7
Tetracycline	3				19.4	73.5	4.1		3.1		
Trim-Sulph.	12			86.7	1.0			12.2			

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

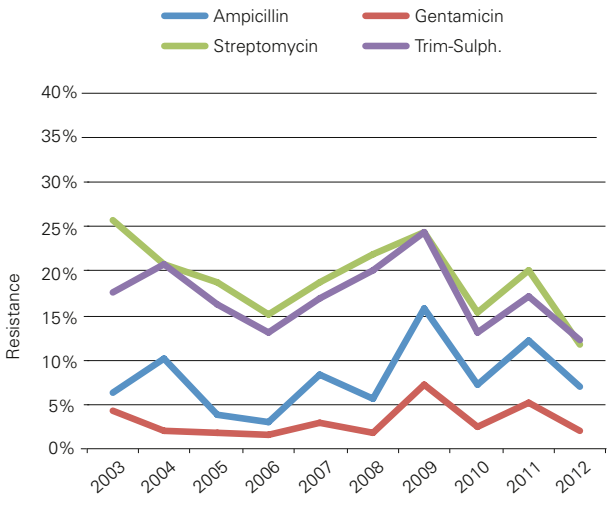


FIGURE 6.22 Percent resistance to ampicillin, gentamicin, streptomycin and trimethoprim-sulphametoxazole in *Escherichia coli* from the female genital tract in horses 2003-2012.

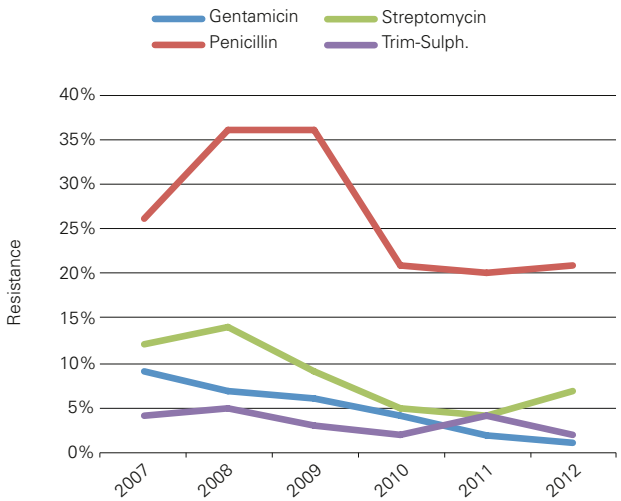


FIGURE 6.23 Percent resistance to gentamicin, penicillin, streptomycin and trimethoprim-sulphametoxazole in *Staphylococcus aureus* from skin disorders in horses, 2007-2012.

to gentamicin, trimethoprim-sulphonamides and to tetracycline and fluoroquinolones, respectively. For further information on ESBL-producing Enterobacteriaceae isolated from horses in Sweden, see Section Antimicrobial resistance as notifiable diseases.

Streptococcus zooepidemicus

Isolates included are from the respiratory tract. As in previous years, resistance in *Streptococcus zooepidemicus* is rare (Table 6.30). Occurrence of resistance to trimethoprim-sulphonamides has been high during the last 15 years. However, in 2011 only 8% of the isolates were resistant to this combination which is the lowest figure since the beginning of the 90s. Isolates of *S. zooepidemicus* are uniformly susceptible to penicillin but have a low inherent susceptibility to fluoroquinolones and aminoglycosides (*i.e.* gentamicin, neomycin and streptomycin). MICs for these substances are above concentrations that can be obtained during systemic therapy with these antimicrobials.

Staphylococcus aureus

Isolates included are from skin samples, excluding wounds and abscesses. Resistance to gentamicin, penicillin, streptomycin and trimethoprim-sulphametoxazole during the last five years is shown in Figure 6.23. Over these years resistance to penicillin has dominated, although the level has decreased. In 2012, 21% of the isolates were resistant to penicillin due to penicillinase production (Table 6.31). Multiresistance occurred in three isolates (2.1%).

One isolate with MIC >1 mg/L for oxacillin carried the *mecA*-gene and was thereby confirmed as MRSA. For more information on MRSA isolated from horses in Sweden, see Section Antimicrobial resistance as notifiable diseases.

TABLE 6.30. Resistance (%) in *Streptococcus zooepidemicus* from horses 1995-2012 and distribution of MICs for isolates from 2012. Isolates are from clinical submissions of samples from the respiratory tract.

Antimicrobial	Resistance (%)								Distribution (%) of MICs (mg/L)									
	1995-97 n=402	1998-00 n=409	2001-03 n=505	2004-06 n=534	2007-09 n=491	2010 n=43	2011 n=131	2012 n=140	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	<1	0	0	0	0	0	0	0				100						
Enrofloxacin	NR[b]	NR	NR	NR	NR	NR	NR	NR	3.6		2.9	60.0	33.5					
Florfenicol	-	-	1	<1	0	0	2	<1					94.3	3.6	0.7	1.4		
Gentamicin	NR	NR	NR	NR	NR	NR	NR	NR					2.1	0.7	44.3	47.1	5.7	
Penicillin	<1	0	0	0	0	0	0	0	100									
Spiramycin	1	0	1	<1	<1	0	0	<1						99.3			0.7	
Tetracycline	3	4	5	3	3	7	4	2				57.1	36.4	3.6	0.7	2.1		
Trim-Sulph.[a]	11	57	36	42	18	18	8	14			67.9	12.9	3.6	2.1	13.6			

[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 6.31. Distribution of MICs and resistance (%) in *Staphylococcus aureus* from horses 2012. Isolates are from clinical submissions of samples from the skin.

Antimicrobial	Resistance (%) 2012 n=145	Distribution (%) of MICs (mg/L)									
		≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ceftiofur	<1		1.4	11.7	82.8	3.4	0,7				
Enrofloxacin	<1	69.7	28.3	1.4	0.7						
Florfenicol	<1					6.2	71.0	22.1	0.7		
Gentamicin	1					98.6		0.7		0.7	
Oxacillin	<1			98.6	0.7	0.7					
Penicillin[a]	21										
Spiramycin	0						21.4	77.2	1.4		
Streptomycin	7						36.6	43.4	13.1	2.8	4.1
Tetracycline	4				96.6	1.4			2.1		
Trim-Sulph.[b]	2			97.9	1.4	0.7					

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

Dogs

Escherichia coli

Isolates included are from samples of urine, submitted either as urine or as dip-slide cultures. In 2012, resistance to ampicillin was the most common trait (Table 6.32). In previous years, levels of resistance to ampicillin, gentamicin, streptomycin and trimethoprim-sulphametoxazole have been stable or slightly declining (Figure 6.24) except for an unexplained peak in resistance to trimethoprim-sulphametoxazole in 2004.

In 2012, four isolates of *E. coli* were resistant to cefotaxime. One of them was ESBL-producing and genotypic testing showed CTX-M-1. Of the other three isolates, one had an AmpC phenotype, but no gene was detected and two were not further tested. For more information on ESBL-producing Enterobacteriaceae isolated from dogs, see Antimicrobial resistance as notifiable disease.

Five percent of the isolates were multiresistant and this figure is on the same level as last year. Of the multiresistant isolates, 55% were resistant to at least ampicillin, trimethoprim-sulphonamides and tetracycline. Only four *E. coli* isolates were resistant to five or more antimicrobials, *i.e.* <1% of all isolates.

TABLE 6.32 Distribution of MICs and resistance (%) in *Escherichia coli* from dogs 2012. Isolates are from clinical submissions of samples from the urinary tract.

Antimicrobial	Resistance (%) 2012 n=407	Distribution (%) of MICs (mg/L)									
		≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	15				2.9	57.8	24.1	0.2	14.7		
Cefotaxime	1			98.8	0.5	0.7					
Enrofloxacin	6	93.4	2.0	1.7	1.2	0.2	0.2	1.2			
Gentamicin	<1					96.3	3.2	0.2		0.2	
Nitrofurantoin	1								97.3	1.7	1.0
Polymyxin B	8					92.2	6.6	1.2			
Tetracycline	5				23.9	66.1	4.6		5.4		
Trim-Sulph.[a]	7			91.5	1.5	0.5	0.2	6.3			

[a] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim-sulphametoxazole) and cut-off value >4 mg/L until 2001.

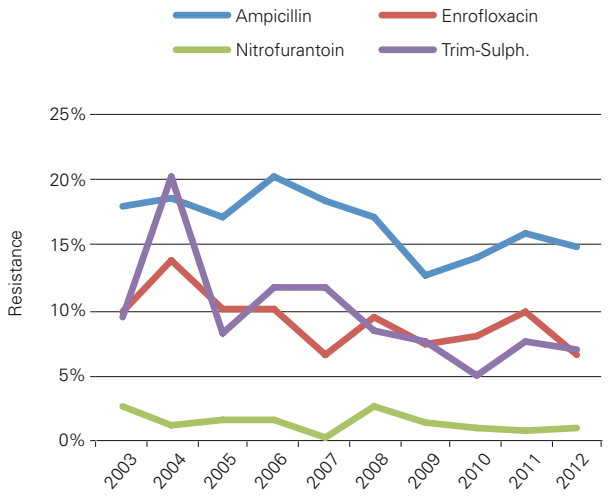


FIGURE 6.24. Percent resistance to ampicillin, enrofloxacin, nitrofurantoin and trimethoprim-sulphametoxazole in *Escherichia coli* from dogs 2003-2012. Isolates are from clinical submissions of samples from the urinary tract.

Staphylococcus pseudintermedius

Isolates included are from skin samples. As in previous years, the prevalence of resistance to penicillin due to penicillinase production in *S. pseudintermedius* is high (Table 6.33). During the last two decades, the resistance frequency has been around 80-90%. Besides penicillin, resistance to clindamycin, erythromycin, fusidic acid or tetracycline was common in 2012, as in previous years.

Multiresistance occurred in 26% of the isolates and 7% of all isolates were resistant to five or more antimicrobials where one fifth of them was MRSP. Resistance to penicillin, clindamycin and erythromycin was the most common phenotype, occurring in 70% of multiresistant isolates (n=42), where 40% of these 42 isolates were also resistant to tetracycline. For more information on MRSP isolated from dogs in Sweden, see Antimicrobial resistance as notifiable diseases.

Pseudomonas aeruginosa

Isolates included are from samples from the external ear canal. *Pseudomonas aeruginosa* is considered clinically resistant to *e.g.* trimethoprim-sulphonamides, tetracyclines and aminopenicillins (including combinations with clavulanic acid). Only products containing fluoroquinolones, gentamicin and polymyxin B, are indicated for treatment of pseudomonal

infections in dogs and therefore, the susceptibility data of these substances are presented in Table 6.34. All isolates were susceptible to polymyxin B. However, resistance to gentamicin or enrofloxacin occurred and two isolates were resistant to both substances.

TABLE 6.33. Resistance (%) in *Staphylococcus pseudintermedius* from dogs 1992-2012 and distribution of MICs for isolates from 2012. Isolates are from clinical submissions of samples from skin.

Antimicrobial	Resistance (%)									Distribution (%) of MICs (mg/L)									
	1992-94 n=304	1995-97 n=322	1998-00 n=433	2001-03 n=382	2004-06 n=374	2007-09 n=859	2010 n=444	2011 n=388	2012 n=229	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Cephalothin	<1	<1	0	1	1	3	4	3	2					98.3	0.4	1.3			
Clindamycin	12	20	21	18	19	23	26	24	18				79.9		1.7	18.3			
Enrofloxacin	-	-	-	2[a]	2	5	6	6	5	72.9	20.1	1.7	2.2		0.4	2.6			
Erythromycin[a]	21	28	27	24	26	28	30	30	22			77.7				22.3			
Fusidic acid	9	14	20	20	25	24	20	24	20					73.8	6.1	20.1			
Gentamicin	<1	<1	<1	0	1	3	3	2	2					97.4	0.4	0.4	1.3	0.4	
Nitrofurantoin	1	1	<1	1	<1	<1	2	1	<1								99.6		0.4
Oxacillin	1	2	1	2	2	1	4	2	2			98.3	0.4	1.3					
Penicillin[b]	79	80	80	80	84	87	86	84	82										
Tetracycline	24	12	28	25[g]	32	30	31	26	24				75.1	0.4			24.5		
Trim-Sulph.[c]	1	2	1	3	6	5	6	6	7			63.3	29.7		0.4	6.6			

[a] Cut-off value >4 mg/L until 2001; [b] Denotes beta-lactamase production; [c] Concentration of trimethoprim given, tested in concentration ratio 1/20 (trimethoprim/sulphamethoxazole).

TABLE 6.34. Resistance (%) in *Pseudomonas aeruginosa* from dogs 2009-2012 and distribution of MICs for isolates from 2012. Isolates are from clinical submissions of samples from the ear canal.

Antimicrobial	Resistance (%)				Distribution (%) of MICs (mg/L)									
	2009 n=261	2010 n=313	2011 n=353	2012 n=178	≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Enrofloxacin	25	20	12	15	1.1	0.6	7.3	47.8	28.7	6.2	8.4			
Gentamicin	5	2	2	2					79.8	14.0	3.9	0.6	1.7	
Polymyxin B	0	0	0	0					93.3	6.7				

Cats

Escherichia coli

Isolates included are from samples of urine, submitted either as urine or as dip-slide cultures. Resistance to ampicillin was the most common trait (Table 6.35). Resistance from 2001 to 2012 to ampicillin, enrofloxacin, nitrofurantoin, tetracycline and trimethoprim- sulphametoxazole are shown in Figure 6.25.

In 2012, 2% of the isolates were multiresistant, and this figure is on the same level as last year. None of the isolates were resistant to five or more antimicrobials.

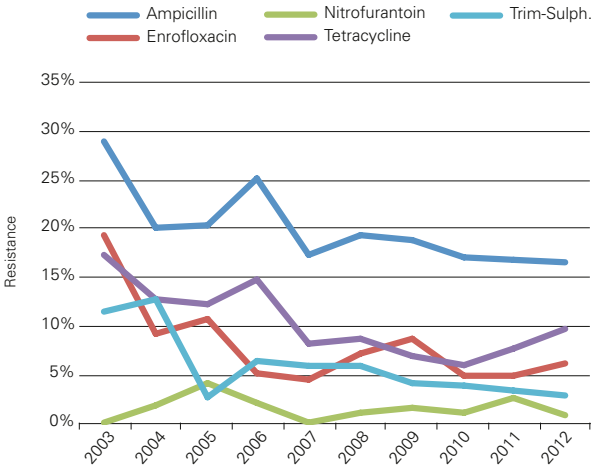


FIGURE 6.25 Percent resistance to ampicillin, enrofloxacin, nitrofurantoin, tetracycline and trimethoprim-sulphametoxazole in *Escherichia coli* from the urinary genital tract in cats, 2003-2012.

TABLE 6.35. Distribution of MICs and resistance (%) in *Escherichia coli* from cats 2012. Isolates are from clinical submissions of samples from the urinary tract.

Antimicrobial	Resistance (%) 2012 n=310	Distribution (%) of MICs (mg/L)									
		≤0.12	0.25	0.5	1	2	4	8	16	32	>32
Ampicillin	16				2.3	70.0	11.3		16.5		
Cefotaxime	1			99.0	1.0						
Enrofloxacin	6	93.9	2.9	1.6	1.0	0.6					
Gentamicin	<1					96.1	3.2		0.3	0.3	
Nitrofurantoin	1								98.7	0.3	1.0
Polymyxin B	9					91.3	7.1	1.6			
Tetracycline	10				22.9	62.6	4.5	0.3	9.7		
Trim-Sulph.[a]	3			96.1	1.0			2.9			

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

Farming practices in Sweden related to feeding milk and colostrum from cows treated with antimicrobials to dairy calves

In 2011, 21 cases of antimicrobial treatments per 100 cow years were reported for dairy cows in Sweden (Swedish Dairy Association, 2012). Most of these treatments are associated with a statutory withdrawal period until the content of antimicrobial residues in the milk has decreased to a safe level (Medical Products Agency, 2012). Milk that is produced during the course of treatment and the withdrawal period must not be sold for human consumption and is often defined as waste milk. Discarding this milk inevitably leads to reduced income and thus, to mitigate some of these losses, farmers sometimes use waste milk as feed for calves.

In SVARM 2009, it was reported that the prevalence of antimicrobial resistance in *E. coli* from the intestines of calves is much higher than from the intestines of older cattle. It has been proposed that the high occurrence of bacteria resistant to antimicrobials from calves is due to feeding of waste milk from cows treated with antimicrobials. Residues in waste milk can impose a selection pressure on the calf's intestinal flora, which may increase the prevalence of resistant bacteria. A few studies have touched upon this, but the results are inconclusive. In some of the studies, the susceptibility of the intestinal flora remained unchanged even though the calves were fed waste milk (Wray et al., 1990;Yndestad & Helmen, 1980). However, in other studies, a higher prevalence of resistant bacteria was found from calves fed milk containing antimicrobials compared to calves fed other liquids (Aust et al., 2012; Langford et al., 2003).

In order to obtain an overview of farming practices related to feeding milk and colostrum from cows treated with antimicrobials to dairy calves, a survey among 457 Swedish dairy farmers was conducted in 2011. These farms were representative to Swedish dairy farms in regard to herd size and geographic location.

Results and comments

As seen in Figure, calves are (always or occasionally) exposed to colostrum from cows treated with antimicrobials at dry off on 89% of the farms. However, since only 30 % of the Swedish dairy cows are treated with long acting antimicrobials at dry off (Swedish Dairy Association, 2012), far from all calves on these farms are expected to be exposed to colostrum that may contain antimicrobial residues. Many farms reported that bull calves were more often fed such colostrum. Transition milk that is produced from the second milking to the fourth day after calving was fed to calves (always or occasionally) on 86% of the farms if the cow was treated with antimicrobials at dry off (Figure). Both colostrum and transition milk was fed to calves on more non-organic than organic farms. This is likely to be explained by the rules for organic certification which state that colostrum and transition milk from cows treated with antimicrobials must not be fed to other calves than the dam's own newborn under the statutory withdrawal period (KRAV, 2013).

When cows were treated with antimicrobials during lactation, 56% of the farmers (always or occasionally) used the milk as calf feed during the course of treatment and the withdrawal period, whereas 79% (always or occasionally) used milk that was produced during the withdrawal period only (Figure). Växa Sverige (former Swedish Dairy Association) recommends that milk from cows treated with antimicrobials should not be fed to calves during the course of treatment and at least one additional day (Landin 2012, personal communication), but this recommendation seems to be followed by only 36% of the Swedish farmers. As for colostrum and transition milk, significantly more non-organic farmers reported that milk from cows treated with antimicrobials during lactation was fed to calves, which is also likely to be related to the rules for organic certification (KRAV, 2013). In addition, farmers in the Southern parts of Sweden were more prone than farmers in other regions to feed such milk to calves. This suggests that farmers in different regions in Sweden perceive risks related to waste milk feeding differently. Seven percent of the farmers reported that cows that have been treated with antimicrobials occasionally were used as nursing cows for calves.

This survey is part of a PhD project initiated in 2011 in which risk factors for the occurrence of antimicrobial resistant *E. coli* from calves are sought. In this project, the association between waste milk feeding and the occurrence of antimicrobial resistant bacteria in the calves' intestines is being investigated. This survey has shown that waste milk feeding is widespread on Swedish farms. If waste milk feeding promotes the selection of antimicrobial resistant bacteria, rules or recommendations should be issued to decrease the use of waste milk as feed for calves on dairy farms.

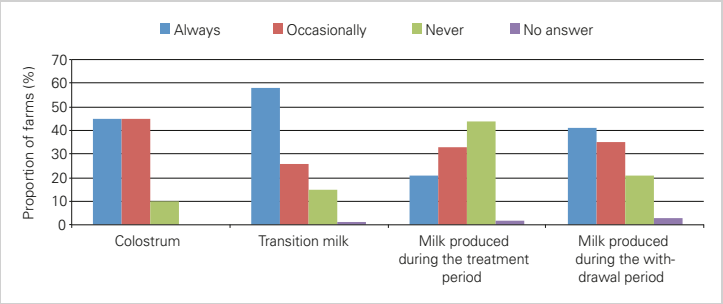


FIGURE. Proportion of Swedish dairy farms (n=457) where milk from cows treated with antimicrobials is fed to calves always, occasionally or never. This is specified for colostrum and transition milk (from the second milking to the fourth day after calving) from cows treated with antimicrobials at dry off as well as for milk from cows treated with antimicrobials during lactation, divided in the treatment and the withdrawal period.

Resistance in indicator bacteria from animals

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

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

In 2012, samples of intestinal content and meat of broilers and intestinal content from laying hens were cultured for indicator *E. coli* and enterococci. Also rectal swabs from dogs were cultured for indicator *E. coli*. In addition, all samples were screened for *E. coli* resistant to third generation cephalosporins by selective culture on media supplemented with cefotaxime. For details on methodology see Appendix 4.

Escherichia coli

Broilers

Escherichia coli was isolated from 194 (97%) of 199 samples cultured. Most isolates (62%) were susceptible to all antimicrobials tested but 74 isolates (38%) were resistant to at least one substance (Tables 6.36 and 6.37). Resistance to ampicillin (14%), ciprofloxacin (14%), nalidixic acid (12%), tetracycline (11%), sulphonamide (10 %), streptomycin (9%) or trimethoprim (8%) were the most common traits. Resistance to the other antimicrobials tested was rare or not observed. Twenty isolates (10%) were resistant to three or more antimicrobials.

Over the period studied resistance to sulphonamides has decreased but resistance to ampicillin, quinolones (ciprofloxacin and nalidixic acid) or tetracycline has increased (Fig. 6.26). Likewise the proportion of multiresistant isolates has increased from 3% in 2000 to 10% in 2012.

On screening for resistance to third generation cephalosporins, *E. coli* phenotypically resistant to cefotaxime (MIC ≥2 mg/L) was isolated from 102 (51%) of 200 samples. For details and comments see Section ESBL-producing Enterobacteriacae, animals.

Broiler meat

Escherichia coli was isolated from 92 (95%) of 97 samples cultured. Most isolates (63%) were susceptible to all antimicrobials tested but 27 isolates (35%) were resistant to at least one substance (Table 6.36 and 6.37). Resistance to ampicillin (18%), sulphonamide (16 %) or tetracycline (14%) were the most common traits. Nine isolates (10%) were resistant to three or more antimicrobials.

In comparison to the study of broiler meat in 2010, resistance to ampicillin or to tetracycline are about twice as prevalent in 2012. For the other antimicrobials tested levels of resistance are roughly similar in 2010 and 2012.

On screening for resistance to third generation cephalosporins, *E. coli* phenotypically resistant to cefotaxime (MIC of ≥2 mg/L) was isolated from 41 (43%) of 97 samples. For details and comments see ESBL-producing Enterobacteriacae, animals.

Laying hens

For the first time in SVARM, resistance in indicator *E. coli* from laying hens was investigated as a part of SVARM 2012. The sampling took place from October 2012 to January 2013. *Escherichia coli* was isolated from 61 (88%) of 69 samples cultured. Most isolates (80%) were susceptible to all antimicrobials tested (Tables 6.36 and 6.37). Resistance to tetracycline (13%) or sulphonamide (8%) were the two most common traits. Resistance to the other antimicrobials tested was rare or not observed. Five isolates (8%) were resistant to three or more antimicrobials.

The occurrence of resistance is comparable to that of broilers, and also to that of diseased laying hens reported previously (SVARM 2007).

On screening for resistance to third generation cephalosporins, *E. coli* phenotypically resistant to cefotaxime (MIC of 1->2 mg/L) was isolated from 11 (16%) of 69 samples. For details and comments see Section ESBL-producing Enterobacteriacae, animals.

Dogs

Escherichia coli was isolated from 74 (88%) of 84 samples cultured. Most isolates (82%) were susceptible to all antimicrobials tested but 13 isolates (18%) were resistant to at least one substance (Tables 6.36 and 6.37). Resistance to ampicillin (9%) or tetracycline (8%) were the most common traits. Four isolates (5%) were resistant to three or more antimicrobials.

The levels of resistance to individual antimicrobials as well as multiresistance are about the same as in the study of dogs carried out in 2006.

On screening for resistance to third generation cephalosporins, *E. coli* phenotypically resistant to cefotaxime (MIC of ≥2 mg/L) was isolated from 1 (1%) of 84 samples. For details and comments see Section ESBL-producing Enterobacteriacae, animals.

TABLE 6.36. Resistance (%) and multiresistance (%) in indicator *Escherichia coli* from broilers, broiler meat, laying hens and dogs, 2012. Data from previous SVARM-reports are given for comparison.

Antimicrobial	Cut-off value (mg/L)	Resistance (%)								
		Broilers 2012 n=194	Broiler meat 2012 n=92	Laying hens 2012[b] n=61	Pigs 2011 n=167	Pig meat 2011 n=20	Horses 2010-11 n=274	Calves[a] 2009 n=223	Sheep 2006-09 n=115	Dogs 2012 n=74
Ampicillin	>8	14	18	3	13	30	2	<1	2	9
Cefotaxime	>0.25	0	0	2	<1	0	0	0	0	1
Chloramphenicol	>16	<1	0	0	4	0	<1	0	0	0
Ciprofloxacin	>0.06	14	4	5	2	10	<1	0	<1	3
Colistin	>2	0	1	0	0	0	<1	-	-	0
Florfenicol	>16	0	0	0	0	0	0	0	0	0
Gentamicin	>2	<1	3	2	1	0	<1	0	3	0
Kanamycin	>8	3	3	2	1	5	4	<1	2	1
Nalidixic acid	>16	12	4	5	2	0	<1	0	0	0
Streptomycin	>16	9	7	5	16	10	13	4	3	4
Sulphonamide	>64	10	16	8	17	10	15	2	7	4
Tetracycline	>8	11	14	13	8	0	2	2	<1	8
Trimethoprim	>2	8	7	5	11	10	16	<1	2	1
Multiresistance										
Susceptible to all above		62	63	79	72	70	81	95	88	82
Resistant to 1		21	20	7	9	10	4	3	9	11
Resistant to 2		6	8	8	5	5	3	<1	2	1
Resistant to 3		5	2	5	3	5	9	<1	1	4
Resistant to >3		5	8	2	10	10	3	<1	1	1

[a] Calves 6-8 months old; [b] Samples collected from October 2012 to January 2013; [c] Ciprofloxacin and nalidixic acid counted as one antimicrobial.

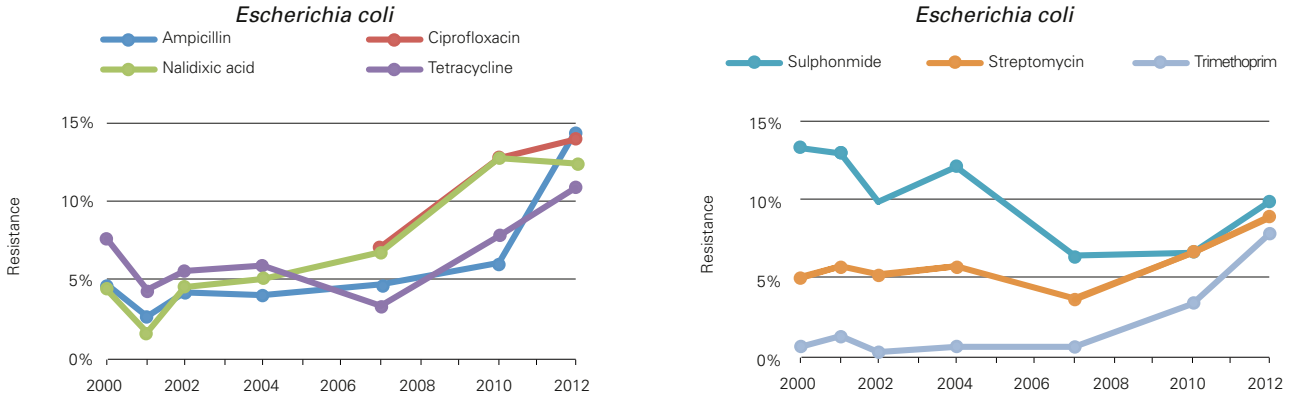


FIGURE 6.26. Percent resistance in *Escherichia coli* from broilers 2000-2012. The number of isolates each year varies (n=181-306).

TABLE 6.37. Distribution of MICs and resistance (%) in *Escherichia coli* from from broilers (n=194), broiler meat (n=92), laying hens (n=61) and dogs (n=74), 2012[a].

Antimicrobial	Source	Resistance %	Distribution (%) of MICs (mg/L)																		
			≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Ampicillin	Broilers	14								5.2	58.8	21.6						14.4			
	Broiler meat	18								19.6	51.1	10.9					5.4	13.0			
	Laying hens	3								8.2	78.7	9.8					1.6	1.6			
	Dogs	9								5.4	67.6	17.6				1.4		8.1			
Cefotaxime	Broilers	0			3.1	50.5	44.8	1.5													
	Broiler meat	0			3.3	52.2	43.5	1.1													
	Laying hens	2			3.3	63.9	31.1					1.6									
	Dogs	1			6.8	51.4	39.2	1.4	1.4												
Chloramphenicol	Broilers	<1									5.7	69.6	24.2				0.5				
	Broiler meat	0									3.3	83.7	13.0								
	Laying hens	0									4.9	70.5	24.6								
	Dogs	0									1.4	68.9	29.7								
Ciprofloxacin	Broilers	14			34.0	52.1	1.5	3.6	8.2	0.5											
	Broiler meat	4		2.2	51.1	42.4	2.2	1.1	1.1												
	Laying hens	5		1.6	68.9	24.6			1.6	1.6	1.6										
	Dogs	3		4.1	43.2	50.0	2.7														
Colistin	Broilers	0							30.4	53.1	16.5										
	Broiler meat	1							21.7	51.1	26.1		1.1								
	Laying hens	0							42.6	45.9	11.5										
	Dogs	0							28.4	51.4	20.3										
Florfenicol	Broilers	0										42.3	55.7	2.1							
	Broiler meat	0										60.9	38.0	1.1							
	Laying hens	0										44.3	55.7								
	Dogs	0										28.4	70.3	1.4							
Gentamicin	Broilers	<1						1.0	42.8	49.0	6.7	0.5									
	Broiler meat	3						1.1	43.5	44.6	7.6	1.1			2.2						
	Laying hens	2							50.8	41.0	6.6	1.6									
	Dogs	0						1.4	44.6	45.9	8.1										
Kanamycin	Broilers	3											96.9	2.1	1.0						
	Broiler meat	3											96.7	2.2	1.1						
	Laying hens	2											98.4	1.6							
	Dogs	1											98.6	1.4							
Nalidixic acid	Broilers	12								1.0	43.3	41.2	2.1		1.0	2.6	5.7	3.1			
	Broiler meat	4								2.2	58.7	33.7	1.1		1.1	2.2		1.1			
	Laying hens	5									47.5	47.5					4.9				
	Dogs	0								1.4	39.2	58.1	1.4								
Streptomycin	Broilers	9										18.6	64.9	7.7	1.0	4.1	3.1	0.5			
	Broiler meat	7										15.2	68.5	9.8	3.3	2.2	1.1				
	Laying hens	3										11.5	75.4	8.2		1.6	1.6		1.6		
	Dogs	4									1.4	28.4	58.1	8.1			2.7		1.4		
Sulphonamide	Broilers	10											1.0	43.3	38.7	7.2					9.8
	Broiler meat	16											2.2	45.7	30.4	5.4					16.3
	Laying hens	8											6.6	65.6	18.0	1.6					8.2
	Dogs	4											2.7	13.5	66.2	13.5				1.4	2.7
Tetracycline	Broilers	11								26.8	61.3		1.0		2.6	6.7	1.5				
	Broiler meat	14								83.7	2.2				5.4	6.5	2.2				
	Laying hens	13								75.4	11.5				1.6	4.9	6.6				
	Dogs	8								83.8	8.1				1.4	1.4	5.4				
Trimethoprim	Broilers	8					1.0	33.0	41.2	16.5	0.5				7.7						
	Broiler meat	7					3.3	35.9	38.0	14.1	2.2				6.5						
	Laying hens	5					1.6	59.0	29.5	4.9					4.9						
	Dogs	1					1.4	9.5	75.7	12.2			1.4								
			≤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**

[a] Samples from laying hens were collected from October 2012 to January 2013.

Enterococcus faecalis and *E. faecium*

Broilers

A total of 44 isolates of *Enterococcus faecalis* and 136 isolates of *Enterococcus faecium* were obtained from 199 samples cultured. Erythromycin resistance was the most common trait (34%) in *E. faecalis* but resistance to narasin (23%) or tetracycline (20%) also occurred at substantial levels (Tables 6.38 and 6.40). In *E. faecium* narasin resistance was by far the most frequent trait (79%) (Tables 6.39 and 6.41). Resistance to bacitracin (13%) or tetracycline (10%) also occurred but were much less common. Multiresistance was rare in both species. In the period studied in SVARM, there are no indications of increased resistance in neither *E. faecalis* nor in *E. faecium* (Fig 6.27). On the contrary, resistance to bacitracin or tetracycline has declined.

Broiler meat

From 96 samples of broiler meat, 78 isolates of *E. faecalis* and 10 isolates of *E. faecium* were obtained. Resistance to narasin (37%), tetracycline (36%), bacitracin (23 %) or erythromycin (13%) were the most common traits in *E. faecalis* (Table 6.38 and 6.40). In the ten isolates of *E. faecium* available for susceptibility testing, narasin resistance was the most frequent trait (80%) (Tables 6.39 and 6.41). Resistance to bacitracin (40%) or tetracycline (30%) also occurred but was less common. Multiresistance was rare in both species. The levels of resistance are similar to those in the study 2010 and roughly mirror the levels in isolates from broilers.

Laying hens

For the first time in SVARM, resistance in indicator *E. faecalis* and *E. faecium* from laying hens was investigated in 2012. A total of 20 isolates of *E. faecalis* and 36 isolates of *E. faecium* were obtained from 69 samples. Almost 50% (9 of 20) of *E. faecalis* were resistant to tetracycline, but apart from that resistance was scarce in both *E. faecalis* and *E. faecium* (Tables 6.38 - 6.41). In all, the level of resistance is comparable to that of healthy broilers.

TABLE 6.38. Resistance and multiresistance in *Enterococcus faecalis* from broilers, broiler meat, laying hens and dogs, 2012. Data for other animals from previous SVARM-reports given for comparison.

Antimicrobial	Cut-off value (mg/L)	Resistance (%)								
		Broilers	Broiler meat	Laying hens	Pigs	Pig meat	Horses	Calves[a]	Sheep	Dogs
		2012 n=44	2012 n=78	2012[b] n=20	2011 n=22	2011 n=29	2010-11 n=34	2009 n=10	2006-09 n=24	2006 n=135
Ampicillin	>4	0	0	0	0	0	0	0	0	<1
Bacitracin	>32	7	23	10	0	0	0	0	0	1
Chloramphenicol	>32	0	5	0	0	0	18	0	0	7
Erythromycin	>4	34	13	10	43	0	21	0	0	14
Gentamicin	>32	0	1	0	4	0	21	0	0	<1
Kanamycin	>1024	0	0	0	4	0	21	0	0	4
Linezolid	>4	0	1	0	0	0	0	0	0	0
Narasin	>2	23	37	0	0	0	0	0	0	1
Streptomycin	>512	2	5	0	17	3	9	0	4	9
Tetracycline	>4	20	36	45	74	7	44	30	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		43	27	45	17	90	56	70	92	25
Resistant to 1		32	37	45	35	10	24	30	4	38
Resistant to 2		20	29	10	43				4	27
Resistant to 3		5	1							2
Resistant to >3			5		4		21			7

[a] Calves 6-8 months old; [b] Samples collected from October 2012 to January 2013.

TABLE 6.39. Resistance and multiresistance in *Enterococcus faecium* from broilers, broiler meat, laying hens and dogs, 2012. Data for other animals from previous SVARM-reports given for comparison.

Antimicrobial	Cut-off value (mg/L)	Resistance (%)								
		Broilers	Broiler meat	Laying hens	Pigs	Pig meat	Horses	Calves[a]	Sheep	Dogs
		2012 n=136	2012 n=10	2012[b] n=36	2011 n=22	2011 n=1	2010-11 n=27	2009 n=24	2006-09 n=15	2006 n=29
Ampicillin	>4	<1	0	0	0	0	15	0	0	0
Bacitracin	>32	13	40	3	9	0	0	4	0	3
Chloramphenicol	>32	0	0	0	0	0	0	0	0	0
Erythromycin	>4	4	0	6	9	0	0	4	0	28
Gentamicin	>32	0	0	0	0	0	0	0	0	0
Kanamycin	>1024	0	0	0	9	0	0	0	0	0
Linezolid	>4	0	0	0	0	0	0	0	0	0
Narasin	>2	79	80	0	0	0	0	0	0	7
Streptomycin	>128	0	0	0	13	0	7	0	7	0
Tetracycline	>4	10	30	11	13	0	4	0	7	17
Vancomycin	>4	0	0	0	0	0	0	0	0	0
Virginiamycin	>4	1	10	8	4	100	4	0	0	0
Multiresistance (%)										
Susceptible to all above		15	50	78	74		74	92	87	62
Resistant to 1		63	40	17	13	100	22	8	13	30
Resistant to 2		21	10	6	4		4			6
Resistant to 3		1								
Resistant to >3					9					2

[a] Calves 6-8 months old; [b] Samples collected from October 2012 to January 2013.

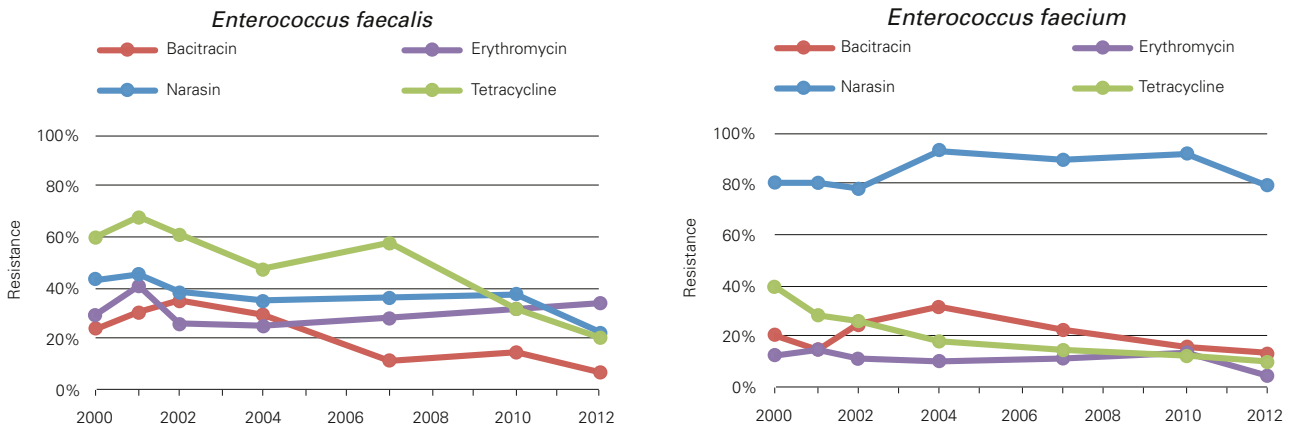


FIGURE 6.27. Percent resistance in *Enterococcus faecalis* and *Enterococcus faecium* from broilers 2000-2012. The number of isolates each year varies; *E. faecalis* n=35-57 and *E. faecium* n=136-204.

TABLE 6.40. Distribution of MICs and resistance (%) in *Enterococcus faecalis* from broilers (n=44), broiler meat (n=78), laying hens (n=20) and dogs (n=135), 2012[a].

Antimicrobial	Source	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	Broilers	0		2.3	13.6	81.8	2.3											
	Broiler meat	0			43.6	56.4												
	Laying hens	0			50.0	50.0												
Bacitracin[b]	Broilers	7								93.2			4.5	2.3				
	Broiler meat	23						6.4	55.1	15.4		1.3	6.4	15.4				
	Laying hens	10						15.0	60.0	15.0			10.0					
Chloramphenicol	Broilers	0						70.5	27.3	2.3								
	Broiler meat	5					2.6	55.1	37.2			5.1						
	Laying hens	0						40.0	60.0									
Erythromycin	Broilers	34			13.6	34.1	15.9	2.3	9.1	9.1	2.3		13.6					
	Broiler meat	13			35.9	17.9	26.9	6.4		7.7	1.3		3.8					
	Laying hens	10			15.0	60.0	15.0		5.0	5.0								
Gentamicin	Broilers	0							38.6	59.1	2.3							
	Broiler meat	1						1.3	53.8	42.3	1.3	1.3						
	Laying hens	0						5.0	60.0	35.0								
Kanamycin	Broilers	0												100				
	Broiler meat	0									16.7	83.3						
	Laying hens	0									10.0	75.0	10.0	5.0				
Linezolid	Broilers	0				22.7	72.7	4.5										
	Broiler meat	1				41.0	57.7		1.3									
	Laying hens	0				20.0	80.0											
Narasin	Broilers	23	15.9	40.9	2.3	9.1	9.1	22.7										
	Broiler meat	37	1.3	46.2	6.4		9.0	29.5	7.7									
	Laying hens	0	10.0	65.0	25.0													
Streptomycin	Broilers	2									2.3	25.0	68.2	2.3			2.3	
	Broiler meat	5										43.6	44.9	3.8	2.6	3.8	1.3	
	Laying hens	0									5.0	50.0	45.0					
Tetracycline	Broilers	20			68.2	4.5	6.8				11.4	9.1						
	Broiler meat	36			24.4	38.5		1.3	1.3	1.3	15.4	17.9						
	Laying hens	45			20.0	35.0					20.0	25.0						
Vancomycin	Broilers	0				29.5	36.4	34.1										
	Broiler meat	0				87.2	12.8											
	Laying hens	0				95.0	5.0											
Virginiamycin	Broilers	0						2.3	31.8	61.4	4.5							
	Broiler meat	0					1.3	6.4	57.7	34.6								
	Laying hens	0					5.0		65.0	30.0								
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048

[a] Samples from laying hens collected from October 2012 to January 2013; [b] MIC in U/mL, see Appendix 4 for details.

TABLE 6.41. Distribution of MICs and resistance (%) in *Enterococcus faecium* from broilers (n=136), broiler meat (n=10), laying hens (n=36) and dogs (n=29), 2012[a].

Antimicrobial	Source	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	Broilers	<1		14.0	36.8	25.7	16.2	6.6	0.7									
	Broiler meat	0		40.0	40.0	20.0												
	Laying hens	0		30.6	22.2	33.3	8.3	5.6										
Bacitracin[b]	Broilers	13								80.1	6.6	7.4	0.7	5.1				
	Broiler meat	40				10.0				40.0	10.0	10.0	10.0	20.0				
	Laying hens	3				30.6		8.3	16.7	30.6	11.1	2.8						
Chloramphenicol	Broilers	0					2.2	77.9	19.1	0.7								
	Broiler meat	0					10.0	70.0	20.0									
	Laying hens	0					2.8	75.0	19.4		2.8							
Erythromycin	Broilers	4			37.5	45.6	3.7	8.8	2.2	0.7			1.5					
	Broiler meat	0			50.0	10.0	10.0	30.0										
	Laying hens	6			30.6	41.7	5.6	16.7		2.8	2.8							
Gentamicin	Broilers	0						12.5	69.9	17.6								
	Broiler meat	0					10.0	30.0	60.0									
	Laying hens	0					2.8	19.4	55.6	19.4	2.8							
Kanamycin	Broilers	0												94.1	5.9			
	Broiler meat	0									10.0	50.0	30.0	10.0				
	Laying hens	0								2.8	2.8	25.0	41.7	22.2	5.6			
Linezolid	Broilers	0				3.7	85.3	11.0										
	Broiler meat	0				20.0	70.0	10.0										
	Laying hens	0				33.3	66.7											
Narasin	Broilers	79	5.1	2.9	2.2		10.3	76.5	2.9									
	Broiler meat	80	10.0				10.0	60.0	20.0									
	Laying hens	0	8.3	33.3	50.0	8.3												
Streptomycin	Broilers	0									18.4	77.9	3.7					
	Broiler meat	0								10.0	50.0	40.0						
	Laying hens	0									25.0	66.7	8.3					
Tetracycline	Broilers	10			86.8	3.7			2.2	0.7	1.5	5.1						
	Broiler meat	30			60.0	10.0			10.0		10.0	10.0						
	Laying hens	11			75.0	13.9				2.8		8.3						
Vancomycin	Broilers	0				88.2	11.0	0.7										
	Broiler meat	0				100												
	Laying hens	0				97.2	2.8											
Virginiamycin	Broilers	1			19.9	37.5	25.7	15.4	0.7	0.7								
	Broiler meat	10			30.0	20.0	30.0	10.0		10.0								
	Laying hens	8			58.3	13.9	16.7	2.8	5.6	2.8								
			≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048

[a] Samples from laying hens collected from October 2012 to January 2013; [b] MIC in U/mL, see Appendix 4 for details.

7. Appendices

Appendix 1: Demographics and denominator data

Humans

TABLE 7.1. Population by county and age group, December 31st 2012.

County	0-6 years	17-19 years	20-64 years	65-79 years	80 years -	All ages
Blekinge	11 432	5 920	85 697	24 810	9 336	152 979
Dalarna	20 286	11 441	154 549	43 993	17 492	276 565
Gävleborg	19 843	11 387	155 241	44 249	16 821	276 130
Gotland	3 962	2 456	32 549	9 318	3 333	57 308
Halland	24 994	12 802	168 984	43 739	16 818	301 724
Jämtland	9 573	5 090	71 368	19 397	7 992	126 299
Jönköping	27 617	14 648	190 828	46 650	20 027	337 896
Kalmar	16 174	9 745	129 752	38 489	15 185	233 090
Kronoberg	14 665	7 712	104 698	26 171	11 335	184 654
Norrbotten	17 202	10 011	142 118	39 818	13 878	248 545
Skåne	106 504	48 015	731 962	167 472	66 696	1252 933
Södermanland	21 608	11 326	152 244	41 826	15 269	272 563
Stockholm	196 948	78 193	1 269 968	232 278	85 050	2091 473
Uppsala	28 281	13 873	202 457	42 338	15 193	338 630
Värmland	19 343	11 092	153 903	43 021	17 496	272 736
Västerbotten	20 189	10 939	151 280	36 611	13 995	259 667
Västernorrland	18 011	9 466	134 963	39 373	14 843	242 155
Västmanland	19 655	10 631	144 483	37 882	14 440	254 257
Västra Götaland	131 632	63 673	934 999	208 407	83 257	1590 604
Örebro	22 487	11 347	160 398	40 917	15 945	281 572
Östergötland	34 228	18 221	249 100	59 691	23 817	431 075
Sweden	**784 634**	**377 988**	**552 1541**	**1 286 450**	**498 218**	**9 482 855**

TABLE 7.2. Population in Sweden 2000-2012. Numbers represent the population by December 31st 2012.

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Population	8 861 426	8 882 792	8 909 128	8 940 788	8 975 670	9 011 392	9 047 752	9 113 257	9 182 927	9 256 347	9 340 682	9 415 570	9 482 855

TABLE 7.3. Number of admissions and patient-days in somatic medical care in Sweden, 2000-2011.

Year	Admissions	Patient-days
2000	1 388 366	7 679 982
2001	1 372 700	7 489 056
2002	1 359 678	7 340 467
2003	1 358 783	7 289 158
2004	1 370 536	7 157 683
2005	1 390 564	7 128 087
2006	1 402 952	7 181 693
2007	1 432 360	7 240 096
2008	1 437 985	7 176 021
2009	1 460 919	7 103 953
2010	1 492 323	6 943 409
2011	1 492 323	6 943 409

TABLE 7.4. Number of admissions and patient-days in somatic medical care 2011. Data represent production by acute care hospitals in the counties.

County	Admissions	Patient-days
Blekinge	22 576	112 864
Dalarna	47 682	204 499
Gotland	9 689	42 629
Gävleborg	42 383	185 451
Halland	44 109	194 460
Jämtland	18 426	89 919
Jönköping	54 556	264 320
Kalmar	41 662	164 220
Kronoberg	26 692	125 974
Norrbotten	40 177	191 466
Skåne	200 634	945 318
Stockholm	274 890	1 117 291
Södermanland	38 869	191 653
Uppsala	61 456	317 446
Värmland	41 385	204 017
Västerbotten	51 269	267 596
Västernorrland	37 477	168 625
Västmanland	39 753	185 575
Västra Götaland	247 229	1 177 916
Örebro	48 917	222 777
Östergötland	66 753	278 883
Sweden	**1 456 584**	**6 652 899**

TABLE 7.5 Denominator data from the microbiological laboratories 2012.

Laboratory	Number of analyses 2012									Number of positive samples 2012	Number of positive cultures 2012				
	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 (toxin-positive)
Aleris Medilab	901	0	11053	4318	10145	20486	45616	7680	1350	NA	NA	NA	NA	NA	NA
Borås	18282	226	3586	2626	6428	2088	23585	4946	1917	1903	4286	651	709	6890	146
Eskilstuna (Unilabs)	12093	210	6594	3491	7724	1638	27657	4250	1690	1705	4021	889	739	7169	274
Falun	15921	416	3808	1477	11242	3688	27677	3419	1731	1705	4704	579	541	7498	294
Gävle	12015	259	2455	939	11860	2673	22428	3367	2039	1619	4600	498	474	7604	473
Göteborg	38575	1337	2515	3730	17339	43918	68880	11542	4475	5366	9591	737	1108	16448	932
Halmstad	13231	148	2096	2791	7755	9075	24594	4569	2125	1848	3920	485	747	7513	441
Jönköping	19350	152	4890	3550	17265	24890	34880	7190	1510	2490	6960	670	950	10830	489
Kalmar	12385	149	3702	2074	8013	9403	26443	2659	1525	1688	4250	552	600	7755	246
Karlskrona/Växjö	17878	172	5346	3213	10949	3002	34787	5546	2982	2362	4669	717	921	9317	519
Karlstad	17568	101	2864	2955	12257	9539	34254	3705	1811	3239*	5568	478	897	8980	304
Karolinska Stockholm	83000	2658	32550	9882	57367	218738	144578	20229	10552	10033	28958	3168	3365	38447	1250
Linköping	21658	906	6914	3495	18950	10087	41276	6313	4050	3894	7828	742	815	11431	685
Lund/Malmö	68669	1789	20792	15607	43490	49298	161578	25747	10531	8422	22802	3283	3473	44526	1806
Skövde (Unilabs)	12690	141	4185	3179	10587	10336	49736	8090	2015	2272*	5717	479	834	11330	306
S:t Göran (Unilabs)	10858	86	7735	3558	12684	43651	45780	9687	3287	1393	6156	896	1058	10972	320
Sunderby Luleå	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sundsvall	12036	155	2117	1451	6609	11638	25931	4238	1930	1482	3882	417	369	7085	272
NÄL Trollhättan	19773	223	1715	2125	8554	14413	32662	4033	1608	2198	4754	407	593	8961	174
Umeå	15322	519	3384	2170	13217	5989	30983	5324	1568	1215	4412	579	728	9267	146
Uppsala	20855	925	6168	2674	14923	4838	34071	5437	3651	2173	5557	671	832	8864	785
Visby	3931	32	2507	563	2679	NP	6535	928	558	405	1359	335	216	1985	61
Västerås	11963	184	2195	1752	9939	3533	27036	4372	2021	1749	4074	301	577	8214	438
Örebro	16611	260	10422	1637	14107	5136	32034	5286	2683	1517	5745	1351	794	7857	421
Östersund	8610	140	3319	1627	13050	8449	19184	8686	1068	1712	3202	487	434	5753	132
Total	**484175**	**11188**	**152912**	**80884**	**347133**	**516506**	**1022185**	**167243**	**68677**	**56879**	**157015**	**19372**	**21774**	**264696**	**10914**

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.sjv.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 concomitantly with an increase in herd size. 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. The data document 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) 1980-2012 (Yearbook of Agricultural Statistics Sweden 2001 & 2011 and Statistical Message JO 20 SM 1201 & JO 24 SM 1101).

Animal Species	1980[a]	1985[a]	1990	1995	2000	2005	2010	2011	2012
Cattle									
Dairy cows	656	646	576	482	428	393	348	346	348
Beef cows	71	59	75	157	167	177	197	196	193
Other cattle >1 year	614	570	544	596	589	527	513	495	479
Calves <1 year	595	563	524	542	500	509	479	475	481
Total, cattle	1 935	1 837	1 718	1 777	1 684	1 605	1 537	1 512	1 500
Sheep									
Ewes and rams	161	173	162	195	198	222	273	297	297
Lambs	231	252	244	266	234	249	292	326	314
Total, sheep	392	425	406	462	432	471	565	623	611
Pigs									
Boars & sows	290	260	230	245	206	188	156	153	142
Fattening pigs >20 kg [b]	1 254	1 127	1 025	1 300	1 146	1 085	937	901	851
Piglets <20kg [c]	1 170	1 113	1 009	769	566	539	427	429	370
Total, pigs	2 714	2 500	2 264	2 313	1 918	1 811	1 520	1 483	1 363
Laying hens									
Hens	5 937	6 548	6 392	6 100	5 670	5 065	6 061	6 376	6 735
Chickens reared for laying	2 636	2 159	2 176	1 812	1 654	1 697	1 647	1 828	1 551
Total, hens	8 573	8 708	8 568	7 912	7 324	6 762	7 707	8 204	8 286
Turkeys									
Total, turkeys						122	130		
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, 1980-2012 (Yearbook of Agricultural Statistics, Sweden 2001 & 2011 and Statistical Message JO 20 SM 1201 & JO 24 SM 1101).

Animal Species	1980	1985	1990	1995	2000	2005	2010	2011	2012
Cattle									
Dairy cows	44 143	35 063	25 921	17 743	12 676	8 548	5 619	5 260	4 968
Beef cows	12 436	10 310	10 883	17 069	13 861	12 821	12 190	11 809	11 375
Other cattle >1 year	63 179	52 652	42 696	39 160	30 457	24 808	20 295	19 107	18 182
Calves <1 year	62 314	52 001	41 986	36 542	27 733	22 888	18 494	17 721	17 001
Total holdings with cattle	70 503	58 872	47 292	41 990	32 063	26 179	21 586	20 503	19 561
Sheep	10 238	10 595	9 749	10 037	8 089	7 653	8 657	9 449	9 263
Pigs	26 122	19 937	14 301	10 753	4 809	2 794	1 695	1 515	1 318
Laying hens	23 603	17 531	12 900	9 593	5 678	4 916	3 703	3 827	3 876
Chickens reared for laying	5 093	2 714	1 875	1 405	715	634	487	733	673
Broilers						234	181	202	217
Turkeys						383	102		
Horses						56 000[a]	78 000		

[a] Data from 2004.

TABLE 7.8. Number of animals slaughtered (in thousands) at slaughterhouses, 1980-2012. (Yearbook of Agricultural Statistics, Sweden 1981, 1986, 1991 & 2009 and Statistical Message JO 48 SM 1302).

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

[a] Data supplied by the National Food Administration.

TABLE 7.9. Quantity of livestock slaughtered (in 1000 tonnes) at slaughterhouses, 1990-2012 (Yearbook of Agricultural Statistics, Sweden 1991 & 2009 and Statistical Message JO 48 SM 1302).

Animal Species	1990	1995	2000	2004	2005	2010	2011	2012
Cattle								
Cattle >1 year	139.5	140.1	145.4	137.8	131.4	133.5	133.5	121.0
Calves < 1 year	6.8	3.2	4.4	4.6	4.5	4.3	4.4	4.5
Total, cattle	146.3	143.3	149.8	142.4	135.9	137.8	138.2	125.5
Sheep	5.0	3.5	3.9	3.8	4.1	5.0	5.1	5.0
Pigs	293.1	308.8	277.0	294.5	275.1	263.5	256.1	233.7
Broilers	44.0[a]	73.6[a]	89.9	91.2	96.2	112.0	111.5	110.5
Turkeys						3.2	3.7	3.0

[a] Data supplied by the National Food Administration.

Appendix 2: Materials and methods, use of antimicrobials

Legal framework and distribution of medicines

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

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

All pharmacies in Sweden are required to provide statistics on sales of all products on a daily basis to an infrastructure company owned by the state: Apotekens Service. This company maintains a database and provides statistics to the competent national and regional authorities and to others on a commercial basis.

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

The ATC classification system and defined daily doses (DDD)

Since 1988, the Anatomical Therapeutic Chemical (ATC) and ATCvet classification system recommended by the WHO is used in Sweden for national drug statistics. For drugs sold for use in humans, to facilitate drug utilisation studies from a medical point of view, the concept of defined daily dose (DDD) is used as a unit of comparison in drug statistics. The DDD for a drug is established on the basis of the assumed average dose per day for the drug given to adults for its main indication. If possible, the DDD is given as the amount of active substance. The DDDs are usually equal for all dosage forms of a preparation. The statistical data systems of Apotekens Service are upgraded yearly according to the recommendations made by the WHO Collaborating Centre for Drug Statistics methodology in Oslo, Norway. The DDDs used in this report are shown in Table 7.10. The sales of drugs are presented as number of DDDs per 1000 inhabitants and day (DDD/1000 and day), which give an estimate of the proportion of the population daily exposed to a particular drug. This figure is a rough estimate and should be interpreted with caution.

Antimicrobial consumption in humans

Swedish national statistics on drug utilization

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

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

Data sources and inclusion criteria

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

Antimicrobial use in hospital care is measured as DDD/1000 inhabitants and day and DDD/100 patient-days or admissions. The number of DDDs is obtained from Apotekens Service and from local medicines statistics systems in the counties. The National Board of Health and Welfare has provided data on patient-days and admissions to hospitals. Admission is calculated as number of discharges (one patient can be discharged and admitted multiple times if transferred between wards during one hospital stay). Patient-day is calculated as each additional day during one hospital stay.

When this report was compiled, data on patient-days and admissions in 2012 is not available. Therefore, data from 2011 is used. The number of patient-days and admissions represent production of somatic medical care by each county (to be distinguished from consumption of the county's inhabitants). This gives a more accurate comparison of antibiotic use in hospitals, since the amount of medicines used is related to the quantity of medical care produced.

TABLE 7.10. DDD for all substances sold in Sweden in 2012. 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 - sulfametoxazol and trimethoprim	0.4
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 – fusididic 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		

The Swedish Prescribed Drug Register

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

Number of admissions and patient-days

Each of the 21 county councils in Sweden deliver once a year data to the National Patient Register kept by The National Board on Health and Welfare. Administrative data within hospital care include, among others, date of admission, date of discharge and length of stay. Since data for 2012 is not available until August 2013, denominator data from 2011 are used in some figures in this report. The number of admissions and patient-days in Swedish somatic medical care 2011 is shown in Appendix 1, Table7.3. The National Board of Health and Welfare keeps a searchable database at the web, http://www.socialstyrelsen.se/statistik.

Antimicrobial consumption in animals

Data sources, inclusion criteria and analysis

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

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

In rare cases, premixes mixed in medicated feed may be delivered from feed mills without the sales being recorded by a pharmacy. Examination of the reports by all feed mills to the SBA shows that this happened only once during 2005-2009 (a total quantity of 40 kg active substance). The ionophoric antibiotics are presently regulated as feed additives and not sold through pharmacies. However, the SBA collects figures on sales of ionophores from the feed mills as a part of the feed control system. As the source differs, data on ionophores are given only in the Table 5.10.

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. From 2012 no information on sales of these products can be retrieved from the database of Apotekens Service. 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 data on sales of products for intramammary use, as the amounts sold have historically been very low. The obtained information on number of packages sold per product-pack-type was added to the data provided by Apotekens Service.

Appendix 3: Materials and methods, resistance in bacteria from humans

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

The disk diffusion method has been successfully standardized by the Swedish clinical microbiology laboratories in collaboration with the former SRGA-M, which since 2011 is replaced by NordicAST, a Nordic AST Committee with representatives from Denmark, Norway and Sweden. Until 2009 all laboratories used the methodology based on ISA medium and a semi-confluent bacterial inoculum as recommended by SRGA-M. In 2010 several laboratories had already 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), and from 2011 all laboratories use this methodology. 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".

Programmes for surveillance of antibiotic resistance

Surveillance regulated in the Communicable Disease Act

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

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

Infections (or colonisation) with different antibiotic resistant pathogens are included in the list of notifiable diseases. *Streptococcus pneumoniae* with bensylpenicillin MIC $\geq$ 0.5 mg/L (PNSP) have been notifiable since 1996. In 2012 the definition for notifiable *S. pneumoniae* was changed to MIC > 1 mg/L. 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 ($ESBL_{CARBA}$). In 2012 notifications of $ESBL_{CARBA}$ were extended to require also a clinical notification.

As an important complement to the notifications, the MRSA, VRE and PNSP isolates are sent to SMI for epidemiological typing. For MRSA *spa*-typing is the primary typing method, for VRE it is pulsed-field gel electrophoresis (PFGE), and for PNSP serotyping. Depending on needs also other molecular biology methods are used, *e.g.* MLST.

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

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

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

ResNet, an application for surveillance of resistance in commonly encountered infections

In Sweden there are at present 28 clinical microbiology laboratories, each covering a county (or part of county) of Sweden. The demographics of the laboratories, their geographic areas and their corresponding populations are well characterized. The antimicrobial susceptibility testing methods of the laboratories have been standardized through the combined work of the former SRGA-M (since 2011 replaced by NordicAST)

and the microbiological laboratories.

In 1994 a model for the concomitant surveillance of antimicrobial resistance and quality assurance of antimicrobial susceptibility testing was devised. 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 the web-based software ResNet has recieved the aggregated data from the laboratories and, following approval of registered data by the web administrator, 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). Each laboratory will also get a tabular presentation of all its own data and will be able to link this information to the local website of its own local health care system.

EARS-Net for surveillance of pathogens from blood cultures

The European network of national surveillance systems of antimicrobial resistance performed on-going surveillance of invasive infections of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus faecalis/faecium*, and monitors variations in antimicrobial resistance over time and place. From 2005 invasive isolates of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are also part of the scheme.

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

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

The participation from twenty laboratories in Sweden is coordinated through the SMI, where electronic data collection, validation and verification of specific resistance mechanisms are performed. Sweden, because of its well organised network of clinical laboratories and high quality of routine susceptibility testing, is one of the largest contributors of national data to EARS-Net.

Surveillance of blood cultures additional to EARS-Net data

Data on invasive isolates on all positive blood cultures were obtained from ten laboratories that are using the same laboratory information system (ADBakt). Their total catchment population is at present 5 millions, thus representing more than 55% of the Swedish population. From these laboratories data for the pathogens specified by the EARS-net network are retrieved, but also data on all other bacterial pathogens consecutively isolated from blood cultures. In the SWEDRES reports from 2007 to2012 data for *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Haemophilus influenzae* are presented.

Surveillance of other pathogens

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. In 2012, however, data on *Salmonella* from blood cultures were added, using the ten laboratories database as described above.

Neisseria gonorrhoeae and *Neisseria meningitidis* are analysed and presented by the National Reference Laboratory for Pathogenic Neisseria in Örebro, and *Mycobacterium tuberculosis* are reported from SMI.

Appendix 4: Materials and methods, resistance in bacteria from animals

Sampling strategy

Antimicrobial resistance as notifiable diseases

ESBL

$ESBL_A$ and $ESBL_M$-producing *Escherichia coli* was isolated from the same samples as the indicator bacteria, *i.e.* caecal content from broilers and laying hens, rectal swabs from dogs and from broiler meat, see below. In the research project regarding dairy calves, the farms where chosen by convenience and at each farm rectal swabs were collected from 3 calves aged 7-28 days. Clinical isolates were submitted to the Dept. of Animal Health and Antibiotic Strategies, SVA (DOA) as bacterial strains.

MRSA and MRSP

Findings of MRSA in animals are notifiable in Sweden and hitherto almost all isolates from notified incidents have been confirmed at SVA. For monitoring strategies see Antimicrobial resistance as notifiable diseases, MRSA.

Monitoring MRSA in dairy cattle was performed by screening isolates of penicillinase producing *S. aureus* from routine submission of milk samples sent to SVA. From each submission of milk samples where penicillinase producing *S. aureus* was found, one isolate, selected by convenience, was tested. In addition, 40 dairy herds in Southern Sweden were screened for MRSA in 2012. In each herd, a sample of bulk tank milk, individual milk samples from five cows, hock skin samples from the same five cows and nasal swabs from five preweaned calves were analysed at SVA.

Screening for MRSP and MRSA in dogs was performed by culture of swabs from corner of mouth, throat, wounds and perineal area. Swabs were taken from healthy animals presented for routine vaccination, selected by convenience. Thirteen animal hospitals participated in the study which was carried out in the autumn 2012. Clinical isolates were submitted to DOA as bacterial strains.

Zoonotic pathogens

Salmonella

Salmonellosis in animals is a notifiable disease in Sweden and isolates from each notified incident must be confirmed at SVA. Data presented in SVARM are from susceptibility testing of these isolates. The summary for each year includes one isolate of each serovar, and when appropriate phage-type, from each warm-blooded animal species in notified incidents. 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 2012, 217 flocks were positive for Campylobacter. From these, 100 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. Isolates of *Actinobacillus pleuropneumoniae* from pigs and part of the isolates of *Pasteurella* spp. from calves are, however, isolated from samples collected in surveys initiated within the SVARMpat programme.

In pigs, isolates of *E. coli* are from the gastro-intestinal tract (gut content, faecal samples or mesenteric lymph nodes) 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 the gastro-intestinal tract and isolates of *Pasteurella* spp. are from the respiratory tract.

In horses, isolates of *E. coli* are from the genital tract of mares, *Streptococcus zooepidemicus* from the respiratory tract and *S. aureus* from skin samples.

In dogs, isolates of *E. coli* are from the urinary tract, *S. pseudintermedius* from skin samples and *Pseudomonas aeruginosa* from the external ear. In cats, isolates of *E. coli* are from the urinary tract.

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

Indicator bacteria

Broilers

Indicator bacteria, *i.e. E. coli* and *Enterococcus faecalis* and *E. 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 seven abattoirs that in 2012 accounted for >99% 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.

Broiler meat

Indicator bacteria as above were isolated from frozen chicken filets. One hundred packages of frozen broiler filets from four cutting plants were purchased in various shops and locations during October-December. Each package represents a separate batch of broilers slaughtered. Together the four cutting plants account for >90% of the annual volume of broilers slaughter.

Laying hens

Indicator bacteria as above were isolated from caecal content of healthy laying hens sampled at slaughter. Sampling was performed at one of two abattoirs, from October 2012 to January 2013. Each sample is from a unique flock but not always from a unique production site. This was a pilot study and how representative the samples are for the whole production is not known. One bias is that not all farmers send laying hens for slaughter at abattoirs.

Dogs

Indicator bacteria, *E. coli* only, from dogs were isolated from rectal swabs from healthy animals presented for routine vaccination, selected by convenience. Thirteen animal hospitals participated in the study which was carried out in the autumn 2012.

Isolation and identification of bacteria

Antimicrobial resistance as notifiable diseases

ESBL

$ESBL_A$ and $ESBL_M$-producing *E. coli* was isolated by culture on MacConkey agar with cefotaxime (1mg/L) after incubation overnight at 37°C. For additional information, see section about indicator bacteria below. In the research project regarding dairy calves, material from rectal swabs was suspended in saline and 0.1 mL was streaked on MacConkey agar with cefotaxime (1mg/L).

MRSA

In the screening for MRSA among isolates of penicillinase producing *S. aureus* from dairy cows, isolates were susceptibility tested using microdilution (see below). Isolates with MICs of oxacillin and/or cefoxitin ≥4 mg/L were tested for the presence of *mecA* and *mecC* with PCR (see below).

In the screening for MRSA in 40 dairy herds, milk samples were centrifuged and the supernatant was removed, enrichment broth Tryptone Soy Broth (TSB) with mannitol and phenol red, 4% NaCl, 3.5 mg/L cefoxitin and 50 mg/L aztreonam) was added and the sample was incubated overnight at 37°C. Nasal swabs from five animals were pooled in enrichment broth and incubated overnight in 37°C. After incubation, 100 µL of the broth were spread on MRSA-agar (Brilliance MRSA, Oxoid) and 10 µL were spread on bovine blood-agar. The plates were incubated at 37°C and inspected after overnight incubation and after 48 hours.

MRSP

Swabs collected from healthy dogs (see above) were incubated overnight at 37°C in TSB (mannitol and phenol red, 4% NaCl, 1.0 mg/L cefoxitin and 50 mg/L aztreonam). After incubation, 10 µl was spread on Mannitol Salt Agar (MAST) with cefoxitin 1mg/L and incubated overnight. In addition, TSB tubes were incubated for an additional 24 hours. If there was no growth on the MAST plate, 10µl from the TSB tube incubated 48 hours was spread on a second MAST plate and incubated. Typical staphylococcal colonies were subcultured on bovine blood-agar. PCR was performed on isolates for species identification and genotyping of the *mecA* gene, see below (Genotyping).

Zoonotic pathogens

Salmonella

Salmonella was isolated and identified at the Dept. of Bacteriology (BKT), 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* Typhimurium and *S.* Enteritidis were phage-typed by the Swedish Institute for Infectious Disease Control (SMI), Stockholm using the Colindale scheme.

Campylobacter

Campylobacter spp. from broilers was isolated and identified at BKT. Samples were cultured for thermophilic *Campylobacter* spp. according to ISO 10272-1:2006 with 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. Bacteria from terrestrial animals were isolated at BKT, and bacteria from fish at DOA. Part of the isolates of *Pasteurella* spp. from pigs and cattle and part of the isolates of *E. coli* from cattle were isolated and identified following standard procedures at a regional laboratory.

Indicator bacteria

Escherichia coli

Approximately 0.5 g of 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 MacConkey agar with cefotaxime (1mg/L) and incubated overnight at 37°C. Isolation for indicator bacteria in dogs was performed as above but rectal swabs were streaked directly on the solid media.

Twenty-five grams of broiler meat was homogenized thoroughly in 2 min with 225 mL in buffered pepton water (BPW). Thereafter 20 mL was transferred to 20 mL double concentrated MacConkey broth and incubated at 37°C for 18-24 hours. From the pre-enrichment 100 µL was spread on MacConkey agar and incubated overnight at 37°C.

For selective culture for *E. coli* resistant to third generation cephalosporins in broiler meat, 100 ml of the homogenized BPW with addition of cefotaxime (1mg/L) was incubated at 37°C overnight. From the pre-enrichment 100 µL was spread on MacConkey agar with cefotaxime (1mg/L) and incubated overnight at 37°C.

One lactose positive colony with morphology typical for *E. coli* was sub-cultured onto horse-blood agar (5% v/v), after which the isolate was tested for production of tryptophanase (indole). Only lactose and indol positive isolates with typical morphology were selected for susceptibility tests. Colonies growing on MacConkey agar with cefotaxime were sub-cultured on horse-blood agar (5% v/v) and further tested for ESBL detection.

Enterococci

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.

Twenty mL of the BPW from homogenized broiler meat (above) was mixed with 20 mL double concentrated Enterococcosel broth and incubated at 37°C overnight. From the enriched Enterococcosel broth, 100 µL was spread on SlaBa agar and incubated at 37°C for 48 h. Two 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 according to Devriese et al. (1993) by use of the following biochemical tests: mannitol, sorbitol, arabinose, saccharose, ribose, raffinose and methyl-α-D-glucopyranoside. If available, one isolate of *E. faecium* and one isolate of *E. faecalis* from each sample were tested for antimicrobial susceptibility.

Susceptibility testing

Microdilution

At SVA, the departments DOA and BKT test bacteria from terrestrial animals for antimicrobial susceptibility with accredited methodology using dilution methods in cation adjusted Mueller-Hinton broth (CAMHB) (Difco). Tests are performed following the standards for microdilution of the Clinical and Laboratory Standards Institute (CLSI, 2008). The microdilution panels used, VetMIC, are produced at the Dept. of Vaccines and Blood products, SVA. Different panels are used depending on the bacterial species tested and the purpose of the investigation (monitoring or clinical diagnostics). Minimum inhibitory concentration (MIC) is recorded as the lowest concentration of an antimicrobial that inhibits bacterial growth.

Some adaptations from the CLSI standard are employed. For *Pasteurella* spp. three different protocols are used at SVA. Either by dilution in CAMHB supplemented with 5-10% horse serum followed by incubation in aerobic atmosphere, 37°C for 16-18 hours, or by dilution in Haemophilus test medium (HTM) followed by incubation in CO_2, 37°C for 16-18 hours. Also dilution in CAMHB supplemented with 5-10% horse serum and incubation in CO_2, 37°C for 16-18 hours was used. For testing of *Actinobacillus pleuropneumoniae* dilution in HTM broth is used followed by incubation in CO_2 at 37°C for 16-18 hours. Also, S*treptococcus* are 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*, are tested for susceptibility by a broth dilution method described by Karlsson et al. (2003). The antimicrobials are dried in serial twofold dilutions in the 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.

Also bacteria from fish are tested for antimicrobial susceptibility at DOA. The same methodology as described above is used but adapted for aquatic bacteria according to Alderman & Smith (2001), which *e.g.* implies incubation at 20°C for two days.

Phenotypic confirmatory test for production of extended spectrum beta-lactamases (ESBLs) in *E. coli* was performed by the double disc diffusion test according to CLSI (2008).

Genotyping

Suspected isolates of MRSA was confirmed by detection of the *nuc*, *mecA* and *mecC* genes by polymerase chain reaction (PCR) as described by Stegger et al. 2012 and suspected MRSP was confirmed by detection of *mecA* and *nuc* genes by PCR (Nilsson et al. 2005 and Sasaki e al. 2010). *Spa* typing, a single locus sequence typing method using the polymorphic region X of the protein A gene, was performed on all isolates confirmed as MRSA. It was performed according to the method described by Harmsen et al. (2003) and the specific *spa* type was determined using BioNumerics® (Applied Maths).

PCR was performed for identification of plasmid-mediated AmpC (Perez-Perez and Hanson 2002), CTX-M mediated ESBL (Woodford et al. 2006) and OXA-1 group, TEM and SHV genes (Fang et al. 2006).

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

Quality assurance system

The departments DOA and BKT are accredited according to SS-EN ISO/IEC 17025 by the Swedish Board for Accreditation and Conformity Assessment (SWEDAC) to perform antimicrobial susceptibility tests with microdilution methods. In addition, BKT is accredited for isolation and identification of animal pathogens and of *Salmonella* and *Campylobacter* according to the same standard.

For susceptibility tests of zoonotic, pathogen and indicator bacteria, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* CCUG15915 (analogue to ATCC 29213) and *Campylobacter jejuni* CCUG 11284 (analogue to *Campylobacter jejuni* ATCC 33560) were included as quality controls. Relevant control strains were also included and evaluated at least once weekly for animal pathogens. For testing of *Brachyspira*, the *B. hyodysenteriae* type strain B78^{T} ATCC 27164T was used for quality control.

The department DOA participates in several proficiency tests for antimicrobial susceptibility testing. These are arranged either by the European Union Reference Laboratory - Antimicrobial resistance or as national studies. Likewise, BKT participates in proficiency tests concerning isolation and identification of *Salmonella* spp. and general clinical veterinary bacteriology and susceptibility tests.

Data handling

Records on *Salmonella* and animal pathogens such as source of cultured sample, identification results, antimicrobial susceptibility etc. were registered in a database at SVA. Data for indicator bacteria data was recorded in an Access database.

Cut-off values for resistance

For interpretation of results of susceptibility testing of zoonotic bacteria (*Salmonella* and *Campylobacter*) and indicator bacteria (E*scherichia coli* and enterococci) epidemiological cut-off values (ECOFF) issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (www.eucast.org) were used. When no ECOFF is issued, a value based on MIC distributions obtained in the SVARM programme was used. This approach was also used for interpretation of narasin MICs for *E. faecium* because the recommended cut-off value (>4 mg/L) cuts through MIC distributions in SVARM in a manner not in agreement with the concept of wild-type distributions.

ECOFFs were used when available also for animal pathogens. When no ECOFFs were available, or the range of concentrations tested is inappropriate for a recommended value, values based on MIC distributions obtained in the SVARM programme were used. Clinical breakpoints issued by CLSI (2008) were also taken into consideration. ECOFFs classify 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.

Bacitracin values in this report are given in units/mL. In an attempt to convert units/mL to mg/L it was evident that there appears to be some confusion in the matter. The bacitracin compound used in SVARM is obtained from Sigma and meets the standards set by the United States Pharmacopoeia (USP), stating that one unit is equivalent to 26 µg of the US standard. However, according to the International Standard Preparations, one international unit is equivalent to 13.51 µg. On the other hand, if the bacitracin is of a very high degree of purity, though unstable, it correspond to 66 (-70) units/mg, that is, one unit is equivalent to approximately 15 µg. Feedingstuff grade of bacitracin correspond to 42-50 units/mg (one unit=20-24 µg) (Otten et al., 1975).

TABLE 7.11. Cut-off values (mg/L) for resistance. Values in red are current (March 2013) EUCAST epidemiological cut-off values (ECOFFs), blue underlined values deviate from ECOFFs and for values in black, ECOFFs are not defined.

Antimicrobial	*Actinobacillus pleuropneumonia*	*Brachyspira hyodysenteriae*	*Campylobacter jejuni*	*Campylobacter coli*	*Enterococcus faecalis*	*Enterococcus faecium*	*Escherichia coli* (indicator)	*Escherichia coli* (pathogen)	*Pasteurella* spp.	*Pseudomonas aeruginosa*	*Salmonella enterica*	*Staphylococcus pseudintermedius*	*Staphylococcus aureus*	*Streptococcus zooepidemicus*
Ampicillin	>1		>8	>8	>4	>4	>8	>8	>1		>8			>8
Bacitracin[a]					>32	>32								
Cefotaxime	>0.06						>0.25	>0.5			>0.5			
Cefoxitin													>4	
Ceftiofur							>1	>1			>2		>2	
Cephalothin												>2	>1	
Chloramphenicol	>2				>32	>32	>16		>2		>16		>16	
Ciprofloxacin	>0.06		>0.5	>0.5			>0.06		>0.06		>0.06		>1	
Clindamycin												>4	>0.25	
Colistin							>2							
Doxycycline		>0.5												
Enrofloxacin							>0.12	>0.12	>0.25	>2	>0.25	>0.5	>0.5	
Erythromycin			>4	>8	>4	>4						>1	>1	
Florfenicol	>16						>16	>16	>16		>16		>8	>8
Fusidic acid												>4	>0.5	
Gentamicin	>8		>2	>2	>32	>32	>2	>4	>8	>8	>2	>4	>2	
Kanamycin					>1024	>1024	>8				>16		>8	
Linezolid					>4	>4								
Nalidixic acid	>16		>16	>16			>16		>16		>16			
Narasin					>2	>2								
Neomycin								>8			>4			
Nitrofurantoin								>32				>32		
Oxacillin												>0.5	>1	
Penicillin	>1								>1			[c]	[c]	>1
Polymyxin B								>2		>4				
Spiramycin													>16	>16
Streptomycin	>32		>4	>4	>512	>128	>16	>16	>32		>16		>16	
Sulphametoxazole							>64				>256			
Tetracycline	>2		>1	>2	>4	>4	>8	>8	>2		>8	>8	>1	>8
Tiamulin		>0.25												
Trimethoprim	>4						>2	>2	>4		>2		>2	
Trim & sulph[b]								>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.

Appendix 5: SVARM 2000-2012

Data on antimicrobial susceptibility of more than 30 000 isolates of bacteria have been presented in SVARM since 2000. The annual number of isolates of different categories is presented below.

TABLE 7.12. *Salmonella enterica*, number of isolates 2000-2012.

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

TABLE 7.13. *Campylobacter* spp., number of isolates 2000-2012.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Cattle		67					68						
Pigs		98		105		100	46		97			83	
Broilers		50	100		100				38		100		100
Raw meat		74											
Water		19											

TABLE 7.14. Indicator *Escherichia coli*, number of isolates 2000-2012.

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Cattle	293						314			223			
Pigs	260	308		303		390		342	349			167	
Pig meat									19			20	
Broilers	274	296	306		300			296			181		194
Broiler meat											77		92
Laying hens													61
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 2000-2012 (*E. faecalis/E. faecium*).

Source	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Cattle	22/71						13/98			10/24			
Pigs	56/48	52/106		87/71		55/47			68/39			22/22	
Pig meat									17/3			29/1	
Broilers	24/151	49/204	57/189		48/163			28/197			35/136		44/136
Broiler meat											81/17		78/10
Laying hens													20/36
Horses											34/27		
Dogs							135/29						
Wild boars		12/35											
Sheep									24/15				

TABLE 7.16. Clinical isolates from animals, number of isolates 2000-2012.

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

Appendix 6: References

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SWEDRES|SVARM 2012

The introduction of antimicrobials some 70 years ago was a true paradigm shift with an immense impact on the possibility to treat infectious diseases in human and veterinary medicine. Unfortunately, the usefulness of these lifesaving drugs has been undermined by increasing antimicrobial resistance in bacteria of both humans and animals. Further efforts are needed to counter the selection and spread of resistance, and one key component in that work is good quality information on the situation. The SWEDRES-SVARM is an integrated report from SMI and SVA on use of antimicrobials and antibacterial resistance with data from humans, animals and food.

The Swedish situation regarding antimicrobial resistance in bacteria from humans and animals is still favorable when seen in an international perspective. The Swedish strategy to promote rational use and to contain antimicrobial resistance in bacteria from animals and humans has been effective, but this year's report also shows unfavorable trends. For example, the number of notified human cases of ESBL-producing Enterobacteriaceae and of methicillinresistant Staphylococcus aureus (MRSA) are steadily increasing. These resistant bacteria are also found in animals, and the zoonotic aspects are discussed in the report. The need for continuous surveillance of the situation, and for translating data into action, is emphasised. Only through continued collaborative efforts of all parties concerned can we preserve the effectiveness of antimicrobials for treatment of current and future generations of people.

The report covers:

- Use of antimicrobials in humans and animals
- Occurrence of resistance in
  - Notifiable diseases, for example ESBL-producing bacteria, MRSA and VRE
  - Zoonotic pathogens
  - Clinical isolates from humans and animals
  - Indicator bacteria from animals

Swedish Institute for Communicable Disease Control, SMI, is a Government agency with the mission to monitor the epidemiology of communicable diseases among Swedish citizens and promote control and prevention of these diseases. SMI is responsible for national surveillance of antibiotic use and antibiotic resistance, and aims at providing expert analyses and advice to laboratories, infection control officers, Strama-groups and county medical officers.

Swedish National Veterinary Institute, SVA, is a Government expert authority within the field of risk assessments, prevention, diagnostics and the control of contagious and other serious infectious diseases including zoonotic agents and antimicrobial resistance. SVA is mandated to monitor antimicrobial resistance in animals and food and to promote rational use of antimicrobials in animals.